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The prognostic role of albumin-bilirubin grade in the mortality of extrahepatic cholangiocarcinoma patients

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Abstract

Objective Cholangiocarcinoma (CCA) has a low survival rate of 5–17%, despite advancements in diagnosis and treatment. Liver function impacts disease prognosis, and the albumin-bilirubin (ALBI) score is a new assessment model for this purpose. While research suggests a correlation between ALBI score, liver failure and mortality in intrahepatic CCA (iCCA), predicting outcomes for extrahepatic CCA (eCCA) is challenging. Our objective was to assess the prognostic role of ALBI grade in predicting overall survival of eCCA patients.

Methods Patients with diagnosis of eCCA who had visited Firuzgar Hospital from 2015 to 2019 were consecutively included in the study. These individuals had previously undergone Endoscopic Ultrasound-Guided Fine Needle Aspiration (EUS-FNA) or ERCP brush cytology followed by surgery. Exclusion criteria were patients with benign bile duct strictures, prior biliary tract surgery, concurrent liver disease impacting liver tests, inadequate data, or inconsistent monitoring. Clinical data of patients were collected to calculate ALBI score which was subsequently divided into three distinct grades (grade 1: ≤ -2.60, grade 2: > -2.60 to ≤ -1.39, grade 3: > -1.39). Kaplan-Meier analysis and Cox regression model were used to analyze overall survival, 1-, 3- and 5-year survival and parameters affecting patient survival.

Results In this study, 80 patients with diagnosis of eCCA with a median age of 67 (58.25-74) years (67.5% male) who visited Firuzgar Hospital from 2015 to 2019 were included. The average survival time of patients was 13.9 ± 16.4 months, and the 1-year, 3-year, and 5-year survival rates of patients were 36.6%, 27.1%, and 15.8%, respectively. The results showed that ALBI grade, Aspartate Aminotransferase (AST), white blood cell (WBC) and international normalized ratio (INR) have significant effects on the survival of patients (all $P < 0.05$). Based on the results of Cox regression, the risk of mortality due to CCA in patients with ALBI grade 3 (HR = 1.87, $P = 0.0111$), AST > 82.5 (HR = 1.90, $P = 0.0091$), WBC > 7.70×10^9/L (HR = 2.46, $P = 0.0004$), and INR > 1.08 (HR = 1.78, $P = 0.0202$) increases significantly.

Conclusion We showed that ALBI grade, AST > 82.5 units/L, and INR > 1.08 can be used as predictive factors of survival in cholangiocarcinoma patients.

Keywords Cholangiocarcinoma, Prognostic, ALBI score

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Introduction

Cholangiocarcinoma (CCA) represents a diverse group of invasive malignancies arising from damaged biliary epithelial cells, and accounts for approximately 10–25% of all hepatobiliary malignancies. There is no data available on the incidence of cholangiocarcinoma in Iran. One study, however, found that biliary tract cancer accounted for approximately 0.5% of all new cancer cases in 2020 [1]. This malignancy has a poor prognosis and between 50 and 90% of patients are diagnosed at a stage where the tumor is unresectable [2–4], CAA can be categorized into two types based on the tumor's location: intrahepatic cholangiocarcinoma (iCCA) and extrahepatic cholangiocarcinoma (eCCA), while approximately 80% of cases fall under the category of eCCA [3]. In the last few decades, the incidence and mortality rates of this disease are increasing despite advances in diagnosis and treatment [5] and the overall 5-year survival rate for this disease has been 5–17% [6].

Several studies have highlighted the significance of liver function in predicting outcomes for different types of solid tumors, such as iCCA and bile duct neoplasms [7–10], therefore, accurate assessment of liver function is very important to predict the survival of patients. Child-Pugh (CP) is the most widely utilized model in liver function assessment, and prognosis of liver cirrhosis and hepatocellular carcinoma [11]. CP grade is also significantly associated with survival in other neoplasms, including eCCA [7, 8, 12], but due to the high prevalence of obstructive jaundice, especially in advanced stages of CCA [13, 14] most patients have advanced CP grade and in eCCA, ascites and encephalopathy can be due to tumor expansion and cholangitis; Therefore, CP grade may not be very suitable to assess liver function reserve in CCA. Recently, a new assessment model for liver function called albumin-bilirubin score (ALBI) has been proposed [15, 16]. Patients with chronic obstruction of the bile duct show elevated levels of total and direct bilirubin, as well as alkaline phosphatase. This condition results in liver dysfunction, leading to higher levels of aminotransferases and prolonged prothrombin time, and a decrease in serum albumin [17]. Several studies have shown that a rise in ALBI score correlates with a higher risk of liver failure, and mortality in iCCA, making it a crucial biomarker for predicting survival in these patients [16, 18–21]. Also, albumin levels reflect a patient's nutritional status and the body's capacity to manage inflammation. Moreover, elevated bilirubin levels can impair the immune system's antitumor response, promoting tumor progression and negatively impacting patient survival [22]. As a result, a higher ALBI grade is associated with poorer survival, similar to HCC. The calculation of ALBI grade is significantly simpler than other prognostic factors such as the TNM staging system and histological grading. Unlike the Child-Pugh classification, ALBI grade is not influenced by subjective factors such as ascites or hepatic encephalopathy [23]. Considering the higher mortality and poor outcome of eCCA compared to iCCA, as well as the differences in molecular profiling and treatment patterns between them, the role of ALBI grade in predicting the survival of patients with eCCA is important [24, 25]. But accurate prediction of prognosis for eCCA patients is still a challenge, and there are few studies on the role of ALBI in predicting the overall survival of these patients [26]. As there is a lack of research on this topic in Iran, in this study we investigated the role of ALBI score and certain associated lab values such as serum level of liver enzymes, white blood cells count, platelet (PLT), Prothrombin time (PT), and international normalized ratio (INR) for predicting the mortality rate of eCCA patients following surgery.

Methods

Study population

This cohort study was conducted on patients with CCA at Firouzgar Hospital in Tehran, Iran from 2015 to 2019. These patients were under the care of the gastroenterology and liver department and had previously undergone Endoscopic Ultrasound-Guided Fine Needle Aspiration (EUS-FNA) or ERCP brush cytology followed by surgery. Patients with eCCA diagnosis were eligible for inclusion, except for those with benign bile duct strictures, prior biliary tract surgery, Patients with perihilar involvement who underwent liver transplantation, concurrent liver disease impacting liver tests, inadequate data, or inconsistent monitoring. The study initially involved 91 patients, but 11 patients were later excluded from the study for failing to respond to phone calls and cooperate during follow-up. As a result, the study ultimately focused on 80 patients. All patients were monitored until 2022 or their date of passing. This study has been approved by the ethics committee of Iran University of Medical Sciences and was conducted according to the Helsinki Declaration. Participants enrolled in the study after providing informed consent (obtained from the participants or their immediate family members) with full awareness of the study's objectives.

Clinical and demographic information

Patient demographic and clinical details such as age, gender, and tumor location were obtained from their medical records. The endoscopic ultrasonographic findings were used to establish the site of duct involvement. Laboratory results extracted from patient records included serum level of total bilirubin (TBIL), albumin (ALB), liver enzymes: aspartate aminotransferase (AST), alanine aminotransferase (ALT), Alkaline phosphatase (ALP), white blood cells (WBC) including neutrophil and lymphocyte, platelet (PLT), Prothrombin time (PT), and, international normalized ratio (INR). Albumin/bilirubin ratio, neutrophil/lymphocyte ratio, and platelet/lymphocyte ratio were also calculated. All tests were conducted before the surgery/biliary drainage and at the time of the patient's hospital admission.

The ALBI score was calculated using the following formula [15].

(0.66 × log10 TBIL [μmol/L]) + (−0.0852 × albumin [g/L])

Additionally, ALBI grades were determined as follows: grade 1: ≤−2.60, grade 2: > −2.60 to ≤ −1.39, grade 3: >−1.39.

Statistical analysis

Data was analyzed using SPSS version 22 software. $P<0.05$ was considered significant in all tests. In the descriptive part, quantitative variables were reported using median, 95% confidence interval, and qualitative variables with number and percentage. In the analytical part, firstly, the relationship between the examined variables and the outcome of the disease (death and survival) was investigated using the Chi square test (in qualitative variables) and Mann-Whitney U test (in quantitative variables). Then the cut-off points of the significant variables in differentiating disease outcome (death and survival) were determined using ROC test, and the validity of the model was checked using the area under the curve (AUC). Diagnostic parameters of determined cut points including sensitivity, specificity, positive predictive value, negative predictive value and accuracy were determined.

Then the significant variables were entered in the cox proportional hazards regression model. The variables that remained in the model were checked using the results of the long-rank test. The assumption of cox regression was checked and confirmed using the proportional hazard assumption test ($P<0.05$). In Cox regression, Hazard Ratio (HR) of model variables with 95% confidence interval was reported. Kaplan-Meier curves were used to introduce the importance of identified subgroups on patients' survival.

Results

Demographic and clinical information

The study included 80 patients with eCCA diagnosis. The median age of the patients was 67 (58.25-74) years, ranging from 27 to 80 years. The majority of patients were male (67.5%), and mostly diagnosed with distal extrahepatic CCA (65%). The two most common grades of ALBI were grade 2 at 42.5% and grade 3 at 38.8% (Table 1).

The findings indicate that there was no significant difference in demographic details (age and sex) between the group of patients who survived and those who didn't. But AST serum level ($P=0.007$), WBC ($P=0.005$), and INR ($P=0.043$) were significantly higher in patients who passed away compared to those who survived (Table 1).

Furthermore, the correlation between ALBI score and disease prognosis was significant. The outcomes demonstrated that ALBI score was significantly lower ($p=0.01$) in patients who survived compared to those who passed away during the follow-up period, and close to half of the patients who passed away had ALBI grade 3, a significant higher percentage than the patients who survived (48.3% vs. 13%, $P=0.01$) (Table 1).

The findings indicated that age ($P=0.41$), sex distribution ($P=0.11$), 1-year ($P=0.16$), 3-year ($P=0.31$), and 5-year ($P=0.37$) survival rates were not significantly different across the three ALBI grades (Table 2).

The threshold levels for AST, WBC, and INR

According to the results of Table 1, AST, WBC, and INR showed statistically significant differences between the patients who survived and those who passed away in a 5-year follow-up period (all $P<0.05$). Therefore, using the ROC test, the value of the cut-off point in the aforementioned variables in the study population was determined in order to differentiate the outcome of the disease (5-year survival). The results revealed that the areas under the curve (AUC) for AST, WBC, and INR were 0.696, 0.705, and 0.644 respectively (all $P<0.05$) (Table 3), and the determined cut-off points for these variables were as follows: AST = 82.5 U/L, WBC = 7.70×10^9/L and INR = 1.08. Diagnostic parameters, including sensitivity, specificity, positive predictive value, and negative predictive value, are presented for the determined cut-off points (Table 3). The sensitivity, specificity, and accuracy of each identified threshold were higher than 60%, with the exception of the INR threshold which had a sensitivity of 56.9%. The positive predictive value for all thresholds was greater than 80%, however, the negative predictive values were all below 46%.

Cox regression analysis

The average survival time for eCCA patients was 13.9 ± 16.4 months. The findings indicated that the survival rates at 1 year, 3 years, and 5 years for patients were 36.6%, 27.1%, and 15.8%, respectively (Fig. 1).

Then Cox regression analysis was used to examine the association between the identified threshold levels for AST, WBC, INR and ALBI grades (grade 3 vs. grades 1 and 2) and survival rate. The results from the log-rank test demonstrated that all the risk factors in the model were statistically significant ($P=0.0111$, $P=0.0091$, $P=0.0004$, and $P=0.0202$ for ALBI grade 3 vs. 1 and 2, serum AST level > 82.5 IU/L, WBC > 7.70×10^9/L, and INR > 1.08). According to the results of the Cox regression analysis, eCCA patients with ALBI grade 3 (HR = 1.87, $P=0.01$), those with AST levels exceeding 82.5 IU/l (HR = 1.90,

Table 1 Description of demographic and medical information of the patients

Variable		Median (25th and 75th percentiles)/ Number (%)			
		Total (*N* = 80)	**Survived (*N* = 22)**	**Passed away (*N* = 58)**	***P*-Value**
Age (years)		67(58.25-74)	70.50(63.50-76.25)	64(58-72.25)	0.085
Sex	Female	26 (32.5)	6 (27.3)	20 (34.5)	0.53
	Male	54 (67.5)	16 (72.7)	38 (65.5)	
History of chemotherapy	Yes	24 (30)	7 (31.8)	17 (29.3)	0.82
	No	56 (70)	15 (68.2)	41 (70.7)	
Types of Extrahepatic CCA	Distal and proximal of CBD	69 (86.3)	18 (81.8)	51 (87.9)	0.478
	PeriHilar	11 (100)	4 (36.4)	7 (63.6)	0.366
AST (units/L)		84.50(54-146.50)	62(36.50-97.25)	98(63.75-156.75)	**0.007**
ALT (units/L)		76(46.25-129.25)	58.50(29.25–113.20)	87(50-140.50)	0.080
ALP (units/L)		1032.50(511-1426.25)	670(413.75–1193)	1098(601.25-1484.25)	0.111
Bil T (mg/dL)		12.62(5.30-24.23)	10.31(2.97–19.80)	12.97(5.68–25.18)	0.298
Bil.D (mg/dL)		7(3–13)	7(1.88–13.73)	7.30(3.30–13.30)	0.605
ALB (g/l)		2.8(2.2–3.48)	3.10(2.70–3.79)	2.50(2.10–3.40)	0.06
WBC		8300(67000 – 11000)	7000(6280–8250)	8900 (7150–11975)	**0.005**
NEU		5967.9(4722.9-9215.7)	5020(4481-6356.1)	6759.7(4929.6-9842.8)	**0.016**
Lymph		1273.2(879.3-1584.5)	1286.9(1058.3-1519.5)	1273.2(852.5-1666.5)	0.906
PLT		251,000(196500–330250)	211,000(178500–343250)	268,000(217000–318750)	0.090
PT		13.70(13.13–15.45)	13.50(12-14.55)	13.90(13.50-15.93)	0.191
INR		1.07(1-1.30)	1.01(1-1.11)	1.10(1-1.48)	**0.043**
ALB/Bili ratio		(0.23(0.13–0.44)	0.29(0.14–0.95)	0.20(0.12–0.38)	0.143
NEU/Lymph ratio		(4.44(3.18–9.26)	3.78(2.96–6.07)	4.97(3.29–10.03)	0.101
PLT/Lymph ratio		96.7(130.9-328.6)	174.3(129.9-278.5)	210.7(130.8-340.1)	0.055
ALBI score		-1.64(-2.42- -1.19)	-1.92(-2.67- -1.66)	-1.41(-2.19- -1.12)	**0.012**
ALBI Grades	Grade 1 (%)	15 (18.8)	6 (27.3)	9 (15.5)	**0.01**
	Grade 2 (%)	34 (42.5)	13 (59.1)	21 (36.2)	
	Grade 3 (%)	31 (38.8)	3 (13.6)	28 (48.3)	

Chi square test (in qualitative variables) and Mann-Whitney U test (in quantitative variables) were used to analyze data

$P < 0.05$ was considered significant in all tests

Abbreviations: aspartate aminotransferase (AST), alanine aminotransferase (ALT), albumin-bilirubin ratio (ALBI), Alkaline phosphatase (ALP), cholangiocarcinoma (CCA), international normalized ratio (INR), lymphocyte (lymph), neutrophil (NEU), platelet (PLT), prothrombin time (PT), total bilirubin (BiliT), Direct bilirubin (Bili D), white blood cells count (WBC)

Table 2 Age, sex, and survival rates of eCCA patients based on ALBI grade

Variable		Total (*N* = 80)	ALBI Grades			*P*-Value
			Grade 1 (*N* = 15)	**Grade 2 (*N* = 34)**	**Grade 3 (*N* = 31)**	
Age (years)		67(58.25-74)	64(53–72)	68.50(58.25–76.25)	69(58–74)	0.411
Sex, N (%)	Female	26(32.5)	8(53.3)	11(32.4)	7(22.6)	0.113
	Male	54(67.5)	7(46.7)	23(67.6)	24(77.4)	
Survival 1-year, N (%)	No	49(61.3)	8(53.3)	18(52.9)	23(74.2)	0.168
	Yes	31(38.8)	7 (46.7)	16 (47.1)	8 (25.8)	
Survival 3-year, N (%)	No	69(86.3)	12(80)	28(82.4)	29(93.5)	0.313
	Yes	11(13.8)	3(20)	6(17.6)	2(6.5)	
Survival 5-year, N (%)	No	77(96.3)	14(93.3)	32(94.1)	31(100)	0.370
	Yes	3(3.8)	1(6.7)	2(5.9)	0(0)	

Chi square test (in qualitative variables) and Kruskal Wallis Test (in quantitative variables) were used to analyze data

$P < 0.05$ was considered significant in all tests

Abbreviations: albumin-bilirubin ratio (ALBI), extrahepatic cholangiocarcinoma (eCCA)

Table 3 Identifying the threshold levels for AST, WBC, and INR to distinguish the prognosis of eCCA patients in terms of 5-year survival rate

	ROC cure analysis		Cut-off	Diagnostic parameters (%)				
	Area (95% CI)	*P*-value		Sensitivity	Specificity	PPV	NPP	Accuracy
AST	0.69 (0.56–0.83)	**0.007**	82.5	60.3	68.2	83.3	39.5	63.5
WBC * 1000	0.70 (0.58–0.82)	**0.005**	7.70	69	68.2	83.3	45.5	68.8
INR	0.64 (0.51–0.77)	**0.048**	1.08	56.9	68.2	82.5	37.5	60

$P < 0.05$ was considered significant in all tests

Abbreviations: aspartate aminotransferase (AST), extrahepatic cholangiocarcinoma (eCCA), international normalized ratio (INR), white blood cells count (WBC)

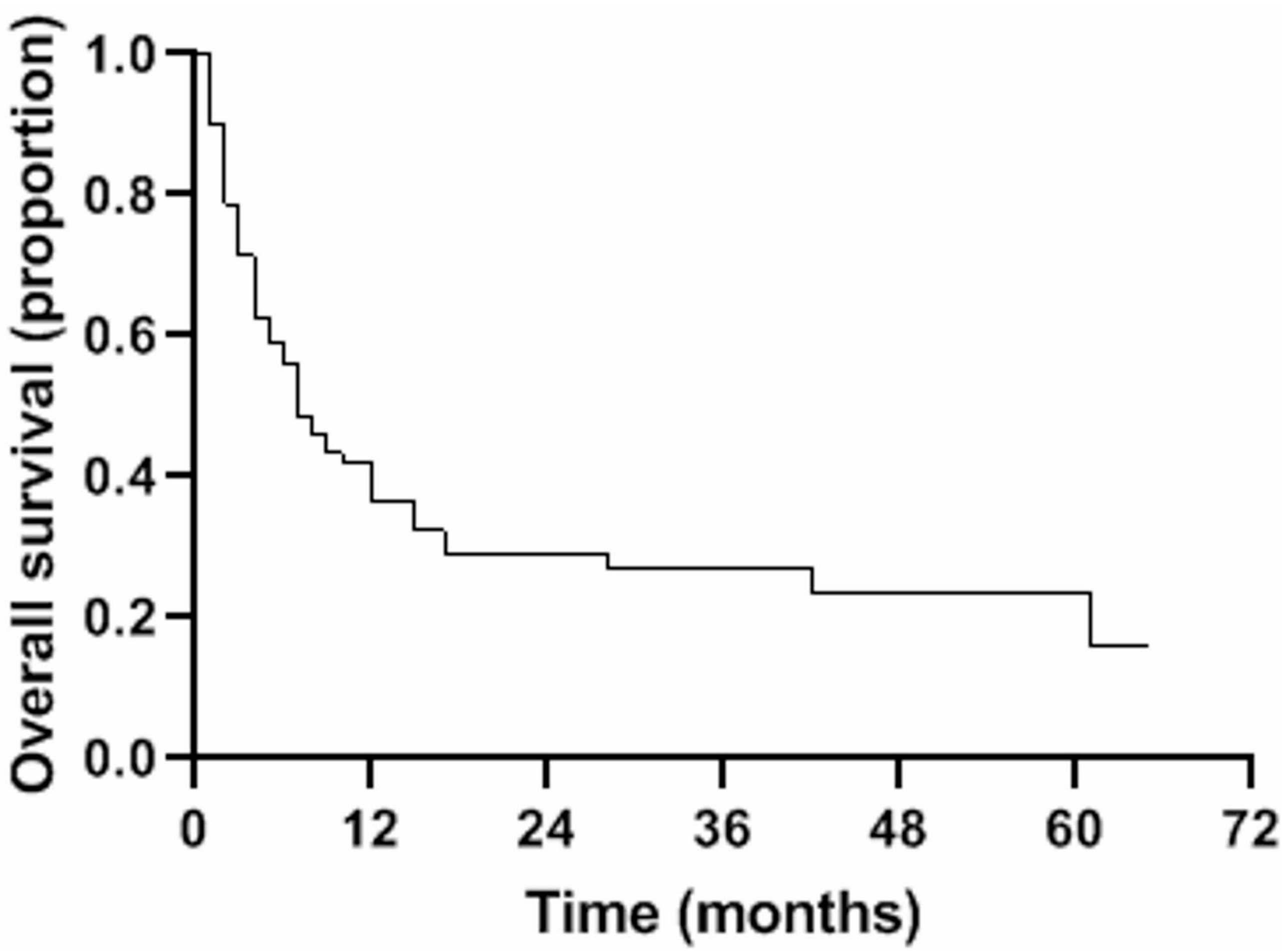

Fig. 1 Overall survival curve from Kaplan-Meier analysis. survival rates at 1 year, 3 years, and 5 years were 36.6%, 27.1%, and 15.8%, respectively

$P = 0.009$), individuals with WBC count higher than 7.70 (HR = 2.46, $P = 0.0004$), and patients with an INR level above 1.08 (HR = 1.78, $P = 0.02$) were found to be at an increased risk of mortality (Table 4). Figure 2 displays survival curves from Kaplan-Meier analysis using the specified cutoff points for serum AST level, WBC count, INR, and ALBI grades.

Discussion

A large amount of evidence has emphasized that liver function plays an important role in the prognosis of several types of solid tumors, including bile duct neoplasms [7, 8, 10]. At present, the CP grade, is the most widely utilized model in clinical assessment of liver function. However, because CP grade faces difficulties in accurately determining the extent of liver dysfunction in CCA [26–28], a new option called ALBI grade has been introduced [29]. Several studies have shown that a rise in ALBI score correlates with a higher risk of liver failure, and mortality in iCCA patients [16, 18–21], but its accurate prediction for eCCA patients is still a challenge, and there are few studies on the role of ALBI in predicting the overall survival of these patients [26].The purpose of this study was to explore the predictive significance of ALBI grade

Table 4 Analyzing the influence of risk factors on patient survival through log-rank test and Cox regression model

	Log-rank test			Cox regression analysis	
	Chi square	**df**	***P*-value**	**Hazard Ratio**	**95% CI**
Serum AST (< 82.5 vs. ≥ 82.5)	6.79	1	**0.009**	1.92	1.14–3.22
WBC (< 7.70 vs. ≥ 7.70)	12.46	1	**0.0004**	2.46	1.47–4.46
INR (< 1.08 vs. ≥ 1.08)	5.39	1	**0.02**	1.78	1.05–2.99
ALBI grade (grade 3 vs. 1, 2)	6.45	1	**0.01**	1.86	1.08–3.22

P < 0.05 was considered significant in all tests.

Abbreviations: aspartate aminotransferase (AST), albumin-bilirubin ratio (ALBI), cholangiocarcinoma (CCA), international normalized ratio (INR), white blood cells count (WBC)

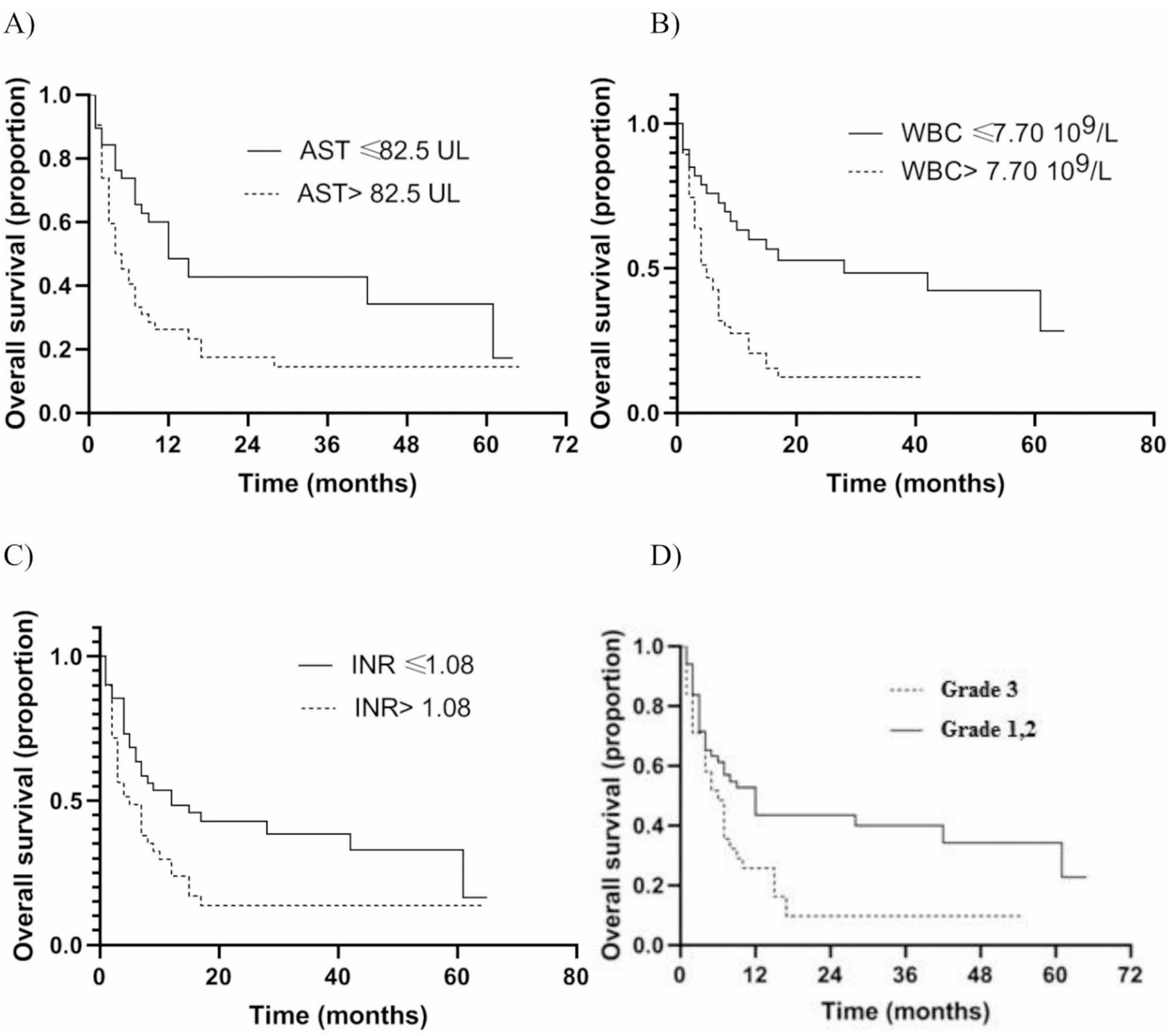

Fig. 2 Survival curves from Kaplan-Meier analysis using the specified cutoff points for serum AST level, WBC count, INR, and ALBI grades. (**A**) Kaplan-Meier survival curves based on specified serum AST level cutoff points; (**B**) Kaplan-Meier survival curves based on specified WBC count cutoff points; (**C**) Kaplan-Meier survival curves based on specified INR cutoff points; (**D**) Kaplan-Meier survival curves based on ALBI grades

and certain associated lab values in the mortality rate of eCCA patients.

In our study, the 1-year, 3-year, and 5-year survival rates of eCCA patients were 36.6%, 27.1%, and 15.8%, respectively (Fig. 1), and the mean overall survival was 13.9 months. This finding is similar to the average survival time of 12 months reported by Wang et al. in a group of advanced eCCA patients [26]. Also, in a study by Yu zhang, the 1-, 2-, and 3-year cancer-specific survival rates for patients with advanced eCCA were 41.3%, 25.8%, and 22%, respectively which is near to our results [30]. On the other hand, although research shows that eCCA typically has a better survival rate than iCCA [31], but the survival rate of eCCA patients in the present study was significantly lower, when compared to the reported overall survival of 41.5 or 39 months in iCCA patients [32, 33]. Tsilimigras et al. and Sasaki et al. estimated the 5-year survival to be 39.8% and 39% respectively in these patients [32, 33]. Tawarung et al. also reported that 1 year, 3 years, and 5 years survival rates were 57.8%, 32.5%, and 26.4%, respectively in a group of iCCA patients [34]. Differences in characteristics of patient population (such as sex, age, economic status, stage of cancer…), variations in treatment protocols, confounding factors that have not been adequately controlled, may explain these discrepancies.

The present study found a strong correlation between ALBI grading and disease prognosis ($P=0.01$). According to the results of Cox regression analysis, patients with grade 3 ALBI have a 1.867 times higher risk of death compared to grades 1 and 2 ($P=0.011$). A study by Wang et al. is the only other research that has explored the connection between ALBI grading and disease prognosis in eCCA. They found that ALBI grade, but not CP score, was an independent prognostic factor for survival in patients with eCCA (HR = 1.65, 95% CI: 1.04–2.61) [26]. Most previous research has examined this association in iCCA patients and have also found that as the ALBI grade increases, the overall survival of these patients decreases. Kaneko et al. reported that the prognosis of patients with iCCA can be stratified by ALBI grade (grade 1: 54.3 months; grade 2a: 8.4 months; grade 2b: 3.9 months; and grade 3: 1.4 months; $p<0.001$) [19]. A study by Ni et al., in a group of iCCA patients undergoing CT-PMWA, found that patients with grade 2 ALBI had 9.56 times higher risk of death compared to grades 1 ALBI [16]. According to Pang et al., a meta-analysis of 12 studies involving 21,348 patients revealed that mortality risk was significantly higher (OR = 2.35) in patients with a higher ALBI grade before surgery compared to those with a lower grade [20]. In a different study, an odds ratio of 8.23 indicated that a higher ALBI grade predicted poorer survival among iCCA patients [21]. The stronger association between the ALBI score and survival in iCCA compared to patients can be attributed to the different underlying pathophysiological mechanisms and disease characteristics of these two types of cholangiocarcinoma. In ICC, where liver function plays a crucial role due to the primary tumor site, the ALBI score, which reflects liver function, becomes a more significant prognostic factor [35].

While our study did not analyze CP grade, some researchers have suggested that using the ALBI grade may be more effective than CP in predicting patient survival [19, 26, 36].

In addition to the ALBI grade, our research confirmed that AST, WBC, and INR are also significant independent factors linked to the survival of eCCA patients. Serum AST ≥ 82.5 IU/l, WBC ≥ 7.70, and INR ≥ 1.08 were all associated with a significant higher rate of mortality in these patients underlining the need to address these factors through various interventions to enhance treatment efficacy and boost patient survival.

Previous studies have also shown that elevated AST levels are associated with poorer prognosis in patients. Zhao et al. reported that serum AST levels ≥ 85.0 IU/L were associated with poor survival in perihilar cholangiocarcinoma (a kind of eCCA) patients after radical resection [37]. It is important to note that elevated levels of AST may be caused by factors other than liver issues, such as damage to skeletal or cardiac muscle, or hematologic disorders. In fact a study by Han et al., on 430 patients with AST levels > 400 U/L unrelated to liver disease, reported peak AST < 3000 U/L (OR = 2.94, 95% CI = 1.36–6.35), and peak AST ≥ 3000 U/L (OR = 9.61, 95% CI = 3.54–26.08) were associated with increased 30-day mortality in patients [38].

Similar to the results of this study, a higher white blood cell count has been found to be linked to an increased risk of overall cancer-related deaths [39], but the balance between different types of white blood cells, as indicated by NEU/Lymph ratio (NLR), didn't serve as prognostic markers in eCCA patients in the present study. The results on the association between NLR and survival in eCCA patients are conflicting. Some report that NLR, served as prognostic markers in these patients [40–42] but some not [43–46]. However, in general, Liu and colleagues' meta-analysis indicated that when looking at studies specifically focusing on eCCA, there was no notable impact of NLR on overall survival, which aligns with our own discovery. Conversely, significant results were observed for iCCA [47].

In line with our findings, studies have shown that coagulation markers are useful in determining the overall survival of patients with biliary tract cancers, with INR being particularly effective [48]. Another research found that these markers can successfully predict the postoperative mortality of patients with cholangiocarcinoma (76% of whom had eCCA diagnosis) undergoing major hepatectomy with extrahepatic bile duct resection [49].

In a study on HCC patients with renal failure, the ALBI grade was identified as the most informative and predictive marker (Hazard ratio: 1.43 for grade 2 and 2.36 for grade 3) compared to the Model for End-Stage Liver Disease 3.0 (MELD 3) and the platelet- ALBI grade [50]. However, further studies are needed to compare ALBI with MELD in eCCA patients for survival prediction.

In addition, although the ALBI grade is advantageous for its simplicity and accessibility, emerging biomarkers such as ctDNA and miRNAs offer more precise information about tumor biology and may enhance survival predictions in cholangiocarcinoma patients. However, these advanced biomarkers typically demand sophisticated technology and may not be as widely applicable as the ALBI grade.

This research is the sole investigation that assesses the significant predictors of mortality in patients with eCCA in Iran, with a specific focus on ALBI grade. With a high mortality rate among the participants in our study, the use of ALBI grade may have the potential to reduce mortality rates and improve treatment outcomes. However, since the study is retrospective, there may be inherent biases in patient selection and data collection that could impact the validity of the results. Controlling for all potential confounding variables that could impact the connection between ALBI grade and mortality rates in eCCA patients is another challenge identified in this study. Due to the small sample size, the findings of the study may not be applicable to all eCCA patients, as the sample may not be representative of the larger population.

Conclusion

ALBI grade, serum AST ≥ 82.5 IU/l, and INR ≥ 1.08 are significant independent factors linked to the survival of eCCA patients.

Abbreviations

ALB	Albumin
ALBI	Albumin-bilirubin index
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AST	Aspartate Aminotransferase
AUC	Area under the curve
Bili D	Direct bilirubin
CCA	Cholangiocarcinoma
eCCA	Extrahepatic CCA
CP	Child-Pugh
EUS-FNA	Ultrasound-Guided Fine Needle Aspiration
HR	Hazard Ratio
iCCA	Intrahepatic CCA
INR	International normalized ratio
Lymph	Lymphocyte
MELD	Model for End-Stage Liver Disease
NEU	Neutrophil
PLT	Platelet
PT	Prothrombin time
TBIL	Total bilirubin
WBC	White Blood Cell

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Author contributions
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Data availability
The authors confirm that the data supporting the findings of this study can be made available upon reasonable request.

Declarations

Ethics approval and consent to participate
This study has been approved by the ethics committee of Iran University of Medical Sciences by the number: IR.IUMS.FMD.REC.1400.616, and was conducted according to the Helsinki Declaration. Participants enrolled in the study after providing informed consent (obtained from the participants or their immediate family members) with full awareness of the study's objectives.

Consent for publication
Not applicable.

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Participants enrolled in the study after providing informed consent (obtained from the participants or their immediate family members) with full awareness of the study's objectives.

Competing interests
The authors declare no competing interests.

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