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Influence of cirrhosis on outcomes of patients with advanced intrahepatic cholangiocarcinoma
receiving chemotherapy

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List of abbreviations:

iCC: intrahepatic cholangiocarcinoma

OS: overall survival

pCC: perihilar cholangiocarcinoma

dCC: distal cholangiocarcinoma

HCC: hepatocellular carcinoma

CA19.9: carbohydrate antigen 19.9

CEA: carcinoembryonic antigen

RECIST: Response Evaluation Criteria In Solid Tumors

PFS: progression-free survival

NASH: non-alcoholic steato-hepatitis

HBV: Hepatitis B Virus

HCV: Hepatitis C Virus

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Abstract

Background: Cirrhosis is a risk factor for intrahepatic cholangiocarcinoma (iCC). However, its exact prevalence is uncertain and its impact on the management of advanced disease is not established.

Methods: Retrospective analysis of patients treated with systemic chemotherapy for advanced iCC in the 1st-line setting at 2 tertiary cancer referral centres.

Cirrhosis was diagnosed based on at least one element prior to any treatment: pathological diagnosis, baseline platelets < 150 x10⁹/L, portal hypertension and/or dysmorphic liver on imaging.

Results: In the cohort of patients (n=287), 82 (28.6%) had cirrhosis (45 based on pathological diagnosis). Patients with cirrhosis experienced more grade 3/4 haematologic toxicity (44% vs 22%, respectively, p=0.001), and more grade 3/4 non-haematologic toxicity (34% vs 14%, respectively, p=0.001) than those without. The overall survival (OS) was significantly shorter in patients with cirrhosis: median 9.1 vs 13.1 months for those without (HR = 1.56 [95%CI: 1.19-2.05]); p = 0.002), confirmed on multivariable analysis (HR = 1.48 [95% CI: 1.04-2.60]; p=0.028).

Conclusion: Cirrhosis was relatively common in patients with advanced iCC and was associated with increased chemotherapy-induced toxicity and shorter OS. Formal assessment and consideration of cirrhosis in the therapeutic management is recommended.

Keywords: Biliary tract cancer; liver fibrosis; systemic treatment; primary liver cancer

Introduction

Cholangiocarcinoma is a type of biliary tract cancer which is subdivided into intrahepatic, perihilar and distal cholangiocarcinoma (iCC, pCC and dCC), depending on its anatomical location. Both incidence and mortality of iCC has been increasing world-wide in recent decades, especially iCC, for reasons that are not fully understood. The prevalence of cirrhosis has also increased (1). Intrahepatic cholangiocarcinoma is the second most common primary liver cancer after hepatocellular carcinoma (HCC), accounting for 10-15% of all primary hepatic malignant tumors. Its prognosis is dismal, as most patients are diagnosed at an advanced stage (>65%)(2), due to a lack of early symptoms.

Hepatocellular carcinoma and iCC have risk factors in common, including inflammation and subsequent injury to the bile ducts (3). Furthermore, there might be common progenitor cells to iCC and HCC, particularly in patients with chronic liver disease (4) (5). Cirrhosis has been reported as a risk-factor for cholangiocarcinoma, but its frequency is still underreported in advanced cases, and conflicting results were reported (6). In a recent epidemiological study, cirrhosis status was missing in 91% of iCCA cases; nevertheless, available data showed that up to 35.8% of the patients with iCCA had cirrhosis(7). The European Network for the Study of Cholangiocarcinoma (ENSCCA) registry suggested that 12.6% of patients with iCCA had cirrhosis (8).

In some surgical series, cirrhosis has been shown to be an independent risk factor for the development of iCCA, and that 8–10% of all iCCs occur in patients with cirrhosis (9). These results remain controversial, as surgical series might have bias towards exclusion of patients with cirrhosis from resection (10) (11). Moreover, while the presence of cirrhosis has been studied as a prognostic factor in surgical series, it has very rarely been studied in advanced cases (12) (13). Cirrhosis is not only a common risk factor, but also a condition that can limit

the treatment options and have a negative impact on prognosis. It also raises the question of whether patients with cirrhosis need to be treated and followed-up differently than other patients. There are difficulties in identifying the presence of cirrhosis in patients with iCC, as cirrhosis may often be well-compensated and not clinically apparent, and in addition the healthy liver is not always biopsied at the time of cancer diagnosis.

This study thus aimed to explore the prevalence and impact of cirrhosis on outcomes of patients treated with systemic chemotherapy for advanced iCC, in a series of patients treated at two tertiary centres.

Patients and methods

Collection of data.

The population of interest were patients with advanced iCC (locally-advanced or metastatic) that were starting first-line systemic treatment. The following variables were collected: patient demographics (gender, age), presence of cirrhosis, performance status, characterisation of the cirrhosis (how the diagnosis was made), liver function blood tests, previous treatment, extent of disease (locally-advanced vs metastatic, sites involved, size of the larger lesion, macrovascular invasion, liver involvement >50%), laboratory results (lymphocytes, neutrophils, platelets, albumin, bilirubin (with calculation of the ALBI score), carbohydrate antigen (CA)19.9, carcinoembryonic antigen (CEA) and alkaline phosphatase), characteristics of the treatment and outcomes (toxicity, response according to Response

Evaluation Criteria In Solid Tumors (RECIST) 1.1, progression and date of progression, status: death/alive and date of death or last follow-up).

The diagnosis of cirrhosis was made retrospectively, based on several parameters including pathological diagnosis (F3 or F4 according to Metavir Classification), platelets less than 150×10^9 G/L, radiological evidence of portal hypertension and/or liver dysmorphism.

This study was approved by the Ethics committee of CHU Pontchaillou, Rennes, France (reference #20.162).

Influence of cirrhosis on outcomes of patients with advanced iCC

The outcome following treatment was compared for 2 groups of patients (iCC with or without underlying cirrhosis, with a sensitivity analysis of patients with pathologically-proven cirrhosis). The primary endpoint was overall survival. The secondary endpoints were progression-free survival (PFS), response rate, assessed by RECIST 1.1, safety, with adverse events evaluated according to NCI-CTCAE v5.0 (National Cancer Institute - Common Terminology Criteria for Adverse Events), cause of discontinuation of first-line treatment, receipt of second-line treatment.

A univariate Cox-model regression analysis was performed, followed by multivariable analysis. The multivariable analysis included variables with a p-value of 0.2 or less in univariable analysis, and with a proportion of less than 20% of missing data. Variables kept in the model were those with a p-value less than 0.1 in the multivariable analysis. Two cohorts of patients, one from Rennes with 185 patients and one from Manchester with 102 patients, were merged into one cohort (n=287), to increase the power of the analysis.

Results

a. Description of the population

The description of the population is reported in Figure 1. Of 287 patients with advanced iCC, 82 patients had underlying cirrhosis (28.6%) and 205 had no cirrhosis (71.4%). Among the 69 patients with cirrhosis with data available to calculate scores, 94.2% (65 patients) had a Child Pugh score A, and all the patients with cirrhosis had an ALBI score 1 or 2 (score based on serum albumin and bilirubin developed to predict survival for patients with HCC (14)). Cirrhosis disease aetiology was reported for the patients with cirrhosis and is reported in Table 3. None of the patients had cirrhosis due to biliary disease.

The characteristics of the population are reported in Table 1. Patients with cirrhosis were more frequently male, were older, had a previous biliary stent less frequently, had lower levels of neutrophils and platelets, lower levels of alkaline phosphatase, and higher ALBI scores (despite similar albumin and bilirubin when taken separately).

b. Treatment received

As first-line chemotherapy, 237 patients (82.6%) patients received gemcitabine + platinum-based chemotherapy; 62 of 82 patients with cirrhosis (75.6%) and 175 of 205 without cirrhosis (85.4%). Twenty-eight (9.8%) patients received gemcitabine monotherapy; 10 with cirrhosis (12.2%) and 18 without (8.8%). Twenty-two (7.6%) patients received other types of chemotherapy, 10 with cirrhosis (12.2%) and 12 without (5.8%). Other regimens used were 5-FU-based (FOLFIRI: 5-FU and irinotecan, FOLFIRINOX: 5-FU, irinotecan and oxaliplatin).

There was no difference in treatment received between patients with cirrhosis and without ($p=0.11$).

Causes of discontinuation of first line chemotherapy were significantly different between the 2 groups ($p<0.001$) and are represented in Figure 2.

Patients with cirrhosis experienced more grade 3/4 haematological toxicity than those without (44.2% vs 22%, respectively, $p=0.001$), as well as more grade 3/4 non-haematological toxicity (33.8% vs 14.1%, respectively, $p=0.001$).

Among 82 patients with cirrhosis, after first line of chemotherapy, 3 patients (4.1%) had a complete response, 21 (28.4%) had partial response, 21 (28.4%) had stable disease and 29 (39.2%) progressive disease. Among 205 patients without cirrhosis, 3 patients (1.6%) had complete response on imaging, 54 (29%) had partial response, 80 (43%) had stable disease and 49 (26.3%) had progressive disease as best response. There was no significant difference in best response between patients with cirrhosis or without ($p=0.066$).

Median duration of first line chemotherapy was 4.14 months [95%CI: 4.15-5.56] for patients without cirrhosis and 3.07 [95%CI: 2.95-4.10] for those with cirrhosis ($p=0.038$). Moreover, administration of second-line treatment was less frequent in patients with cirrhosis (22% vs 41.5%; $p=0.002$).

There was no difference between patients with or without cirrhosis for the indication of selective internal radiation therapy (SIRT); it concerned 27.6% of patients without cirrhosis and 31.7% of patients with cirrhosis ($p=0.49$). Surgery after treatment was infrequent for patients with or without cirrhosis (3.7% vs 9.9% respectively, $p=0.86$).

c. Liver-related events

There was data for the occurrence of liver failure for only one centre: among the 55 patients with cirrhosis in this centre, 22 (40%) demonstrated signs of cirrhotic decompensation during chemotherapy, 20 (36.4%) had ascites during therapy, 7 (12.7%) showed biological signs of deterioration of liver function and 6 (11%) presented with signs of hepatic encephalopathy.

There was no significant difference in the occurrence of death with stable disease for patients with or without cirrhosis (16.7% vs 8.3%, $p=0.071$). There was a low number of biliary infections causing death in both two groups (5.6% vs 5.8%, $p=1.00$).

d. Survival

The median follow-up was 58 months, with 228 (79.4%) having documented progression and 246 (85.7%) patients having documented death.

The median progression free survival (PFS) was 6.5 months [95%CI: 4.4-8.6] for patients with cirrhosis and 7.4 months for those without cirrhosis [95%CI:6.3-8.4] [HR = 1.19 [95% CI: 0.92-1.55], $p=0.18$] (Figure 3). Results were similar in both centres.

The overall survival (OS) was significantly shorter in patients with cirrhosis; median: 9.1 months [95%CI: 6.5 – 11.7] vs 13.1 months [95%CI: 10.9 – 15.3] for those without cirrhosis (HR = 1.56 [95%CI: 1.18-2.05]); $p=0.001$) (Figure 4). The difference in OS was confirmed on multivariable analysis (HR = 1.48 [95% CI: 1.04-2.10]; $p=0.028$) (Table 2). Results were similar in both centres.

The ALBI grade tended to be prognostic in both groups, albeit the power seems insufficient to reach statistical significance in the cirrhosis group ($p < 0.001$ in patients without cirrhosis and $p = 0.12$ in patients with cirrhosis). The prognostic role of cirrhosis in different ALBI groups was also analysed; interestingly, cirrhosis was prognostic in ALBI grade 1 patients ($p = 0.046$), but not in ALBI grade 2 patients ($p = 0.29$) (Figure 5a and 5b).

The median OS was similar between histologically-proven and clinically-diagnosed cirrhosis (7.6 months vs 9.3 months, log-rank $p = 0.20$) (Figure 6).

Discussion

This study showed that cirrhosis is present in a sizeable proportion of patients with advanced iCC (up to a quarter of the population), and notably impacts the management of these patients, with more toxicity reported secondary to chemotherapy, and worse survival. Data showing that cirrhosis is a risk factor for iCC has been published previously, but predominantly in surgical series, which constitutes a bias due to selection of patients with compensated cirrhosis without portal hypertension, where surgery is possible. Moreover, to our knowledge, only one previous study has shown the negative impact of cirrhosis on survival in advanced cases of iCC (15). However, this previous study ($n = 26$) performed in China only evaluated data in hepatitis B-related liver cirrhosis, with a median OS in the group with cirrhosis of six months (range 2–24 months) compared to 16 months (range 6–41 months) in the group without cirrhosis ($p = 0.036$).

In the present study, patients with cirrhosis were more frequently male than those patients without cirrhosis and were older, reflecting the epidemiology of cirrhosis. They experienced less jaundice at presentation than those without cirrhosis. These elements might be

explained by the high mortality rate of advanced iCC in patients with cirrhosis if they have jaundice at presentation, precluding systemic therapy. There was no difference in extent or differentiation of the disease between patients with and without cirrhosis.

Data from one of the centres on liver-related events showed a high proportion of liver decompensation. These might be due either to progression of the cancer, or to toxicity of the treatment, or natural evolution of cirrhosis. This high level of decompensation, together with the increased toxicity, might explain shorter treatment duration, as well as negative on OS, despite no difference in PFS. There was also a trend for higher death without progression of cancer. Patients with cirrhosis had more severe toxicity in general, and specifically more grade 3/4 haematologic toxicity than those without cirrhosis (38% vs 20%, respectively, $p=0,014$), as well as more grade 3/4 non-haematologic toxicity (28% vs 15%, respectively, $p=0.048$). To be noted, portal hypertension can be considered as a confounding factor for haematologic toxicity, but can also lead to difficulties in delivering chemotherapy, leading to dose delays. Perhaps due to increased toxicity and liver dysfunction at the time of progression, second-line treatment was less frequent in patients with cirrhosis (21.8% vs 50.0%; $p=0.001$).

However, gemcitabine full dose, which is known to cause potential hepatotoxicity, does not result in additional toxicity in patients diagnosed with advanced biliary tract cancer with bilirubin > 1.5 x upper limit of normal (2). This suggests that the increased toxicity to treatment of patients with cirrhosis is not related to a difference in metabolism of chemotherapy molecules, but to significant frailty of patients with cirrhosis. The adaptation of the treatment dose can therefore be discussed but cannot be guided by bilirubin levels, in addition, the first line of reference treatment with gemcitabine and cisplatin (15) can be

used even in cases of jaundice, preferably if it is related to a bile duct obstruction than metastatic hepatic invasion.

Our data suggest that it is pertinent to assess for cirrhosis by considering the value of biopsy of non-tumoural liver, when a biopsy of the tumour is proposed in patients with suspected primary liver cancer. Moreover, a tumour biopsy in patients with cirrhosis is needed to differentiate between iCCA and HCC, even when the CT appearances seems typical. Indeed, there is a 10% rate of mismatch between imaging and pathology (16).

The discrepancy between non-significant results in terms of response rates and PFS and clear results in terms of OS probably reflects that cirrhosis does not interfere directly with the efficacy of chemotherapy, but rather impacts both safety and maintenance of quality of life during treatment. Hence, patients with cirrhosis should be more carefully followed up during treatment than those patients without cirrhosis. Interpretation of low platelet count during chemotherapy might also be different depending on whether the patient is known to have underlying cirrhosis or not. Expectations for enabling the start of chemotherapy might for example be lowered if the patient has known cirrhosis with baseline thrombocytopenia. Moreover, the interpretation of appearance of ascites might differ if the patients is known to have underlying cirrhosis (portal hypertension), or not (suspicion of peritoneal involvement). The ALBI score is validated in patients with HCC, whether or not they have cirrhosis. The ALBI score seems to play an important prognostic role with or without cirrhosis. Cirrhosis was associated with worse prognosis in patients with ALBI grade 1 but not in patients with ALBI grade 2. It is only possible to hypothesise on the reason for this observation: patients with ALBI grade 2 and no cirrhosis might have other aggressive tumour features that explain the perturbation of the ALBI grade; also, there might be underdiagnosed cirrhotic patients in this

group, which could explain perturbation of the ALBI grade, and prospective studies may clarify this further.

This series has some limitations. First, this is a retrospective analysis, with all the inherent biases. Secondly, only patients receiving chemotherapy were evaluated; there is a probable selection bias since many patients with advanced biliary tract cancers may only receive palliative care alone (17), and the proportion of cirrhosis might therefore be underestimated in this analysis. Thirdly, the diagnosis of cirrhosis was retrospectively adjudicated from review of the patient records, and could have led to some misclassifications. However, the potential misclassifications could only bias the results towards less difference between patients with or without cirrhosis. Finally, the results come from two tertiary expert European centres, and might not be generalisable to a different population.

Conclusions

Cirrhosis is not a rare occurrence in patients treated for advanced iCC, and has a negative impact on their management and outcomes. Clinicians should be aware of the possibility of cirrhosis to inform their treatment management, and the presence of cirrhosis should be recorded as part of routine care assessment and reported as a potential prognostic variable in future clinical research.

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Legends :

FIGURES

Figure 1. Description of the population

Figure 2. Causes of discontinuation of chemotherapy

Figure 3. Kaplan Meier PFS by cirrhosis

Figure 4. Kaplan Meier OS by cirrhosis

Figure 5a. Kaplan Meier OS by ALBI grade for patients without cirrhosis

Figure 5b. Kaplan Meier OS by ALBI grade for patients with cirrhosis

Figure 6. Kaplan Meier OS by pathologically proof of cirrhosis

TABLES

Table 1: Liver disease aetiology

Table 2: Baseline characteristics in patients with or without cirrhosis.

Table 3: Univariate and multivariate Cox regression model of Overall Survival

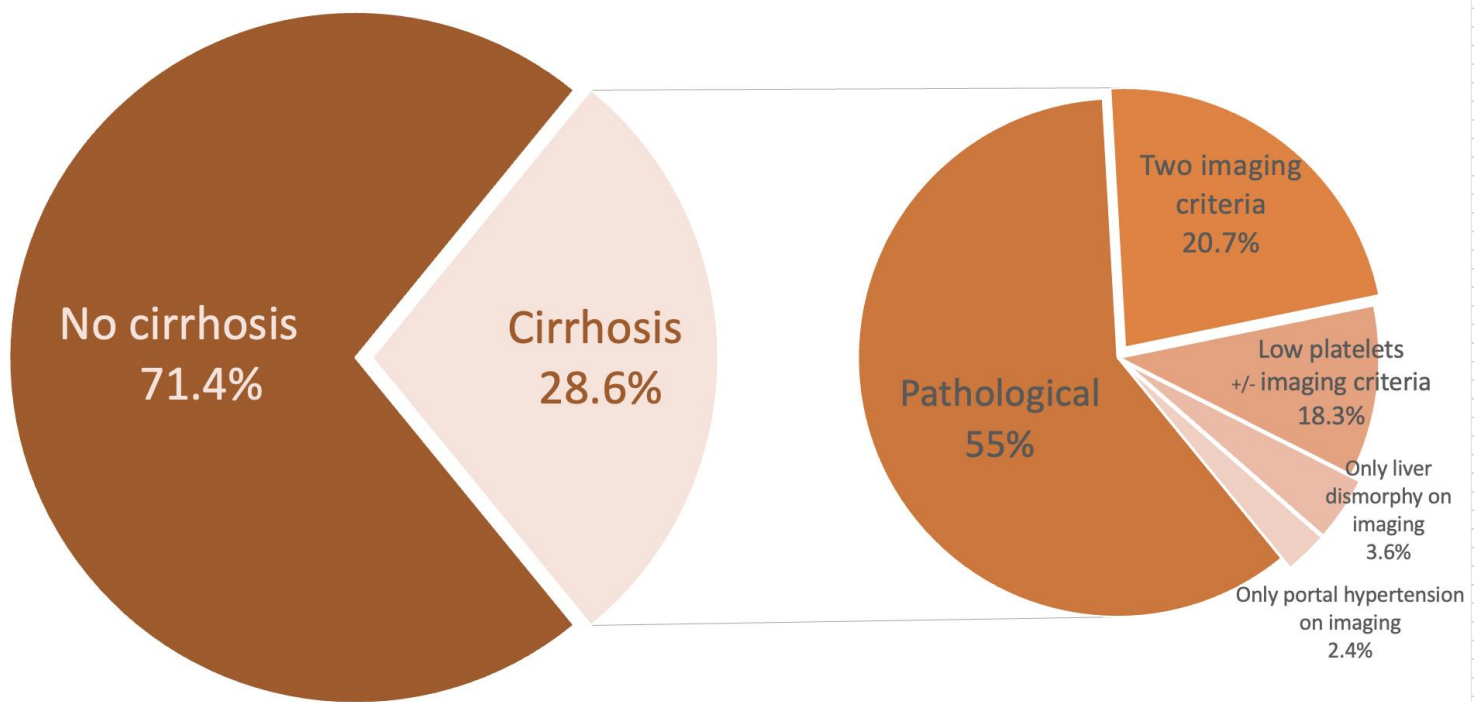


Figure 1. Description of the population

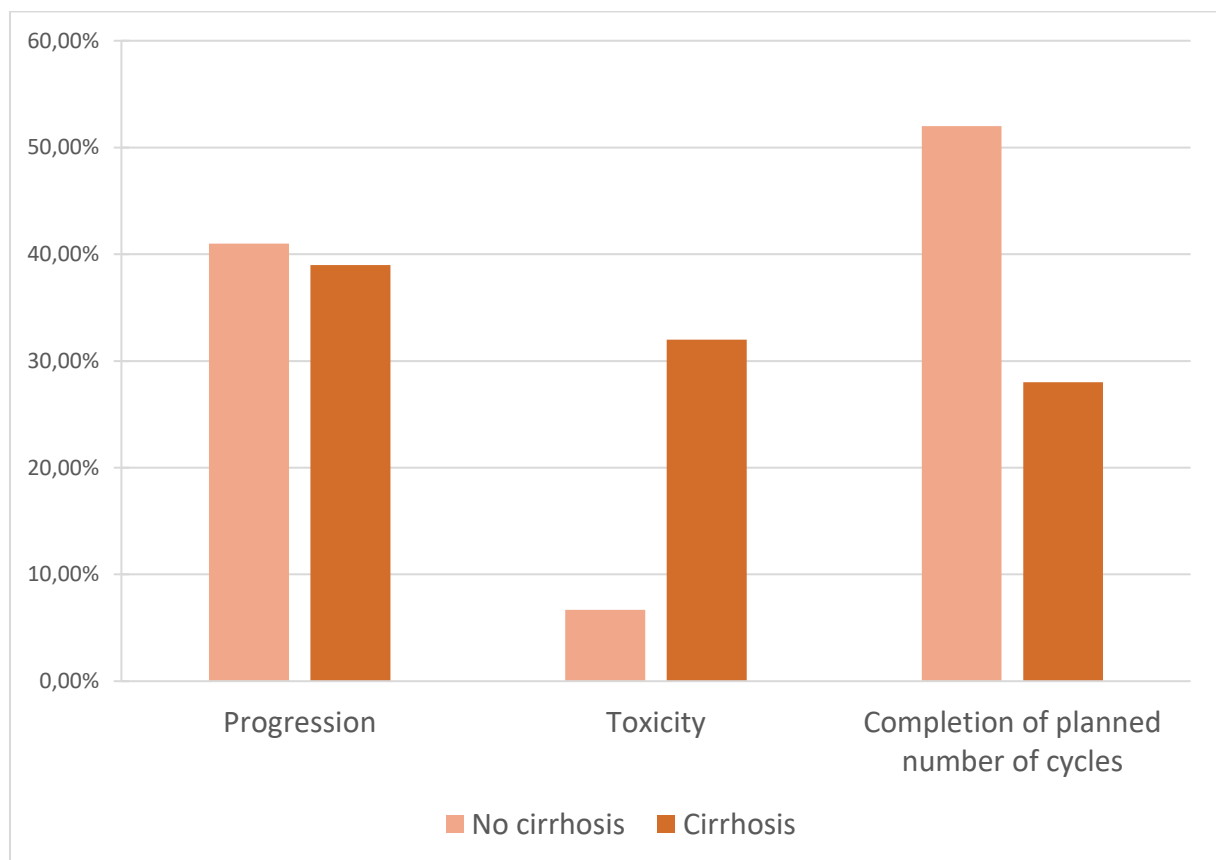


Figure 2. Causes of discontinuation of chemotherapy

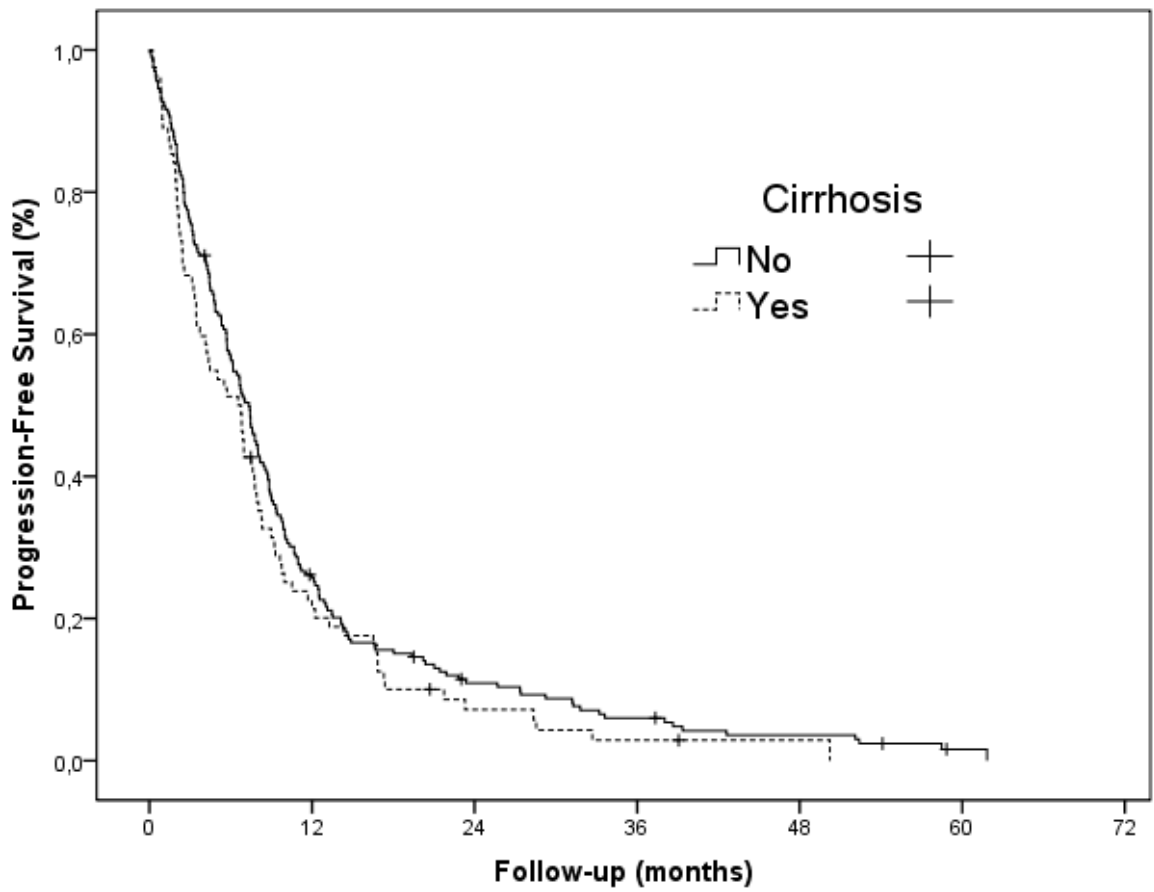


Figure 3. Kaplan Meier PFS by cirrhosis

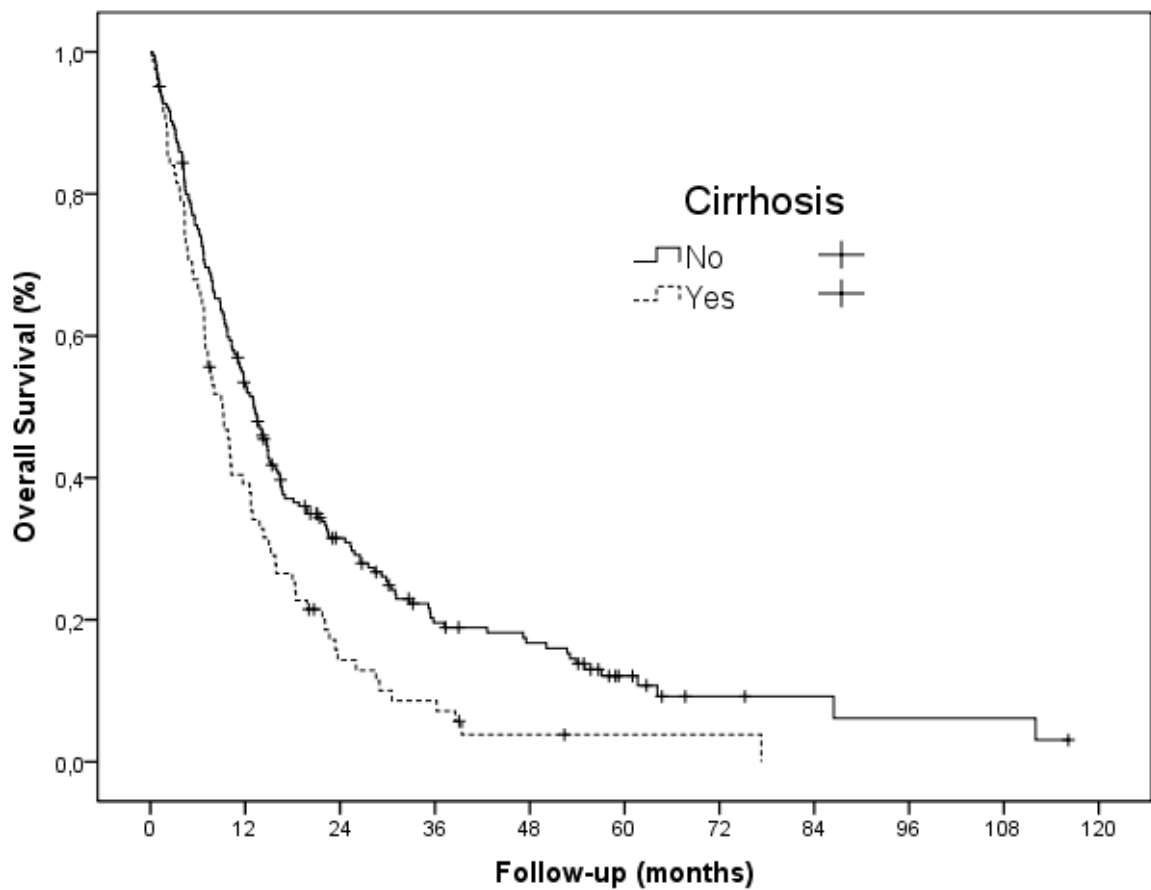


Figure 4. Kaplan Meier OS by cirrhosis

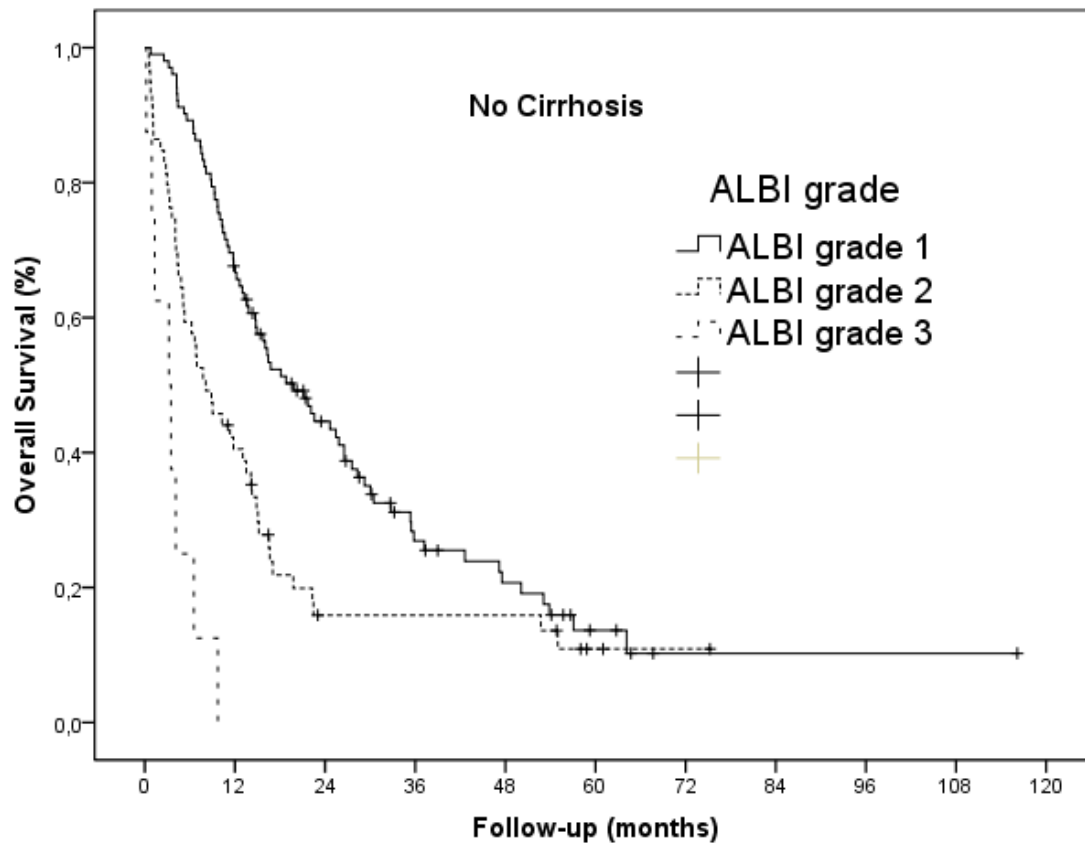


Figure 5a. Kaplan Meier OS by ALBI grade for patients without cirrhosis

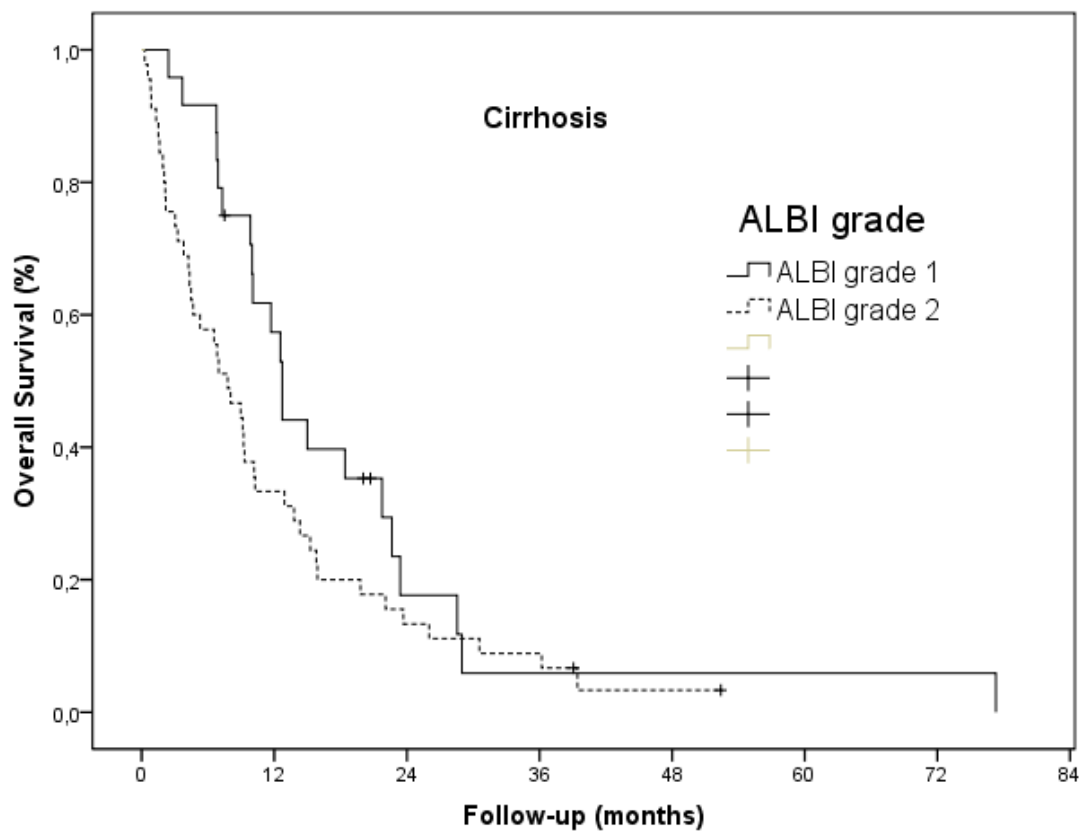


Figure 5b. Kaplan Meier OS by ALBI grade for patients with cirrhosis

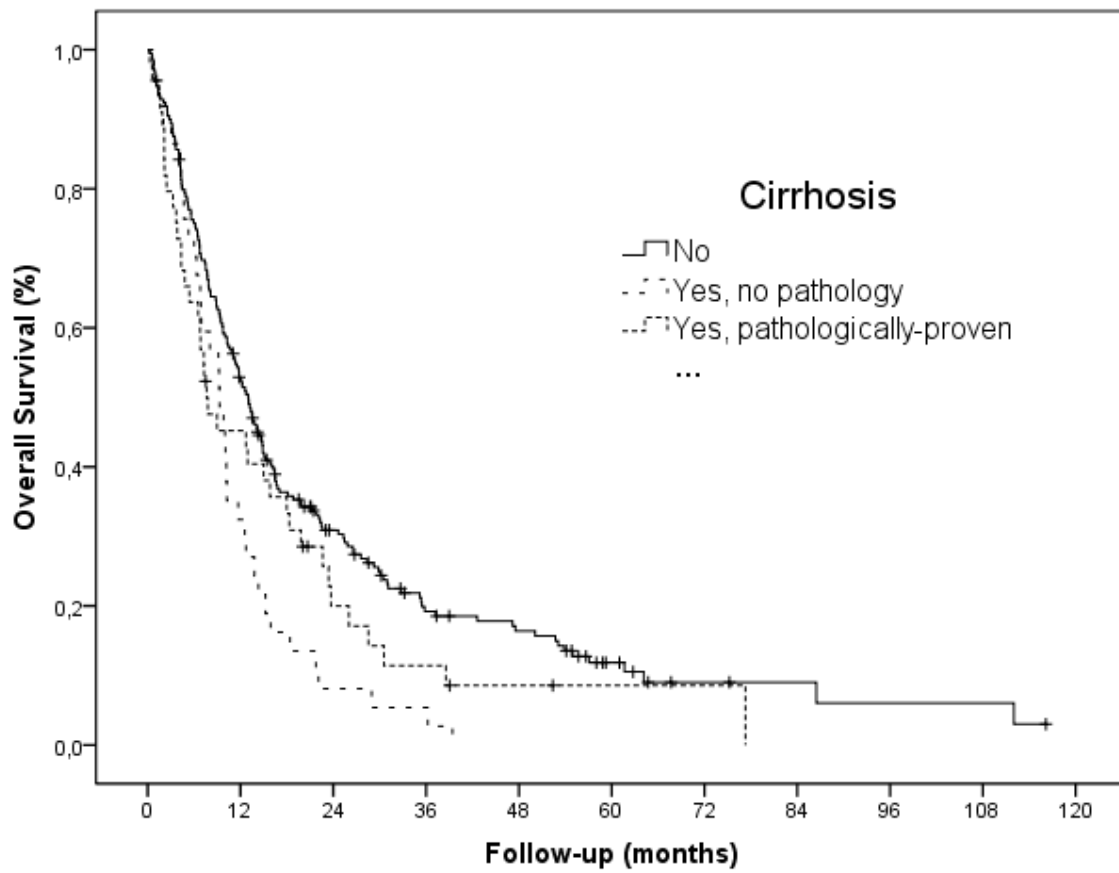


Figure 6. Kaplan Meier OS by pathologically proof of cirrhosis

Tables :

<i>Variable</i>		<i>No cirrhosis</i>	<i>Cirrhosis</i>	<i>p-value</i>
Gender	Male	97 (47.3%)	64 (78%)	0.004
	Female	108 (52.7%)	18 (22%)	
Age (years)		64 [95%CI: 60.3-63.7]	67 [95%CI:64.5-68.7]	0.03
Previous adjuvant treatment	No	196 (96.1%)	80 (97.6%)	0.54
	Yes	8 (3.9%)	2 (2.4%)	
Previous biliary stent	No	181 (89.6%)	80 (97.6%)	0.026
	Yes	21 (10.4%)	2 (2.4%)	
Differentiation	Well	21 (21.2%)	6 (13.6%)	0.34
	Moderately	55 (55.6%)	25 (56.8%)	
	Poorly	23 (23.2%)	12 (27.3%)	
	0	91 (44.6%)	38 (46.9%)	
	1	84 (41.2%)	27 (33.3%)	

ECOG PS	2	24 (11.8%)	15 (18.5%)	0.34
	3	5 (2.5%)	1 (1.2%)	
Liver only disease	Yes	82 (40%)	40 (48.8%)	0.17
	No	123 (60%)	42 (51.2%)	
Tumour liver involvement	>50%	40 (20.7%)	13 (16.5%)	0.42
	<50%	153 (79.3%)	66 (83.5%)	
Macrovascular invasion	No	146 (73%)	63 (76.8%)	0.50
	Yes	54 (27%)	19 (23.2%)	
Liver involvement	Unifocal	111 (56.6%)	39 (48.8%)	0.23
	Multifocal	85 (43.4%)	41 (51.2%)	
	Unilobar	127 (64.8%)	50 (62.5%)	0.72
	Bilobar	69 (35.2%)	30 (37.5%)	
	No	122 (59.5%)	53 (64.6%)	

Lymph node metastasis	Yes	83 (40.5%)	29 (35.4%)	0.42
Peritoneal metastasis	No	155 (75.6%)	66 (80.5%)	0.37
	Yes	50 (24.4%)	16 (19.5%)	
Lung metastasis	No	153 (74.6%)	61 (74.4%)	0.97
	Yes	52 (25.4%)	21 (25.6%)	
Bone metastasis	No	181 (88.3%)	70 (85.4%)	0.50
	Yes	24 (11.7%)	12 (14.6%)	
Other metastasis	No	174 (88.3%)	69 (92%)	0.38
	Yes	23 (11.7%)	6 (8%)	
Hemoglobin baseline (g/dl)		13 [95%CI: 12.7-13.2]	13.3 [95%CI: 12.7-13.4]	0.26
Neutrophil baseline (G/L)		6.4 [95%CI: 6.5-7.5]	5.2 [95%CI: 5.3-6.6]	0.001
Lymphocytes baseline (G/L)		1.4 [95%CI:-1.41-1.78]	1.34 [95%CI:1.22-1.69]	0.50
Platelets baseline (G/L)		249 [95%CI:258.5-292.1]	180 [95%CI:182.2 - 238.3]	0.001

Albumin baseline (g/L)	41 [95%CI:38.1-39.9]	38 [95%CI:36.7-38.9]	0.05
Alkaline Phosphatase baseline (UI/L)	202 [95%CI:246.2-320]	158.5 [95%CI: 169.3-235.7]	0.015
Total bilirubin baseline (mg/L)	12 [95%CI:16.4-23.6]	13.9 [95%CI:14.3-20.2]	0.09
ALBI score	-2.7 [95%CI:-2.7 -2.5]	-2.4 [95%CI:-2.5- -2.3]	0.001
CEA* baseline (ng/ml)	3 [95%CI:0-29.5]	3 [95%CI:3-10.3]	0.34
CA19.9 baseline (U/ml)	143 [95%CI:1889-5362]	81 [95%CI:322.7-1333.5]	0.06

Table 1

* *Carcinoembryonic antigen* ; ‡ *Alpha-fetoprotein*

Variable	Univariable	p-value	Multivariable	p-value
Cirrhosis	HR=1.54 [95%CI : 1.09-2.16]	0.014	HR=1.48 [95%CI: 1.04-2.10]	0.03
Age	HR=1.01 [95%CI: 0.99-1.02]	0.13		
Gender	HR=0.69 [95%CI: 0.53-0.90]	0.005		NS
Previous adjuvant treatment	HR=1.20 [95%CI: 0.61-2.33]	0.20		
ALBI grade	HR=2.11 [95%CI:1.63-2.74]	<0.001	HR=2[95%CI: 1.50- 2.68]	<0.001
Differentiation	HR=1.24 [95%CI:0.95-1.63]	0.12		
ECOG PS	HR=2.27 [95%CI:1.88-2.73]	<0.001	HR=2.00 [95%CI: 1.59-2.52]	<0.001
Liver only disease	HR=0.52 [95%CI:0.4-0.67]	<0.001	HR=0.62 [95%CI: 0.45-0.84]	0.003
Macrovascular invasion	HR=1.08 [95%CI:0.81-1.43]	0.61		

Liver involvement >50%	HR=1.55 [95%CI:1.12-2.13]	0.008		NS
Multifocal liver involvement	HR= 1.15 [95%CI:0.89-1.48]	0.29		
Bilobar liver involvement	HR= 1.12 [95%CI: 0.86-1.46]	0.39		
Hemoglobin baseline (g/dl)	HR=0.82 [95%CI:0.75-0.90]	<0.001		NS
Neutrophil baseline (G/L)	HR=1.09 [95%CI:1.04-1.13]	<0.001	HR=1.06 [95%CI: 1.01-0.11]	0.23
Lymphocyte baseline (G/L)	HR=0.93 [95%CI:0.81-1.07]	0.33		
Platelet baseline (G/L)	HR=1.00 [95%CI:1.00-1.00]	0.26		
Alkaline Phosphatase baseline (UI/L)	HR=1.00 [95%CI:1.00-1.00]	0.14	HR=1.00 [95%CI: 1.00-1.00]	0.09
Ca19.9 baseline (U/ml)	HR=1.00 [95%CI:1.00-1.00]	<0.001		

Treatment regimen received	HR=1.37 [95%CI:1.13-1.67]	0.001	HR=1.46 [95%CI: 1.16-1.85]	0.003
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Table 2

* *Carcinoembryonic antigen* ; † *Alpha-fetoprotein*

Liver disease aetiology	Number of patients and percentages
Alcohol	21 (25.6%)
Non-alcoholic steato-hepatitis (NASH)	30 (36.6%)
Mixed aetiology of NASH and alcohol	10 (12.2%)
Other mixed causes	5 (6%)
Hemochromatosis	4 (4.9%)
Viral hepatitis C	3 (3.7%)
Viral hepatitis B	5 (6.1%)
Undetermined causes	4 (4.9%)

Table 3