CA 19-9 as a Marker of Survival and a Predictor of Metastization in Cholangiocarcinoma

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Abstract

Background: Cholangiocarcinoma is the second most frequent primitive liver malignancy and is responsible for 3% of the malignant gastrointestinal neoplasms. The aims of this study were to determine the association of serum levels of CA 19-9 at diagnosis with other clinical data and serum liver function tests and to identify possible factors that influence the survival rates during follow-up. *Methods:* Retrospective observational study of 89 patients with a diagnosis of cholangiocarcinoma followed at the Department of Gastroenterology during 5 years. Statistical analyses were performed using SPSS version 20.0. *Results:* Patients were followed up for a median time of 127 days (IQR: 48–564), and the median age at diagnosis was 71.0 years (IQR: 62.0–77.5). The median survival rate was 14.0 months (IQR: 4.3–23.7), and the mortality rate was 79%. Patients with CA 19-9 levels ≥103 U/L had lower albumin levels and higher levels of alanine aminotransfer-ase and γ-glutamyltransferase. CA 19-9 levels ≥103 U/L were associated with a higher probability of metastization (*p* = 0.001) and lower rates of treatment with curative intent (*p* = 0.024). In a multivariate analysis, CA 19-9 levels <103 U/L and surgery were independent predictors of survival. *Conclusion:* Predictive factors for overall survival were identified, namely presence of metastasis, surgery, and chemotherapy. CA 19-9 levels ≥103 U/L were predictive factors for survival and metastization.

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CA 19-9 Marcador de Sobrevida e Preditor de Metastização no Colangiocarcinoma

Palavras Chave
Antigénio CA 19-9 · Biomarcadores tumorais · Colangiocarcinoma · Prognóstico

Resumo

Introdução: O colangiocarcinoma é o segundo tumor maligno do fígado primitivo mais frequente sendo responsável por 3% das neoplasias malignas gastrointesti-

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nais. Os objetivos do presente estudo foram determinar a associação entre os níveis séricos de CA 19-9 ao diagnóstico com dados clínicos, testes de função hepática e identificar possíveis fatores preditivos de sobrevida. ***Métodos:*** Estudo retrospetivo de 89 pacientes com diagnóstico de colangiocarcinoma com seguimento em centro único durante 5 anos. A análise estatística foi realizada utilizando o programa SPSS versão 20.0. ***Resultados:*** A média de idades ao diagnóstico dos doentes incluídos foi de 71.0 anos (IQR: 62.0–77.5) com seguimento durante 127 dias (IQR: 48–564). A taxa de sobrevida mediana foi de 14.0 meses (IQR: 4.3–23.7) e a taxa de mortalidade de 79%. Os doentes com níveis séros de CA 19-9 ≥103 U/L apresentavam níveis inferiores de albumina e níveis superiores de alanina aminotransferase e gama-glutamil transferase. Valores de CA 19-9 ≥103 U/L associaram-se a maior probabilidade de metastização ($p = 0.001$) e as taxas inferiores de tratamento com intenção curativa ($p = 0.024$). Em análise multivariada, valores de séros de CA 19-9 <103 U/L e realização de cirurgia foram preditores independentes de sobrevida. ***Conclusão:*** A presença de metastização, a realização de cirurgia ou quimioterapia constituíram-se como fatores preditivos de sobrevida global. Valores séricos de CA 19-9 ≥103 U/L foram preditores de menor sobrevivência e de metastização.

Introduction

Cholangiocarcinoma (CCC) is the second most frequent primitive liver malignancy after hepatocellular carcinoma [1], and it is responsible for 3% of the malignant gastrointestinal neoplasms nowadays [2]. The peak of its incidence occurs in the seventh decade of life [3]. Recent epidemiological data describe an increased incidence of CCC independently of the increased incidence of cirrhosis [1].

CCCs arise from the epithelial cells of the intrahepatic and extrahepatic bile ducts and are classified according to their localization into intrahepatic, perihilar, or distal (extrahepatic). Perihilar tumors, also called Klatskin tumors, occur at the bifurcation of the right and left hepatic ducts and are the most common type. The intrahepatic CCCs (IH-CCCs) can originate in small intrahepatic ductules or large intrahepatic ducts proximal to the bifurcation of the right and left hepatic ducts. They are the least common CCCs, even though, for unknown reasons, the incidence of IH-CCC has increased in the last 2 decades [4–9].

The TNM staging system for CCC from the American Joint Committee on Cancer is mainly based on the extent of ductal involvement of the tumor [10]. There are, nowadays, separate staging systems for cancers of the perihilar and distal bile ducts, which differ in their definitions of the T stage and of the group stages. However, all of them are characterized in 3 stages: T (primary tumor), N (regional lymph nodes), and M (distant metastases).

More than 90% of CCCs are histologically compatible with adenocarcinomas, the remainder being squamous cell tumors. The etiology remains undetermined in most of them [11], despite the identification of several risk factors [11–15], like primary sclerosing cholangitis (PSC), chronic parasitic infection, and fibropolycystic liver disease (e.g., Caroli syndrome, congenital hepatic fibrosis, and choledochal cysts). In these diseases, the underlying process is related to long-standing inflammation that induces hyperplasia, cellular proliferation, and ultimately malignant transformation. There is also a clear and strong association between chronic intrahepatic stone disease (hepatolithiasis) and CCC. There is still no consensus concerning cholelithiasis as a risk factor; in fact, the association between gallstones and gallbladder cancer is well established; however, the association between CCC and cholelithiasis is of low magnitude compared to gallbladder cancer [14, 15].

Most patients with CCC have unresectable disease at diagnosis with an overall survival (OS) rate of 6 months to 1 year [16]. In fact, despite progress in anticancer therapy, more aggressive surgical resection, advances in liver transplantation, and interventional supportive care, the median survival rate remains low [17]. At diagnosis, only 10% of the patients present early-stage disease and can be considered for curative resection [18].

The diagnosis of CCC is based on laboratory studies, such as elevated levels of alkaline phosphatase (ALP) and of total bilirubin (TB), and imaging techniques, such as abdominal computed tomography, magnetic resonance imaging, echo-endoscopy, and/or liver biopsy. The tumor markers carbohydrate antigen 19-9 (CA 19-9) and carcinoembryonic antigen are the most studied tumor markers in CCC and are elevated in 85 and 40% of the cases, respectively [19]. The efficacy of these tumor markers in screening tests has been widely analyzed, mainly in PSC [20–22]; nevertheless, their usefulness as a diagnostic tool has not been established yet [20]. According to Hultcrantz et al. [21], serum levels of carcinoembryonic antigen and CA 19-9 have limited specificity; however, in a paper by Levy et al. [22], a sensitivity and specificity of 78 and 98%, respectively, were reported if an absolute CA

19-9 level of 129 U/mL was considered in patients with PSC and a diagnosis of CCC.

There are few studies evaluating the role of serum levels of CA 19-9 as a predictor of treatment response and OS. Harder et al. [23] determined a cutoff of 300 U/mL as a predictor of survival in patients with advanced biliary tract cancer, including gallbladder and intra- and extrahepatic cancers. However, the role of CA 19-9 serum levels in terms of prognosis and survival rate in patients with CCC is still not known. Predictive survival factors for CCC and its relationship to CA 19-9 serum levels also remain under debate.

The aims of this study were (1) to determine the association of serum levels of CA 19-9 at diagnosis with clinical and serum liver function tests, such as markers of hepatocellular damage (aspartate aminotransferase [AST] and alanine aminotransferase [ALT]), cholestasis (TB and ALP), and synthetic function with albumin levels, and (2) to identify possible factors that influence survival rates during follow-up.

Materials and Methods

A retrospective observational study was carried out based on the medical records of 91 patients with a new diagnosis of CCC followed at the Departments of Gastroenterology and Surgery of a university hospital during a period of 5 years. It is important to emphasize that all decisions were taken in a multidisciplinary context with the participation of gastroenterologists, surgeons, radiologists, and oncologists. The inclusion criteria were a definite diagnosis of CCC (histologic and/or radiologic confirmation), regular follow-up (at least 2 medical visits), and age >18 years.

Demographic information was collected, including the dates of birth and death, the date of symptom onset, and the date of CCC diagnosis. Analytical data at diagnosis, including ALP, TB, γ-glutamyltransferase (G-GT), ALT, AST, and albumin levels, were collected, as well as CA 19-9 and carcinoembryonic antigen serum values at diagnosis. A cutoff, based on the median value of the sample, was established for CA 19-9 levels, and its relationship with other clinical and analytical variables was determined. Predictive survival factors for patients with CCC were determined using Kaplan-Meier survival curves according to clinical and therapeutic options.

Statistical Analysis

Categorical data were reported as absolute frequencies (n) and relative frequencies (%). Continuous data were presented as medians and percentiles. To test for a nonnormal distribution of continuous variables for 2 independent groups, nonparametric tests were used: the Mann-Whitney test for 2 independent groups and the ANOVA test for more than 2 independent groups. The χ^2 test (Fisher exact test) was used to compare quantitative variables between groups.

The median value of CA 19-9, determined at the time of diagnosis of all the patients enrolled in the study, was considered by the authors as a *new* cutoff. The χ^2 test and the Mann-Whitney test

were used to evaluate the association between the tumor marker and analytical and clinical factors.

OS was defined as the estimated time from diagnosis until death or until the last follow-up. Median survival rates with interquartile ranges (IQR) were reported. The Kaplan-Meier survival curves were used with an α value of 0.05, and survival curves were compared with the log-rank test.

All the described p values were 2 sided, and p values of <0.05 were considered statistically significant. Statistical analyses were performed using SPSS version 20.0.

Results

Baseline Patients' Characteristics

The baseline characteristics of the 89 patients enrolled in the cohort (55% men) with a new diagnosis of CCC are presented in Table 1. Patients were followed up for a median time of 127 days (IQR: 48–564), and the median age at diagnosis was 71.0 years (IQR: 62.0–77.5).

The number of CCC diagnoses progressively increased over the years, since the beginning of the cohort study, with an annual incidence of 14 CCCs in the period from 2008 to 2009, 31 CCCs in the period from 2010 to 2011, and 44 CCCs in the period from 2012 to 2013. The mortality rate at 6 months was 40.5%, with a median survival rate of 14.0 months (IQR: 4.3–23.7). Most patients (53%) had perihilar CCC, 24% had extrahepatic CCC, and 24% had IH-CCC, with the age at diagnosis being lower in IH-CCC (median: 68.0 years [IQR: 51.0–72.5] vs. 74.0 years [IQR: 61.0–77.0], $p = 0.014$) than in patients with extrahepatic and hilar tumors.

The majority of the patients (30.3%) presented with jaundice and pruritus, and 20.2% presented with jaundice only. Weight loss and abdominal pain were reported by 9.0 and 13.5% of the patients, respectively. The diagnosis was made by imaging studies in 73% of cases, abdominal computed tomography being most frequently used (45%). Liver biopsy guided by ultrasound was performed in 15 (16.5%) patients, and IH-CCC was statistically significantly associated with a greater need for histology to make a diagnosis ($p < 0.001$). Serum levels of G-GT, ALP, and TB were lower in IH-CCC than in patients with extrahepatic and perihilar tumors ($p < 0.001$) (Table 1).

Thirty-two patients (36.0%) had distant metastasis (M1 according to the TNM classification), with liver metastasis being most common (12%). Twenty-six patients (29.2%) were submitted to surgery, and 28 patients (31%) underwent resection surgery plus adjuvant therapy. Hepatectomy was the most common surgical procedure (20%). Thirty-five patients (39.3%) underwent only palliative

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treatment with endoscopic transpapillary ($n = 23$) and/or percutaneous transhepatic biliary drainage ($n = 21$).

CA 19-9 Serum Levels

The median baseline CA 19-9 level was 103.0 U/mL (IQR: 15.0–576.0), with no differences found between genders and types of CCC. Markers of hepatocellular damage (AST and ALT), cholestasis (TB and ALP), and synthetic function with albumin levels at the time of diagnosis were analyzed in relation to CA 19-9 levels, considering the *new* cutoff established by the authors. Patients with serum levels of CA 19-9 ≥103 U/L had higher levels of ALP (460.0 U/L [IQR: 284.0–849.0] vs. 314.5 U/L [IQR: 101.9–503.3], $p = 0.009$) and G-GT (616.0 U/L [IQR: 120.2–1,044.0] vs. 236.0 U/L [IQR: 49.8–812.0], $p = 0.021$). Albumin serum levels were lower in patients with CA 19-9 levels ≥103 U/L (33.8 g/L [IQR: 29.7–35.7] vs. 36.5 g/L [IQR: 32.4–40.7], $p = 0.002$) (Table 2).

CA 19-9 levels ≥103 U/mL were associated with a lower OS of 7.5 months (IQR 0.0–16.3) versus 29.3 months (IQR: 18.1–40.4) ($p = 0.015$). CA 19-9 levels <103 U/mL were associated with treatment with curative intent (surgery vs. palliative chemotherapy, $p = 0.024$). The probability of metastization at diagnosis was higher in patients with CA 19-9 levels ≥103 U/mL (odds ratio [OR]: 8.751 [95% confidence interval (CI): 2.270–32.264], $p = 0.001$).

Predictive Factors of Survival

The mortality rate during the follow-up period was 79% (37% at 3 months, 42% at 6 months, and 51% at 12 months), with a median survival of 14.0 months (IQR: 4.3–23.7). OS was not different between the 3 types of CCC. Higher survival rates at 3, 6, and 12 months were associated with prescription of chemotherapy ($p = 0.002$, $p = 0.001$, and $p = 0.003$, respectively), surgery ($p < 0.001$), and absence of metastization at diagnosis ($p < 0.001$, $p = 0.006$, and $p = 0.002$) (Table 3). Survival rates at 6 and 12 months were associated with higher levels of albumin ($p = 0.012$ and $p = 0.032$, respectively) and younger age ($p = 0.045$ and $p = 0.038$, respectively).

Survival rate at 3 months was associated with TNM-N0 ($p = 0.022$). Survival at 12 months was associated with lower levels of CA 19-9 ($p = 0.040$), lower levels of ALP ($p = 0.020$), and a shorter period between the beginning of symptoms and diagnosis ($p = 0.029$) (Table 3). Surgery and the presence of metastasis were independently associated with survival at 3, 6, and 12 months in the logistic regression.

In a univariate analysis, OS was associated with CA 19-9 serum levels <103 U/L (29.3 months [95% CI: 18.1–40.4] vs. 7.5 months [95% CI: 0.0–16.3], $p = 0.015$), chemotherapy (21.0 months [95% CI: 12.3–29.6] vs. 2.9 months [95% CI: 1.1–4.9], $p = 0.005$), surgery (8.9 months [95% CI: 14.9–49.9] vs. 2.1 months [95% CI: 1.5–2.8], $p < 0.001$), and absence of metastases at diagnosis (2.5 months [95% CI: 1.6–3.3] vs. 32.2 months [95% CI: 27.6–37.0], $p < 0.001$) (Fig. 1). In a multivariate analysis, CA 19-9 serum levels <103 U/L and surgery were independent predictors of survival (Table 4).

Discussion

CCC is the second most common primary liver malignancy, and its incidence, for unknown reasons, is increasing globally [1]. This increase is probably related to the

Table 1. Characteristics of the population with CCC ($n = 89$) enrolled in the study

Gender	
Male	49 (55.1)
Female	40 (44.9)
Median age at diagnosis (IQR), years	71.0 (62.0–77.5)
CCC risk factors	
Cirrhosis	8 (9)
Obesity	8 (9)
Type 2 diabetes	23 (25.8)
PSC	1 (1.1)
Choledocholithiasis	12 (13.5)
Alcohol >40 g/day	13 (14.6)
CCC localization	
Perihilar	47 (52.8)
Extrahepatic	21 (23.6)
Intrahepatic	21 (23.6)
Diagnostic method	
Hepatic biopsy	24 (27.9)
Imaging	65 (72.1)
CT	40 (52.1)
MRI	17 (19.1)
CPRE	5 (5.6)
EE	3 (3.4)
Treatment	
Palliative	35 (39.3)
Surgical	26 (29.2)
Surgical + adjuvant therapeutic	28 (31.4)
Median follow-up (IQR), days	127 (48–564)
Median survival (IQR), months	14 (4.3–23.7)

Values are numbers with percentages in parentheses unless otherwise indicated. CCC, cholangiocarcinoma; CT, computed tomography; CPRE, endoscopic retrograde cholangiopancreatography; EE, echo-endoscopy; IQR, interquartile range; MRI, magnetic resonance imaging; PSC, primary sclerosing cholangitis.

Table 2. Univariate and multivariate analysis of serum liver function tests at the time of diagnosis comparing patients according to CA 19-9 serum levels (CA 19-9 ≥103 vs. <103 U/L)

	All patients (n = 89)	Patients with CA 19-9 <103 U/L	Patients with CA 19-9 ≥103 U/L	p value univariate analysis	multivariate analysis[b]
G-GT, U/L	482.0 (184.0–841.0)	236.0 (49.8–812.0)	616.0 (120.2–1,044.0)	*0.021*[a]	*0.705*
ALP, U/L	392.5 (243.3–672.8)	314.5 (101.9–503.3)	460.0 (284.0–849.0)	*0.009*[a]	*0.685*
TB, mg/dL	9.9 (2.7–17.3)	6.40 (82.5–14.3)	7.53 (1.00–18.47)	0.950[a]	excluded
AST, U/L	82.0 (48.0–165.8)	96.00 (56.0–147.0)	58.00 (36.0–134.0)	0.122[a]	excluded
ALT, U/L	94.0 (50.0–179.0)	92.0 (32.6–196.0)	69.50 (25.7–105.5)	0.122[a]	excluded
Albumin, g/L	34.0 (30.0–38.5)	36.50 (32.4–40.7)	33.8 (29.7–35.7)	*0.002*[c]	*0.744*
CEA, U/L	3.9 (1.9–10.8)	4.6 (2.3–8.6)	2.8 (1.7–9.6)	0.368	excluded

Values are medians with interquartile ranges in parentheses. Results in italics indicate statistically significant values. ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALP, alkaline phosphatase; CEA, carcinoembryonic antigen; G-GT, γ-glutamyltransferase; TB, total bilirubin. [a] Nonparametric tests for independent samples. [b] Independent variables: ALP, G-GT, and serum albumin levels. [c] χ^2 test was performed considering an albumin cutoff of 38 g/L.

Table 3. Overall survival rate at 3, 6, and 12 months according to clinicopathological characteristics and treatment options

	3 months yes	no	p value*	6 months yes	no	p value*	12 months yes	no	p value*
Age, years	69.0 (61.5–77.0)	73.5 (50.0–80.5)	0.127	69.0 (58.5–76.3)	74.0 (65.0–72.0)	*0.045*	66.0 (55.5–75.0)	75.0 (65.0–72.0)	*0.038*
ALP, U/L	294 (101.5–565.3)	393.0 (155.0–393.0)	0.347	394.0 (22.0–581.0)	597.0 (275.0–854.0)	0.187	304.0 (169.0–557)	590.0 (130.0–339.0)	*0.020*
Albumin, g/L	36.1±5.95	29.6±810.2	0.093	34.9±5.78	31.6±9.2	*0.012*	35.1±5.80	31.2±8.04	*0.032*
TMN-N0			*0.022*			0.234			0.271
Yes	13 (72.2)	4 (100.0)		12 (80.0)	5 (100.0)		13 (86.7)	4 (80.0)	
No	5 (27.8)	0		3 (20.0)	0		2 (13.3)	1 (20.0)	
TMN-M0			*<0.001*			*0.006*			*0.002*
Yes	24 (38.7)	4 (16.7)		18 (38.3)	5 (15.1)		18 (29.0)	5 (13.2)	
No	38 (61.3)	20 (83.3)		29 (61.7)	28 (84.8)		44 (71.0)	33 (86.8)	
CA 19-9 levels, U/L	28.5 (1.92–1.35)	71.0 (2.0–71.0)	0.880	32.0 (1.93–173.5)	247.0 (19.25–90,106.0)	0.467	28.1 (19.0–197.0)	103.0 (36.5–60,212.0)	*0.040*
Chemotherapy			*0.002*			*0.001*			*0.003*
Yes	41 (66.1)	23 (95.8)		28 (59.6)	32 (97.0)		26 (61.9)	34 (89.5)	
No	21 (33.9)	1 (4.2)		19 (40.4)	1 (3.0)		16 (38.1)	4 (10.5)	
Surgery			*<0.001*			*<0.001*			*<0.001*
Yes	29 (61.7)	11 (33.3)		37 (59.8)	8 (33.3)		28 (66.6)	12 (42.9)	
No	18 (28.3)	22 (66.7)		25 (40.2)	16 (66.6)		14 (33.3)	16 (57.1)	

Values are medians with interquartile ranges in parentheses, means ± standard deviations, or numbers with percentages in parentheses. Results in italics indicate statistically significant values. ALP, alanine aminotransferase. * Overall comparison between groups.

increase in the incidence of IH-CCC in Europe, North America, Asia, and Australia, since the incidence of extrahepatic CCC is declining internationally [4, 8, 24]. CA 19-9 was described as an important tool for the diagnosis of CCC in populations at risk, the most studied being patients with PSC.

In our cohort, the diagnosis of new cases of CCC increased during the 5 years of follow-up in a similar manner as in the most recent studies related to CCC incidence. However, these results should be considered with caution, as they might be overestimated since the hospital where the study was performed is a tertiary reference center. We also cannot exclude that more diagnoses are being made due to new and better available diagnostic methods for obstructive jaundice, which can identify biliary malignancies that might have gone undiagnosed previously. Another important factor could be the screening for hepatocellular carcinoma performed nowadays in patients with liver cirrhosis, which may have led to an increase in the diagnosis of CCC.

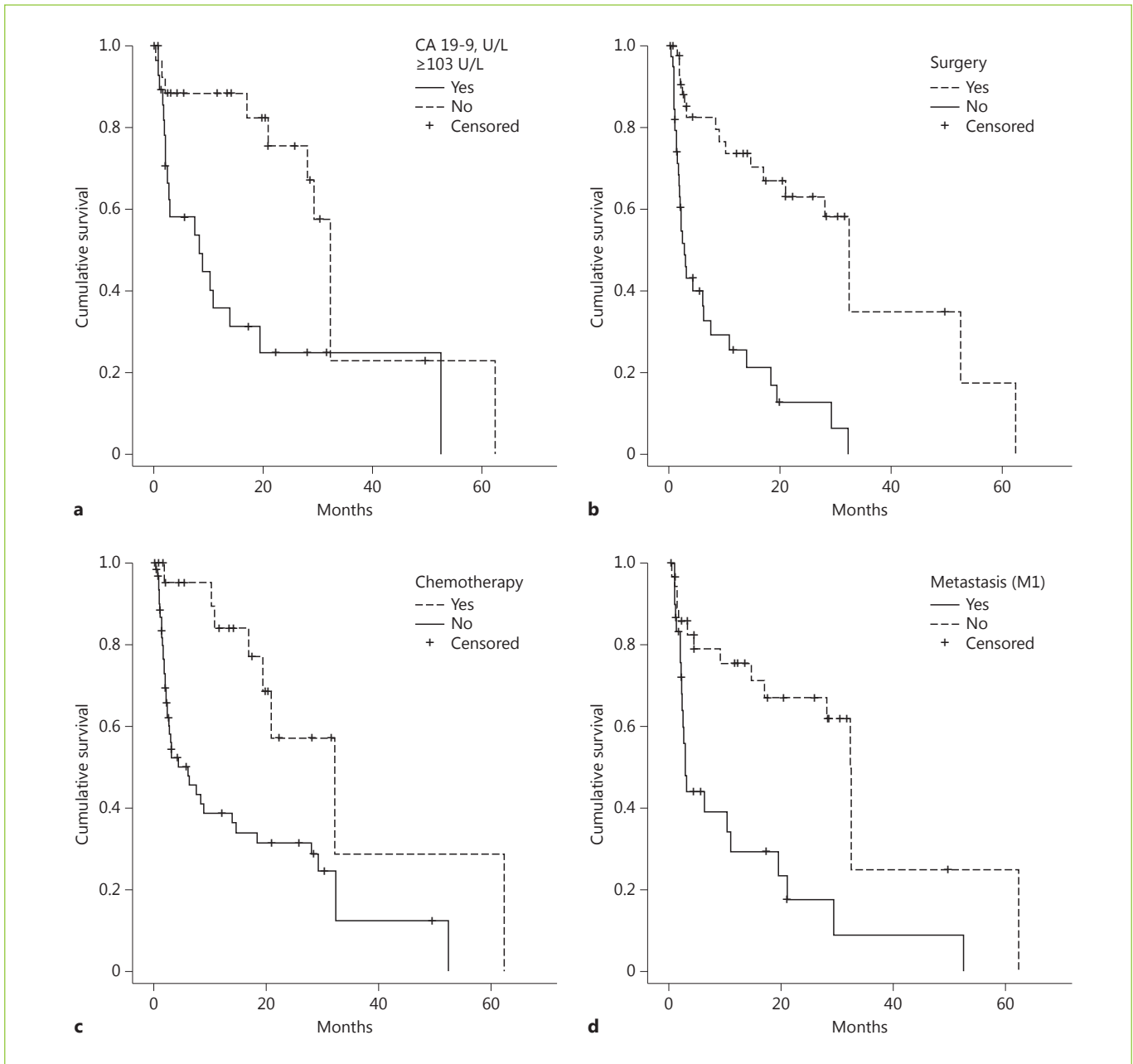Concerning risk factors for CCC, almost 25% of the patients did not have any identified risk factor, as previ-

Fig. 1. a Overall survival curves according to the carbohydrate antigen (CA) 19-9 serum level (CA 19-9 <103 vs. ≥103 U/L) based on the follow-up time (*p* log-rank = 0.003). **b** Overall survival curves according to surgery based on the follow-up time (*p* log-rank <0.001). **c** Overall survival curves according to chemotherapy based on the follow-up time (*p* log-rank = 0.002). **d** Overall survival curves according to the presence of metastases based on the follow-up time (*p* log-rank <0.001).

ously described in the literature, where a specific risk factor cannot be identified in many patients [21]. It is also interesting to note that only 1 patient had PSC and that choledocholithiasis and liver cirrhosis were only present in 13.5 and 9% of the patients, respectively. Twenty-six percent of the patients had diabetes, which has been described in previous case-control and cohort studies as a risk factor for biliary tract cancer [25]. However, it is not

Table 4. Clinicopathological characteristics and treatment options associated with survival in patients with cholangiocarcinoma

	Median survival (95% CI), months	Univariate analysis			Multivariate analysis[a]		
		OR	95% CI	*p* value*	OR	95% CI	*p* value*
Gender							
Male (55%)	4.0 (1.0–27.0)	ref.					
Female (45%)	5.0 (2.0–14.0)	0.843	0.476; 1.495	0.559			
Age							
<60 years (15%)	3.0 (1.0–20.0)	1.492	0.719; 3.100	0.283			
≥60 years (65%)	13.0 (3.0–28.0)	ref.					
Localization							
Hilar (54%)	6.0 (1.5–22.5)						
Intrahepatic (23%)	4.5 (1.5–22.0)	ref.					
Extrahepatic (23%)	2.0 (1.0–17.0)	0.888	0.679; 1.162	0.386			
Albumin							
≥38 g/L (31%)	19.7 (6.0–33.7)	0.549	0.286; 1.044	0.068			
<38 g/L (69%)	4.3 (0.0–9.6)	ref.					
CA 19-9 serum level							
<103 U/L (49%)	29.3 (18.1–40.4)	2.353	1.423; 6.881	*0.015*	2.577	1.697; 9.525	*0.024*
≥103 U/L (51%)	7.5 (0.0–16.3)	ref.			ref.		
Distant metastasis (M stage)							
M0 (44%)	2.5 (1.6–3.3)	3.182	1.717; 5.899	*<0.001*	1.228	0.439; 3.435	0.224
M1 (56%)	32.2 (27.6–37.0)	ref.			ref.		
Chemotherapy							
Yes (27%)	21.0 (12.3–29.6)	4.301		*0.005*	2.008	0.713; 5.653	0.187
No (73%)	2.9 (1.1–4.9)	ref.	1.550; 11.935		ref.		
Surgery							
Yes (54%)	8.9 (14.9–49.9)	4.927	2.737; 8.871	*<0.001*	3.310		
No (46%)	2.1 (1.5–2.8)	ref.			ref.	1.086; 10.085	*0.001*

Results in italics indicate statistically significant values. CI, confidence interval; OR, odds ratio; ref., reference. [a] Independent variables: CA 19-9 serum level, distant metastasis (M stage), chemotherapy, and surgery. * Overall comparison between groups.

clear whether diabetes itself or other associated conditions (obesity or hyperlipidemia) represents a true risk factor for CCC.

The OS rate of 14.0 months (IQR: 4.3–23.7) was higher than previously described (between 6 months and 1 year), despite the fact that 36% of the patients had metastatic disease at the time of diagnosis, 29.2% of the patients were submitted to surgery, and 31% underwent resection surgery plus adjuvant therapy.

Using the median value of CA 19-9 serum levels at diagnosis (103 U/L), a *new* cutoff was established. CA 19-9 levels may reflect disease severity, since higher levels (≥103 U/L) are associated with increased levels of G-GT and ALP and lower levels of albumin. They may also be a prognostic marker, since levels ≥103 U/L were associated with metastasis and lower survival at 3, 6, and 12 months, and thus are an independent prognostic marker of survival. Lower values of this tumor marker were also associ-ated with treatment with curative intent. The OR for survival was significantly higher in patients with CA 19-9 levels <103 U/L (OR: 2.353, *p* = 0.015) and in patients submitted to chemotherapy (OR: 4.301, *p* = 0.005), and it was even higher in patients submitted to surgery (OR: 4.927, *p* < 0.001) in the Cox regression analysis. In the multivariate analysis, the only 2 independent predictive factors of survival were surgery (OR: 3.310 [95% CI: 1.086–10.085], *p* = 0.001) and lower levels of CA 19-9 (OR: 2.577 [95% CI: 1.697–9.525], *p* = 0.024).

To the authors' knowledge, no other studies have shown this association as clearly as the current study, and thus, these results should be taken into account when a diagnosis of CCC is made. The *new* cutoff established seems to be an important tool in detecting patients with a poor prognosis (lower survival rates and higher rates of metastasis), and, perhaps, it could be included in a future multifactorial analysis of survival. Predictive factors for

OS were identified, namely presence of metastasis, surgery, and chemotherapy. In conclusion, this study provides important insights into the relevant role of CA 19-9 levels in the prognosis of CCC, as well as into other prognostic factors.

The retrospective nature and the small number of patients enrolled in the study may be limitations. Also, the authors analyzed all 3 different types of CCC together; however, as it is known from the literature, the biology, clinical behavior, and treatment approach are not the same for the 3 types of CCC. Yet, in our cohort, CA 19-9 serum levels and OS were not different between the 3 groups analyzed.

Nonetheless, one of the strengths of this study that can be pointed out is that all clinical decisions were taken in a multidisciplinary context with the participation of gastroenterologists, surgeons, radiologists, and oncologists, turning clinical decisions more homogeneous. Our results report data from a tertiary and single center and need to be supported by new population-based cohort studies.

Statement of Ethics

All rules of the local ethics committee were followed, preserving patient identity and confidentiality.

Disclosure Statement

The authors declare that there are no conflicts of interest associated with this publication and there has been no financial support for this work.

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