



ORIGINAL ARTICLE

# Serum albumin predicts survival in patients with hilar cholangiocarcinoma

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## Abstract

**Background and aims:** Hilar cholangiocarcinoma is a devastating malignancy with incidence varying by geography and other risk factors. Rapid progression of disease and delays in diagnosis restrict the number of patients eligible for curative therapy. The objective of this study was to determine prognostic factors of overall survival in all patients presenting with hilar cholangiocarcinoma.

**Methods:** All adult patients with histologically confirmed hilar cholangiocarcinoma from 2003 to 2013 were evaluated for predictors of survival using demographic factors, laboratory data, symptoms and radiological characteristics at presentation.

**Results:** A total of 116 patients were identified to have pathological diagnosis of hilar cholangiocarcinoma and were included in the analysis. Patients with a serum albumin level  $>3.0$  g/dL ( $P < 0.01$ ), cancer antigen 19-9  $\leq 200$  U/mL ( $P = 0.03$ ), carcinoembryonic antigen  $\leq 10$  ig/L ( $P < 0.01$ ) or patients without a history of cirrhosis ( $P < 0.01$ ) or diabetes ( $P = 0.02$ ) were associated with a greater length of overall survival. A serum albumin level  $>3.0$  g/dL was identified as an independent predictor of overall survival (hazard ratio 0.31; 95% confidence interval 0.14–0.70) with a survival benefit of 44 weeks.

**Conclusion:** This study was the largest analysis to date of prognostic factors in patients with hilar cholangiocarcinoma. A serum albumin level  $>3.0$  g/dL conferred an independent survival advantage with a significantly greater length of survival.

**Key words:** hilar cholangiocarcinoma; prognostic factors; survival; albumin

## Introduction

Cholangiocarcinoma is the second most common primary hepatic malignancy worldwide, eclipsed only by hepatocellular carcinoma [1]. Hilar cholangiocarcinoma—or Klatskin's tumor—was first described in 1965 and accounts for 40–60% of all cholangiocarcinomas [2–5]. A rare entity in the United States, hilar cholangiocarcinoma is a devastating malignancy that carries a poor prognosis. Its incidence in Asia is as high as 71 per 100 000

men and 31 per 100 000 women. Patients are affected in the sixth or seventh decade of life, with presentation before the age of 40 being a rarity [6]. Incidence varies by geography and other risk factors, such as advanced age (greater than 65), male gender, cirrhosis, parasitic liver disease, inflammatory bowel disease, chronic pancreatitis, biliary disease (cysts and stones), and primary sclerosing cholangitis [1, 7, 8].

Submitted: 19 March 2016; Revised: 9 April 2016; Accepted: 4 May 2016

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Early symptoms for hilar cholangiocarcinoma are non-specific. Abdominal pain, pruritus, weight loss, fatigue, dark urine/clay-colored stool are common [9–11]. As this malignancy affects the bifurcation of the common hepatic biliary duct, unilateral hepatic duct obstruction may not present as overt jaundice until later in the course of the disease. The diagnosis of hilar cholangiocarcinoma remains challenging, as masses are small at clinical presentation and not frequently visualized on computed tomography (CT) scans or magnetic resonance imaging (MRI). Attempts at pathological diagnosis via endoscopic procedures often yields inconclusive results, even after multiple attempts (ranges from 44–80%) [12, 13]. Surgical resection and liver transplantation are curative options for hilar cholangiocarcinoma but require early intervention [14]; further, surgical resection is technically challenging, given the tumor's proximity to critical vascular structures and the need for adequate surgical margins [15]. Only a select few can be offered liver transplantation [16, 17]. Rapid progression of disease and delays in diagnosis further hamper efforts at curative therapy. Despite a paucity of data, chemotherapy may be indicated in patients with adequate functional status and unresectable disease; unfortunately, many patients are limited to palliative measures, including percutaneous transhepatic biliary drainage, biliary stents, or palliative bypass surgery. In recent years, tumor markers such as cancer antigen (CA) 19-9 and carcinoembryonic antigen (CEA) have shown promise for diagnosing and monitoring treatment of hilar cholangiocarcinoma. When combined with other diagnostic modalities, they have a sensitivity of 89% and specificity of 86% [18].

Understanding factors that determine prognosis is important for improving outcomes and allowing clinicians to stratify patients for treatment; unfortunately, data remain limited. The few studies completed have assessed prognostic factors in surgical patients only and no study to date has provided a comprehensive evaluation of prognostic variables in all patients presenting with hilar cholangiocarcinoma. This study assessed presenting laboratory values, demographics, and medical history (e.g. risk factors for cholangiocarcinoma) to determine prognostic indicators in all patients presenting with hilar cholangiocarcinoma.

## Methods

All adult patients with hilar cholangiocarcinoma, pathologically confirmed between September 2003 and September 2013 at the Cleveland Clinic Foundation, were retrospectively identified and included in the analysis. Diagnosis was confirmed histologically by bile duct brushings or biopsies. Patients included those referred to the Cleveland Clinic Foundation for further evaluation or those initially evaluated at our institution. The following data were collected for all patients: demographic data (gender, race and age), laboratory data (total bilirubin, alkaline phosphatase, serum albumin, CEA, CA19-9), symptoms prior to presentation, medical history [diabetes, cirrhosis, primary sclerosing cholangitis (PSC)], therapeutic interventions and overall survival. The presence of cirrhosis was determined by laboratory and radiographical evidence when biopsy evidence was not available. All laboratory data were collected at the time of initial presentation.

The treatment modality received by individual patients was determined by a multidisciplinary treatment team, with final therapy completed at the patient's discretion. Primary operative management was hepatic resection. Patients not eligible for surgical resection were considered for liver transplantation.

After liver transplantation, a standardized immunosuppression regimen was followed. The primary endpoint was overall survival, defined as the time from initial symptom onset until the date of death/survival. This study was approved by the Cleveland Clinic's Institutional Review Board.

## Statistical Analysis

Univariate and multivariate analysis of demographic data (age, gender, and race), risk factors for cholangiocarcinoma (cirrhosis, smoking/alcohol history, diabetes, and primary sclerosing cholangitis), presenting laboratory data (total bilirubin, alkaline phosphatase, serum albumin, CEA and CA19-9) were evaluated. Patients with incomplete data were excluded (those with less than 20% of variables defined) or if current status (alive/dead) could not be verified. Categorical data were compared with Fisher's exact tests and quantitative variables were represented as mean with standard error. Overall survival was described using Kaplan-Meier estimates, with overall survival determined by survival curves. Multivariate analysis was performed using the Cox proportional hazards model. Overall survival was defined as time from start of symptoms to time of death with patients alive at the end of the study censored and was represented as median with 95% confidence interval (CI). Subgroup analysis of patients who underwent surgical resection was completed. A P-value <0.05 was considered significant. Data were analysed using JMP version 9.0 (SAS Institute Inc., Cary, NC, USA).

## Results

One hundred and twenty-four patients with pathologically diagnosed hilar cholangiocarcinoma were identified. Eight patients were excluded for incomplete data. Complete demographic and clinical data are shown in Table 1. Sixty-six percent were male

**Table 1.** Demographics of hilar cholangiocarcinoma patients

Parameter	Number of patients (n = 116)
Gender, n (%)	
Male	76 (65.5)
Female	40 (34.5)
Age at diagnosis, years	67.3 ± 1.2
Body mass index, kg/m <sup>2</sup>	27.1 ± 0.7
Race, n (%)	
Caucasian	92 (79.3)
African American	9 (7.8)
Asian	5 (4.3)
Unknown/not reported	10 (8.6)
Symptom, n (%)	
Jaundice	76 (65.5)
Weight loss	53 (45.7)
Fatigue	32 (27.6)
Abdominal pain	47 (40.5)
Nausea	18 (15.5)
Decreased appetite	27 (23.3)
Pruritus	32 (27.6)
Pale stool	28 (24.1)
Dark urine	39 (33.6)
Social history, n (%)	
Smokers	53 (48.2)
Alcohol use	42 (37.8)

Data presented as n (%) and mean ± standard deviation

and 85% were caucasian. The average age of presentation was  $67.3 \pm 1.2$  years. The predominant presenting symptom was jaundice in 65.5% patients. Weight loss was the second most common symptom at presentation (45.7%; mean  $23.8 \pm 2.1$  pounds lost at presentation). On average, patients presented with  $3.2 \pm 0.2$  symptoms. A history of tobacco use was present in 48.2% patients and 37.8% had a history of alcohol use. Diabetes was present in 27.2% patients. Median overall survival was  $37.8 \pm 4.1$  weeks.

On univariate analysis of variables at patient presentation, predictors of overall survival included albumin  $>3.0$  g/dL, CA19-9  $\leq 200$  U/mL, CEA  $\leq 10$   $\mu$ g/L and patients without a history of cirrhosis or diabetes (Table 2). On multivariate analysis serum albumin  $>3.0$  g/dL was identified as the only independent

**Table 2.** Univariate analysis of parameters on patient presentation

Parameter	Survival time, days, median (95% CI)	P-value
Age, years		0.40
$\leq 65$	271 (221–409)	
$> 65$	255 (191–334)	
Gender		0.56
Male	254.5 (204–344)	
Female	274.5 (194–337)	
Race		0.62
Caucasian	257.5 (210–333)	
African American	380 (55–670)	
Asian	409 (68–487)	
Unknown/not reported	170 (123–217)	
Albumin, g/dL		$<0.01$
$>3.0$	467 (122–194)	
$\leq 3.0$	155 (257–572)	
Cancer antigen 19-9, U/mL		0.03
$\leq 200$	444.5 (210–532)	
$>200$	203 (142–238)	
Carcinoembryonic antigen, $\mu$ g/L		$<0.01$
$\leq 10$	305.5 (221–469)	
$> 10$	188 (84–210)	
Alkaline phosphatase, U/L		0.08
$\leq 400$	210 (122–278)	
$>400$	271 (191–409)	
Total bilirubin, $\mu$ mol/L		0.77
$\leq 10$	271*	
$>10$	241.5*	
Cirrhosis		$<0.01$
Yes	110 (8–155)	
No	271 (221–337)	
Diabetes		0.02
Yes	225 (122–326)	
No	271 (221–366)	
Primary sclerosis cholangitis		0.78
Yes	188 <sup>a</sup>	
No	271 (212–336)	
Smoking		0.97
Yes	258 (204–352)	
No	265 (191–334)	
Alcohol use		0.80
Yes	255 (200–380)	
No	265 (207–336)	
Weight loss, pounds		0.53
$>20$	365 (203–409)	
$\leq 20$	352 (204–469)	

<sup>a</sup>Patient still alive at time of analysis, thus upper limit of 95% CI not determined.

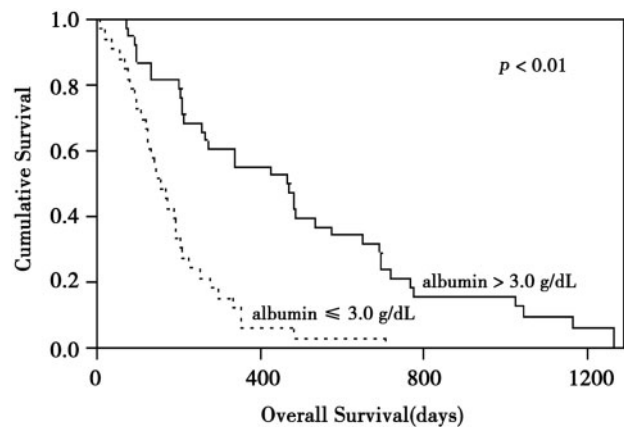
predictor of overall survival ( $P < 0.01$ ; hazard ratio (HR) 0.31; 95% CI 0.14–0.70).

For patients with a serum albumin  $>3.0$  g/dL, the median survival period was 467 days (95% CI 257–572), which is significantly longer than 155 days (95% CI 122–194) in patients with an albumin  $\leq 3.0$  g/dL ( $P < 0.01$ ; Figure 1). In the latter group, concomitant cirrhosis was present in 18.2% of patients. For patients with a CEA  $> 10$   $\mu$ g/L, the median survival was 188 days (95% CI 84–210), compared with 305.5 days (95% CI 221–469) in patients with CEA  $\leq 10$   $\mu$ g/L ( $P < 0.01$ ). Patients with CA19-9  $\leq 200$  U/mL had a median survival period of 444.5 days (95% CI 210–532), compared with 203 days (95% CI 142–238) for those with a value greater than 200 U/mL ( $P = 0.03$ ). In patients with a history or cirrhosis, overall survival was significantly shorter [110 days (95% CI 8–155) vs. 271 days (95% CI 221–337);  $P < 0.01$ ]. Lastly, patients with diabetes experienced a shorter overall survival [225 days (95% CI 122–326)] than those without diabetes [271 (95% CI 221–366) days;  $P = 0.02$ ; Figure 2].

Patients were treated with surgical resection (16.4%;  $n = 19$ ), liver transplantation (0.9%;  $n = 1$ ), brachytherapy (3.4%;  $n = 4$ ), radiation (7.8%;  $n = 9$ ), chemotherapy (22.4%;  $n = 26$ ), biliary stenting (82.8%;  $n = 96$ ) and percutaneous transhepatic biliary catheters (69.8%;  $n = 81$ ). Patients with surgical resection or liver transplantation had an overall survival greater than those who were not surgical candidates [708 days (95% CI 366–1023) vs. 225.5 days (95% CI 200–271);  $P < 0.01$ ]. Elevated tumor markers have been used to aid in the diagnosis of hilar cholangiocarcinoma; the average CEA and CA 19-9 concentrations at presentation were  $12.0 \pm 2.7$   $\mu$ g/L and  $3236.4 \pm 1189.7$  U/mL, respectively (Table 3). The most frequent metastatic locations at presentation were the lymph nodes (23.3%;  $n = 27$ ).

## Discussion

Hilar cholangiocarcinoma is a devastating malignancy with a poor overall prognosis. There is a need for prognostic markers in patients who present with this condition. Previous studies on prognostic factors have been limited in their scope. The majority have assessed prognostic factors only in patients who underwent surgical resection; in these studies, pre-operative albumin, tumor grade/size, extent of resection, lymph node/vascular involvement, and elevated CEA/CA19-9 tumor markers have been established as important prognostic factors [19–26]. The only study to assess variables in all patients diagnosed with hilar cholangiocarcinoma was also limited in the extent of data



**Figure 1.** Kaplan-Meier analysis of overall survival in patients with hilar cholangiocarcinoma and an albumin  $>3.0$  g/dL vs.  $\leq 3.0$  g/dL.

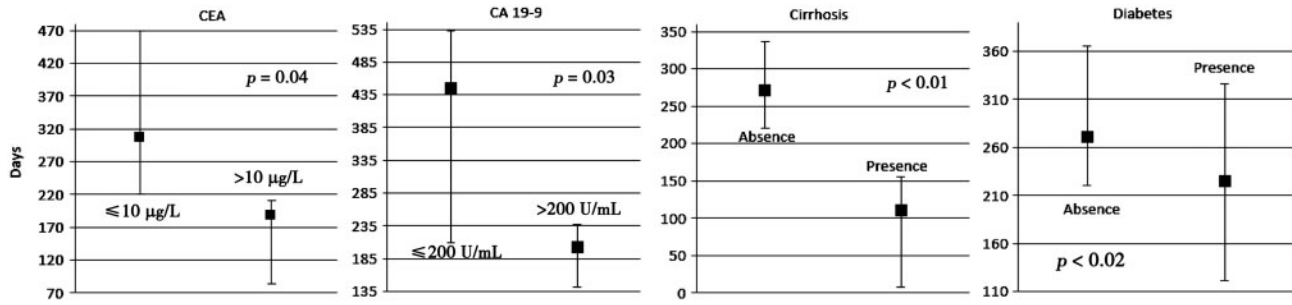


Figure 2. Overall survival [median days (95% CI)] in patients with hilar cholangiocarcinoma and (1) CEA level:  $\leq 10 \mu\text{g/L}$  vs.  $> 10 \mu\text{g/L}$ ; (2) CA19-9:  $\leq 200 \text{ U/mL}$  vs.  $> 200 \text{ U/mL}$ ; (3) Cirrhosis: absence vs. presence; (4) Diabetes: absence vs. presence.

Table 3. Laboratory characteristics at presentation

Laboratory marker	Value
Albumin, g/dL	3.2 ± 0.07
Total bilirubin, $\mu\text{mol/L}$	15.6 ± 0.9
Cancer antigen 19-9, U/mL	3236.4 ± 1189.7
Carcinoembryonic antigen, $\mu\text{g/L}$	12.0 ± 2.7
Alkaline phosphatase, U/L	458.5 ± 33.7

Data presented as mean ± standard deviation

collected and analyzed. Laboratory values assessed on univariate analysis included bilirubin, alkaline phosphatase, GGT and leukocyte count, while multivariate analysis was not completed [27]. The present study included data from all patients diagnosed with hilar cholangiocarcinoma over a 10-year period, including assessment of demographic data, medical history/risk factors, and presenting laboratory data. It demonstrated that albumin level  $> 3.0 \text{ g/dL}$  is an independent predictor of overall survival. Factors such as CA19-9  $\leq 200 \text{ U/mL}$ , CEA  $\leq 10 \mu\text{g/L}$  and a medical history without cirrhosis or diabetes may also be associated with increased overall survival, although these are not independent predictors of survival.

In early epidemiological studies, lower serum albumin concentrations were associated with an increased risk of cancer-related mortality; further, in gastrointestinal malignancies such as colorectal, gastric and hepatocellular carcinoma, low albumin has been found to be a poor prognostic indicator of survival [28–30]. In our study, a serum albumin  $> 3.0 \text{ g/dL}$  conferred an independent survival advantage with a significantly greater median length of survival (45 weeks longer; HR 0.31). Sub-group analysis assessed the impact of cirrhosis on lower albumin levels. Patients with underlying cirrhosis represented 6% of all patients in our data set and were associated with lower overall survival on univariate analysis; but the absence of cirrhosis was not found to be an independent predictor of survival; thus the relationship between low albumin and prognosis in hilar cholangiocarcinoma cannot be explained by cirrhosis alone. Cancer cachexia may provide an alternate explanation. Hypoalbuminemia is present in the setting of a systemic inflammatory response and is associated with weight loss [31, 32]. Weight loss prior to presentation occurred in 46% of our patients, with an average 24 pounds (10.89 kg) lost prior to evaluation. The interplay of hypoalbuminemia, cachexia and the inflammatory response may contribute to progressive loss of vital protein in patients with hilar cholangiocarcinoma; further, the long half-life of serum albumin may provide a longitudinal assessment of the patients' wellbeing. As stated previously, studies have demonstrated that pre-operative albumin concentration is an independent predictor of survival

after surgical resection—a finding that is now extended to the overall survival of all patients presenting with hilar cholangiocarcinoma, regardless of therapeutic management. Serum albumin is inexpensive and reproducible, and nearly all patients with biliary pathology or suspected hilar cholangiocarcinoma will have a hepatic panel measured.

Tumor markers have been evaluated as prognostic factors in patients undergoing surgical resection for cholangiocarcinoma—specifically CEA and CA 19-9 [22, 33]. In our analysis, a CEA  $> 10 \mu\text{g/L}$  and a CA19-9  $> 200 \text{ U/mL}$  were associated with diminished median overall survival by 17 weeks and 35 weeks, respectively. Although not independent predictors of survival, the data suggests that patients with higher CA19-9 and CEA serum concentrations may have diminished survival.

The prevalence of PSC in cholangiocarcinoma ranges from 5–36% [34, 35]. Six patients (5.2%) were identified with PSC and hilar cholangiocarcinoma in this study. Previous data demonstrates that survival is significantly decreased in patients with PSC and cholangiocarcinoma. Given our limited sample set, one should be cautious when interpreting survival in patients with PSC and hilar cholangiocarcinoma from our data set.

There are limitations to our study. Although the sample set was fairly large (given the prevalence of disease), the retrospective nature of the study limited data collection and analysis; further, during the decade-long study period, changes in therapeutic options may have occurred. Despite these limitations, this study has provided a comprehensive assessment of prognostic factors for overall survival in patients with hilar cholangiocarcinoma.

In summary, this study was the largest retrospective analysis of prognostic factors in all patients diagnosed with hilar cholangiocarcinoma at a single institution. Overall, hilar cholangiocarcinoma is associated with a poor prognosis and the data demonstrated that an albumin level  $> 3.0 \text{ g/dL}$  at presentation is an independent predictor of overall survival.

### Author contributions

Abhijeet Waghray: study concept and design; acquisition of data; analysis and interpretation of data; drafting of the manuscript; critical revision of the manuscript  
 Anastasia Sobotka: acquisition of data; drafting of the manuscript  
 Carlos Romero Marrero: critical revision of the manuscript  
 Bassam Estfan - critical revision of the manuscript  
 Federico Aucejo: critical revision of the manuscript  
 KV Narayanan Menon: study concept and design; analysis and interpretation of data; critical revision of the manuscript; study supervision



Conflict of interest statement: none declared.

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