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OUTCOMES OF LIVER TRANSPLANTATION IN INCIDENTALLY DIAGNOSED COMBINED HEPATOCELLULAR-CHOLANGIOCARCINOMA: A 25-YEAR SINGLE-CENTER MATCHED COHORT STUDY

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Background and aim. Combined hepatocellular-cholangiocarcinoma (cHCC-CCA) is a rare liver malignancy, which comprises clinical and morphological features of both hepatocellular carcinoma (HCC) and cholangiocarcinoma (CC) and corresponds to 1–4.7% of cases of primary liver carcinomas. At present, Liver transplantation (LT) is not routinely recommended for known cHCC-CCA due to concerns regarding aggressive behavior and recurrence risk. However, incidental diagnoses after LT performed for presumed HCC raise questions regarding post-transplant outcomes. **Material and methods.** We conducted a retrospective single-center study including patients who underwent LT between 2000 and 2025. Patients with incidentally diagnosed cHCC-CCA on explant pathology were matched 1 : 2 with HCC controls according to age, year of transplantation, donor type, tumor burden at explant (number and size), lymphovascular invasion, locoregional therapy, and BAR score. Overall survival (OS) and disease-free survival (DFS) were analyzed using Kaplan–Meier estimates and compared with the log-rank test. **Results.** After matching, 9 patients with cHCC-CCA were matched with 18 HCC controls. Five-year OS was 41.7% in the cHCC-CCA group and 81.5% in the HCC group ($p = 0.26$) and Five-year DFS was 70% versus 85.9%, respectively ($p = 0.25$). Recurrence occurred in two patients in each group. To date, this 25-year study represents one of the most rigorously matched European analyses, uniquely incorporating lymphovascular invasion and BAR score as matching variables. **Conclusions.** Despite the fact that no statistically significant differences were demonstrated in post-transplant survival or recurrence between the groups, worse results could be observed in the studied group, which is consistent with the current non-indication of LT for cHCC-CCA. This study was substantially underpowered, so the absence of statistical significance should not be interpreted as clinical equivalence.

Key words: hepatocellular carcinoma (HCC), cholangiocarcinoma (CC), combined hepatocellular-cholangiocarcinoma (cHCC-CCA), primary liver cancer (PLC), liver transplantation (LT).

DECLARATIONS

Ethics approval and consent to participate. The study was approved by the institutional research ethics committee (PI-26-59-H) and certified that the study was performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments.

Consent for publication. That publication has been approved by all co-authors at the institute where the work has been carried out.

Availability of data and material. All data generated or analysed during this study are included in this published article.

Competing interests. The authors have stated explicitly that there are no conflicts of interest in connection with this article. The work described has not been published before. It is not under consideration for publication anywhere else.

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LIST OF ABBREVIATIONS

Combined hepatocellular-cholangiocarcinoma (cHCC-CCA)

Hepatocellular carcinoma (HCC)

Cholangiocarcinoma (CC)

Primary liver cancer (PLC)

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Liver transplantation (LT)
Donation after Circulatory Death (DCD)
Donation after Brain Death (DBD)
Overall survival (OS)
Disease-free survival (DFS)
Primary nonfunction (PNF)
Locoregional therapy (LRT)
Transcatheter arterial chemoembolization (TACE)
Radiofrequency ablation (RFA)
Up to seven criteria (U7)
University of California San Francisco (UCSF)

INTRODUCTION

Combined hepatocellular-cholangiocarcinoma (cHCC-CCA) is a rare liver malignancy, which comprises clinical and morphological features of both hepatocellular carcinoma (HCC) and cholangiocarcinoma (CC) [1]. It corresponds to 1–4.7% of cases of primary hepatic carcinomas, but are seen more and more frequently in clinical practice [2]. Due to the overlap in clinical and radiological features, some patients who undergo liver transplantation (LT) for HCC may have a precise diagnosis of cHCC-CCA made only after histopathological evaluation of the explanted liver. Such incidentally identified cHCC-CCA may occur in 1–2% of transplants for HCC [3].

This unique malignant entity was first reported by Wells in 1903 [4]. Since then, there have been several classifications: Allen and Lisa (1949) [5], Goodman et al. (1985) [6] and WHO (2010) [7]. According to the 2010 classification, cHCC-CCA must have an «unequivocal presence of hepatocyte and cholangiocytic differentiation within the same tumor» [7]. Compared to the previous WHO histological classification system, the new version in 2019 now recommends distinctive diagnostic terms for intermediate cell carcinomas and cholangiolocarcinomas (previous cholangiolocellular carcinoma subtype) [8].

Establishment of the correct preoperative diagnosis by means of imaging studies or histopathological biopsy interpretation is difficult, and the majority of patients are misdiagnosed as either HCC or CC [1]. Moreolrver, the treatment of choice has not yet been defined. To date, only a few, small volume case series reporting outcomes of LT in patients with cHCC-CCA have been published, with contradicting results [9]. Traditionally, disease-free survival and overall survival have been reported for patients with cHCC-CCA significantly worse compared to patients with HCC [10–13]. Nevertheless, some recent reports suggest that LT may be an effective therapeutic method for the treatment of cHCC-CCA after strict screening of candidates [4, 14, 15].

At present, cHCC-CCA is not an indication for LT due, in part, to the absence of data supporting improved prognosis following LT and aggressive disease course observed in practice. However, the published reports have several limitations: historical bias, the grouping of cHCC-CCA with CC [11, 16–18], lack of consideration of tumor burden, pre-operative therapy and lymphovascular invasion; and other variables that also influence graft survival and overall survival, such as recipient age, Model for End-stage Liver Disease (MELD) score and type of donation [16].

The aim of this study is to compare the outcomes of LT in patients with cHCC-CCA versus HCC after simple matching. Our hypothesis is that, controlling for the main oncological and non-oncological variables that influence patient survival, LT for cHCC-CCA offers similar outcomes to HCC.

MATERIALS AND METHODS

This is a retrospective and observational study with a simple 1 : 2 matching between cHCC-CCA patients and HCC patients with LT between 2000 and 2025 at the Rio Hortega University Hospital (Valladolid). In our study, cases identified as cHCC-CCA in the histopathological examination of the explanted liver comprised the study group. A control group was created with patients with a proven final diagnosis of HCC.

Exclusion criteria: <18 years, cHCC-CCA patients who do not meet the criteria of the latest classification (WHO 2019), and patients with early retransplantation (<30 days).

Propensity score matching could not be performed due to the low number of cases, so simple matching was performed according to: Age ±10 years; Donor type [Donation after Circulatory Death (DCD) or Donation after Brain Death (DBD)]; Year of transplantation ±5 years; Explant pathologic characteristics: Number of tumor nodules ±1, Size of the largest tumor nodule (cm) ±1, Lymphovascular invasion (Yes/No); Previous locoregional treatment (Yes/No); Balance of Risk (BAR) score ±2.

Epidemiological, anthropometric, analytical data and data relating to medical-surgical history, preoperative study, the surgical procedure itself and postoperative results are included. Overall survival (OS) was defined by the length of time (months) from the date of LT to date of death or date of last follow-up, while Disease-free survival (DFS) was defined by time from transplant date to date of recurrence, date of death, or date of the last follow-up, whichever occurred first.

Statistical analysis of data was performed using SPSS™ software, version 23 (IBM Corp). Qualitative variables were expressed as absolute numbers of frequencies or percentages, and quantitative variables as medians and ranges. Categorical variables were tested with the Pearson chi-square test, and when appropriate, Fisher's exact test. To study the differences between independent means, the Student's t-test (parametric, continuous quantitative variables) or the Mann–Whitney U test (non-parametric, discrete quantitative variables) was used for two groups. Patient survival rates were estimated with the Kaplan–Meier method and compared with

the log-rank test. A univariate Cox proportional hazards analysis was also performed. A P value of less than 0.05 was considered statistically significant.

Sample size and statistical power: Using the Schoenfeld formula, post-hoc power for detecting the observed Hazard Ratio (HR) of 1.93 for overall survival (with 12 events) is approximately 20.6%; for disease-free survival (HR = 3.00, approximately 6 events), it is 26.9%. Achieving 80% power for the observed OS effect would require approximately 73 events. Consequently, the absence of statistical significance is mathematically predetermined at this sample size and should not be interpreted as evidence of clinical equivalence, but rather as an exploratory and hypothesis-generating analysis.

The study was approved by the institutional research ethics committee (PI-26-59-H) and certified that the study was performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments. Written informed consent was obtained from patients or their guardians.

RESULTS

Between 2000 and 2025, 889 patients received a first liver transplant at the Rio Hortega University Hospital. Histopathological examination performed after LT revealed cHCC-CCA in 15 patients. Four patients were excluded from the analysis because they did not meet the diagnostic criteria of the latest classification for cHCC-CCA (WHO 2019) and another two were excluded because they required re-transplantation in less than 30 days due to Primary nonfunction (PNF), leaving 9 individuals in the study group. After performing simple 1 : 2 matching by the criteria mentioned above, a total of 18 patients with HCC were analyzed (Fig. 1).

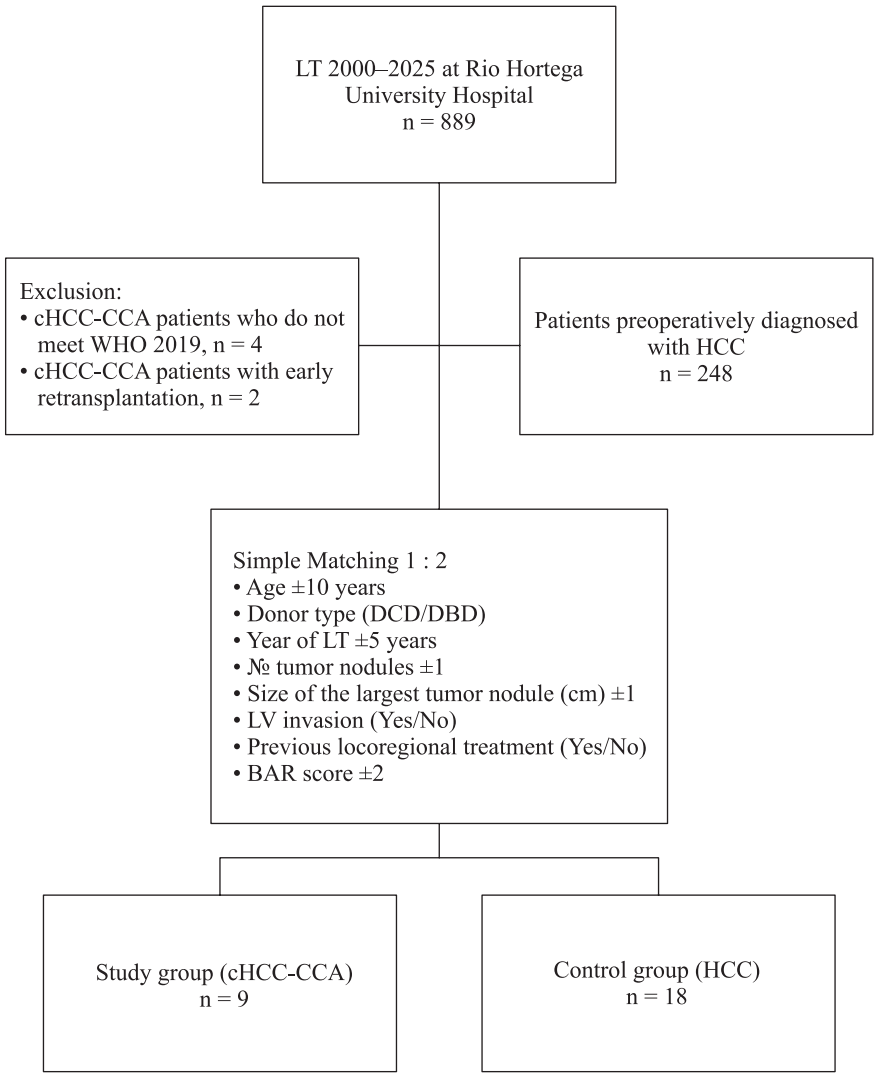


Fig. 1. Patient Flow. cHCC-CCA – combined hepatocellular-cholangiocarcinoma; HCC – Hepatocellular carcinoma; LT – liver transplantation; LV – Lymphovascular; DCD – Donation after Circulatory Death; DBD – Donation after Brain Death. Causes for exclusion and variables for the matching are detailed in the diagram. There were a total of 889 transplant patients in our hospital, of whom the indication for HCC was detected in 248. After reviewing the histopathological examination of all of them, 15 cHCC-CCA cases were found. Finally, 27 patients were analyzed after applying the inclusion and exclusion criteria and simple matching

The study group comprised of 1 female and 8 males. Characteristics are presented in Table 1. The age at transplant for these patients ranged between 53–62 years; and for the 18 HCC patients, four were females and fourteen were males with age at transplant ranging from 54 to 63 years. The analysis of BMI reflects comparable results: median of 26.54 with range 25–29 kg/m^2 in the cHCC-CCA group and median of 29.66 with range

Table 1

Baseline characteristics

Baseline characteristics	cHCC-CCA	HCC	p-value
Gender, n (%)			0.64
• Female	1 (11.1)	4 (22.2)	
• Male	8 (88.9)	14 (77.8)	
Donor age, median (IQR), years	68.5 (65.25–70.75)	69.5 (61–74.25)	0.45
Donor type, n (%)			NA
• DCD	0 (0)	0 (0)	
• DBD	9 (100)	18 (100)	
Recipient age, median (IQR), years	57 (53–61.50)	60 (54–63.25)	0.62
BMI, median (IQR), kg/m^2	26.54 (24.95–29.38)	29.66 (25.44–32.99)	0.24
Indication, n (%)			0.25
• Preoperatively diagnosed with HCC	7 (77.8)	17 (94.4)	
• Decompensated cirrhosis	2 (22.2)	1 (5.6)	
Cirrhosis etiology, n (%)			0.14
• Alcoholic	5 (55.6)	8 (44.4)	
• Viral Hepatitis C	3 (33.3)	2 (11.1)	
• Viral Hepatitis B	1 (11.1)	1 (5.6)	
• Mixed	0 (0)	7 (38.9)	
MELD Score, median (IQR)	9 (7.5–13.5)	9 (8–13)	0.56
Preoperative nºnodules, median (IQR)	2 (0.5–3)	1 (1–2)	0.90
Preoperative largest nodule, median (IQR), cm	2.6 (1.9–3.3)	2.4 (1.95–3.10)	0.86
LRT, n (%)			0.33
• TACE	1 (11.1)	2 (11.1)	
• RFA	1 (11.1)	0 (0)	
• Mixed	0 (0)	1 (5.55)	
• No	7 (77.8)	15 (83.3)	
Tumor location, n (%)			1.00
• Unilobar	6 (85.7)	14 (82.4)	
• Bilobar	1 (14.3)	3 (17.6)	
Previous biopsy	1 (11.1)	2 (11.1)	1.00
Preoperative Milan criteria, n (%)	5 (71.4)	16 (94.1)	0.19
Preoperative UCSF criteria, n (%)	7 (100)	16 (94.1)	1.00
Preoperative U7 criteria, n (%)	7 (100)	17 (100)	NA
Preoperative Metroticket 2.0 (%), median (IQR)	75.3 (69–83.2)	83.9 (71.5–85.5)	0.27
AFP before liver transplant, n (%)			0.28
• <50 ng/ml	7 (77.8)	15 (83.3)	
• 50–200 ng/ml	0 (0)	2 (11.1)	
• >200 ng/ml	2 (22.2)	1 (5.6)	
BAR score, median (IQR)	3 (2–4.5)	3.5 (3–4.25)	0.60

Note. IQR – interquartile range; BMI – Body mass index; LRT – Locoregional therapy; TACE – Trans-arterial chemoembolization; RFA – radiofrequency ablation; AFP – Alpha-fetoprotein; DCD – Donation after Circulatory Death; DBD – Donation after Brain Death; NA – Not applicable. Milan criteria: single tumour ≤5 cm in size or ≤3 tumours each ≤3 cm in size, and no macrovascular invasion. UCSF: University of California San Francisco criteria, single lesion <6.5 cm, maximum of 3 lesions with none >4.5 cm, and cumulative tumor size <8 cm. U7: up-to-seven criteria, hepatocellular carcinomas with seven as the sum of the size of the largest tumour [in cm] and the number of tumours. Metroticket 2.0: 5-year predicted survival after liver transplantation. The Milan, UCSF, U7 preoperative criteria and Metroticket 2.0 were only analyzed in patients previously diagnosed with HCC. Data is missing for some variables due to incomplete records. For variables with missing data, only complete cases were reported. Categorical variables were tested with the Pearson chi-square test or Fisher's exact test. To study the differences between independent means, the Student's t-test or the Mann–Whitney U test was used. A P value of less than 0.05 was considered statistically significant.

25–33 kg/m^2 in the HCC group, p > 0.05. Likewise, the donor's age was similar between both groups: median 68.5 years with range 65–71 in the study group and median 69.5 years with range 61–74 in the control group (p > 0.05) and 100% of donors came from Donation after Brain Death (DBD). The primary underlying disease in each group is also listed in Table 1, with alcoholic disease being the most frequent cause that motivated the LT (55.6% cHCC-CCA and 44.4% HCC). The groups did not differ in preoperative MELD score (median 9 *vs* 9, p > 0.05). 77.8% of the study group and 94.4% of the control group met the radiological criteria for HCC, were presumed to have HCC at the time of inclusion on the list for LT and underwent locoregional therapy (LRT) 22.2% and 16.7% respectively while awaiting LT. The types of LRT received by the patients were transcatheter arterial chemoembolization (TACE), radiofrequency ablation (RFA) or a combination of both. The frequencies are described in Table 1. The most frequent finding was that the tumor was located in a unilobar pattern (85.7% cHCC-CCA and 82.4% HCC). Patients with cHCC-CCA had a median of 2 lesions with a median diameter of 2.6 cm in the preoperative study, while those with HCC had 1 lesion with a median diameter of 2.4 cm. 11% of both groups underwent preLT biopsy, which yielded a result consistent with HCC. 100% of patients met the Up to seven criteria (U7) prior to LT. However, this number decreases for the Milan criteria (71% *vs* 94%, p > 0.05) and University of California San Francisco (UCSF) criteria (100% *vs* 94%, p > 0.05). Five-year predicted survival after liver transplantation by Metroticket 2.0 was lower in the study group compared to the control group, without statistically significant differences (75% *vs* 84%, p > 0.05). The most frequent range in which alpha-fetoprotein (AFP) was found prior to LT was 50 ng/ml in each group (78% cHCC-CCA *vs* 83% HCC). Last but not least; the BAR score, which provides a reliable tool to detect unfavorable combinations of donor and recipient factors (including MELD, Retransplantation, Life support, Recipient Age, Cold ischaemia, Donor Age), was comparable in both groups: median 3 study group *vs* 3.5 control group (p > 0.05). There are no re-transplants in the analyzed cohort and there are no statistically significant differences in any of the variables analyzed, which reflects a good matching.

On pathological evaluation of the study group, the median number of nodules was 2 and the median size of the largest nodule was 2.5 cm, with most tumors being G2 in Edmondson–Steiner grading system (22.2%) and exhibiting the same frequencies in the different degrees of tumor differentiation. There were 22.2% who presented satellite nodules and in all cases that received LRT there was partial tumor regression in the histopathological examination. Similar to this, on pathological evaluation of the control group the median number of nodules was 2 and the median size of the largest nodule was 2.3 cm, with most tumors being G2 in Edmondson–Steiner grading system (55.6%) and moderately differentiated (55.6%). There were 11.1% who presented satellite nodules and in 2 of 3 cases that received LRT there was partial tumor regression in the histopathological examination. The presence of vascular invasion on pathology was similar in the study group (22.2%) compared to the control group (16.7%), with the difference not being statistically significant (p > 0.05). Most cHCC-CCA were located in one liver lobe (88.9%), as in the HCC group (72.2%), p > 0.05. Moreover, there were no statistically significant differences in cold ischemia time (median 366 min cHCC-CCA *vs* 370 min HCC, p > 0.05). The complete descriptive data are presented in Table 2. Of the patients ultimately diagnosed with HCC, 66.7% met the Milan criteria, and 83.3% met the UCSF and U7 criteria. This variable was not analyzed in cHCC-CCA since these criteria only consider HCC. Regarding the postoperative Metroticket 2.0, the control group had a 5-year predicted survival after liver transplantation of 73.8%.

There were two recurrences in both groups (22.2% study group *vs* 11.1% control group, p > 0.05), with average disease-free survival times of 121 and 183 months in the study and control groups, respectively (p > 0.05) (Table 2). Only one had received LRT. All patients had an AFP level between 100 and 1000 ng/ml at the time of relapse, and 100% of cHCC-CCA recurrence group had AFP >200 ng/ml before LT. 50% of both groups experienced both extrahepatic and intrahepatic recurrence. The most commonly used treatment was sorafenib, although radiotherapy was also administered in one case for bone metastases. Most patients experienced early recurrence (<12 months), with greater variability in overall survival time. The cases are detailed in Table 3.

SURVIVAL ANALYSIS

Overall mortality in the study group was 55.6% and 38.9% in the control group (p > 0.05), with average follow-up times of 76 and 123 months in the study and control groups, respectively (p > 0.05). The majority in both groups died with a functioning liver graft (60% cHCC-CCA *vs* 71.4% HCC) (Table 2). Overall survival at 1, 3, and 5 years in the study group was 55.6%, 41.7%, and 41.7%, and in the control group 88.9%, 88.9%, and 81.5% (p = 0.26). The Kaplan–Meier curves are shown in Fig. 2. Disease-free survival (DFS) rates at 1, 3 and 5 years were 70% for cHCC-CCA group and 93.8%, 93.8% and 85.9% respectively for the HCC group (p = 0.25) (Fig. 3). In univariable Cox proportional hazards analysis, there were no statistically significant differences in both OS (HR, 1.93; 95% CI, 0.60–6.13; p = 0.26) and DFS (HR, 3.00; 95% CI, 0.42–21.61; p = 0.27) for patients with cHCC-CCA.

Table 2

Outcomes

Outcomes	cHCC-CCA	HCC	p-value
Primary outcomes			
Overall survival, mean (IC 95%), months	76.42 (22.30–130.53)	123.16 (83.79–162.53)	0.26
Disease-free survival, mean (IC 95%), months	121.2 (63.18–179.22)	182.84 (150.39–215.30)	0.25
Secondary outcomes			
Cold ischaemia time, median (IQR), min	366 (340–401.50)	370 (317.50–466.25)	0.47
Pathology number of nodules, median (IQR)	2 (1–3)	2 (1–2)	0.51
Pathology largest nodule, median (IQR), (cm)	2.5 (2.1–4.35)	2.3 (2–3.62)	0.73
Differentiation, n (%)			0.13
• Well differentiated	1 (11.1)	6 (33.3)	
• Moderately differentiated	1 (11.1)	10 (55.6)	
• Poorly differentiated	1 (11.1)	2 (11.1)	
• Necrosis	1 (11.1)	0 (0)	
• Missing data	5 (55.5)	0 (0)	
Edmondson–Steiner grading system, n (%)			0.80
• I	0 (0)	2 (11.1)	
• II	2 (22.2)	10 (55.6)	
• III	1 (11.1)	4 (22.2)	
• IV	0 (0)	0 (0)	
• Missing data	6 (66.7)	2 (11.1)	
Pathology satellite nodes, n (%)	2 (22.2)	2 (11.1)	0.58
Pathology lymphovascular invasion, n (%)	2 (22.2)	3 (16.7)	1.00
LRT response, n (%)			1.00
• Complete response	0 (0)	0 (0)	
• Partial response	2 (100)	2 (66.7)	
• Progressive disease	0 (0)	0 (0)	
• Non-responders	0 (0)	1 (33.3)	
Pathology tumor location, n (%)			0.63
• Unilobar	8 (88.9)	13 (72.2)	
• Bilobar	1 (11.1)	5 (27.8)	
Postoperative Milan criteria, n (%)	NA	12 (66.7)	NA
Postoperative UCSF criteria, n (%)	NA	15 (83.3)	NA
Postoperative U7 criteria, n (%)	NA	15 (83.3)	NA
Postoperative Metroticket 2.0 (%), median (IQR)	NA	73.8 (68.62–74.4)	NA
Recurrence, n (%)	2 (22.2)	2 (11.1)	0.58
Deaths, n (%)	5 (55.6)	7 (38.9)	0.44
• Functioning graft ◦ Tumor ◦ Infection ◦ Other	 2 (40) 1 (20) 0 (0)	 2 (28.6) 1 (14.3) 2 (28.6)	
• Graft failure	2 (40)	2 (28.6)	

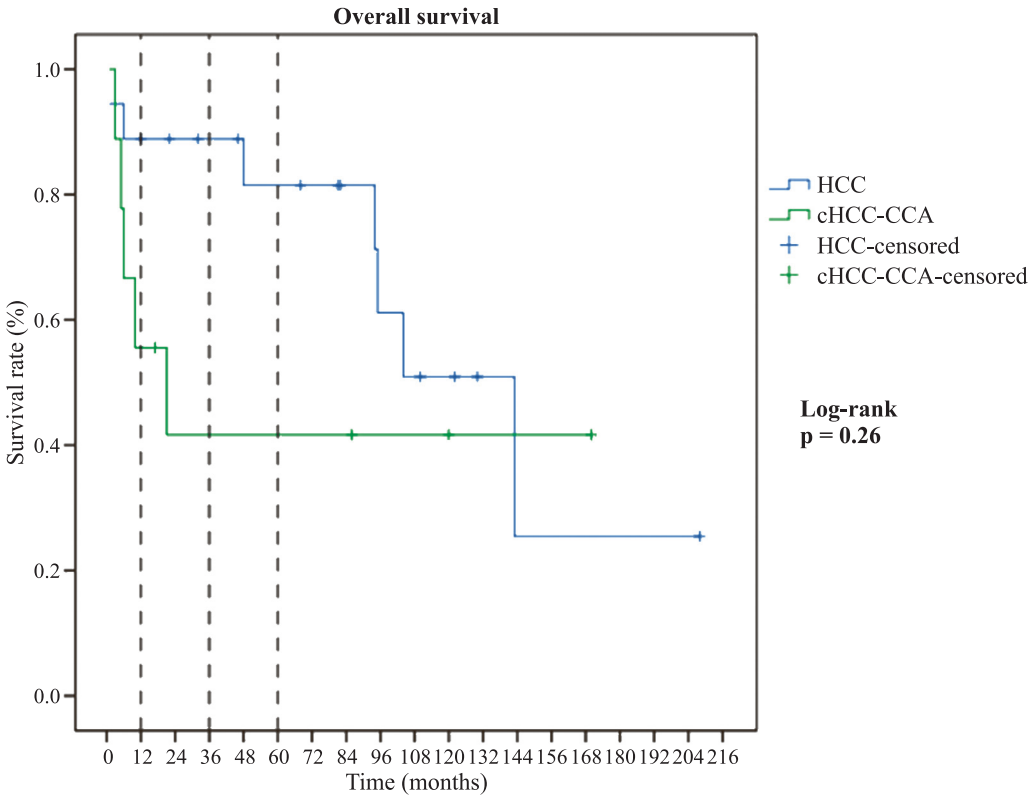
Note. IQR – Interquartile range; LRT – Locoregional therapy; NA – Not applicable. Milan criteria: single tumour ≤5 cm in size or ≤3 tumours each ≤3 cm in size, and no macrovascular invasion. UCSF: University of California San Francisco criteria, single lesion <6.5 cm, maximum of 3 lesions with none >4.5 cm, and cumulative tumor size <8 cm. U7: up-to-seven criteria, hepatocellular carcinomas with seven as the sum of the size of the largest tumour [in cm] and the number of tumours. Metroticket 2.0: 5-year predicted survival after liver transplantation. The Milan, UCSF, U7 preoperative criteria and Metroticket 2.0 were only analyzed in patients finally diagnosed with HCC. Data are missing for some variables due to incomplete records, but these cases were not excluded from the analysis. The log-rank test was used to compare survival between groups. Categorical variables were tested with the Pearson chi-square test or Fisher's exact test. To study the differences between independent means, the Student's t-test or the Mann–Whitney U test was used. A P value of less than 0.05 was considered statistically significant.

Table 3

Characteristics of patients with tumor recurrence

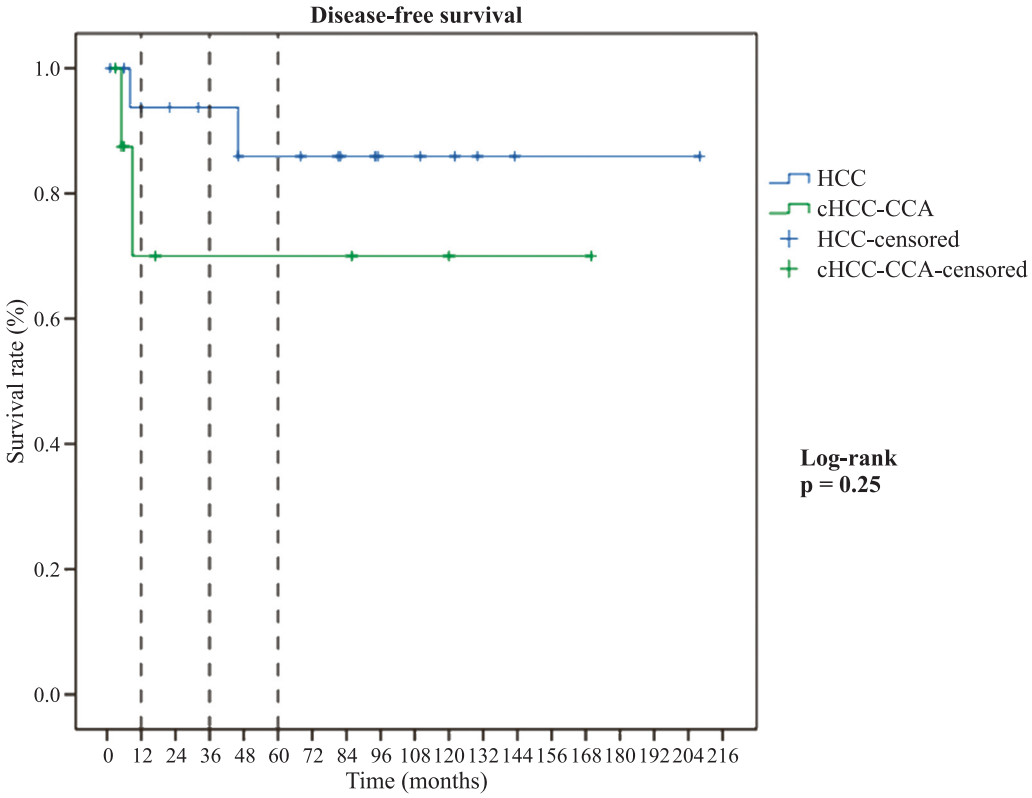
Patient	Age (years)	Cirrhosis etiology	Histological analysis	AFP before liver transplant (ng/ml)	AFP recurrence (ng/ml)	LRT	Location of recurrence (hepatic or extrahepatic)	Treatment	Disease-free survival (months)	Overall survival (months)	Death
1	61, male	VHB	cHCC-CCA, 2 × 6 cm, necrosis, LVI-, unilobar	>200	100–1000	No	Both	Missing data	9	10	Yes
2	59, female	VHC	cHCC-CCA, 4 × 4.5 cm, LVI +, unilobar, partial tumor regression	>200	100–1000	RFA	Extrahepatic	Sorafenib –> regorafenib	5	21	Yes
3	69, male	Mixed	HCC, 2 × 2.2 cm, G2, Moderately differentiated, LVI-, unilobar	<50	100–1000	No	Extrahepatic	RT + Sorafenib	46	104	Yes
4	63, male	Mixed	HCC, 1 × 3 cm, G3, Poorly differentiated, LVI +, unilobar	<50	100–1000	No	Both	Sorafenib	8	48	Yes

Note. LRT – Locoregional therapy; RFA – radiofrequency ablation; AFP – Alpha-fetoprotein; LVI – lymphovascular invasion; RT – radiotherapy.



Number at risk	0	12 m	24 m	36 m	48 m	60 m	72 m	84 m	96 m	108 m	120 m	132 m	144 m	156 m	168 m	180 m	192 m	204 m	216 m
Control group	18	15	14	13	11	11	10	8	6	5	4	2	1	1	1	1	1	1	0
Study group	9	5	3	3	3	3	3	3	2	2	1	1	1	1	1	0	0	0	0

Fig. 2. Overall survival according to Kaplan–Meier curves. The 1-, 3- and 5-year overall survival rates for study group were 55.6%, 41.7% and 41.7%, respectively and in control group were 88.9%, 88.9% and 81.5%. The censored cases correspond to end of the follow-up period. The log-rank test was used to compare survival between groups, without statistically significant results (p = 0.26)



Number at risk	0	12 m	24 m	36 m	48 m	60 m	72 m	84 m	96 m	108 m	120 m	132 m	144 m	156 m	168 m	180 m	192 m	204 m	216 m
Control group	18	14	13	12	10	10	9	7	5	5	4	2	1	1	1	1	1	1	0
Study group	9	4	3	3	3	3	3	3	2	2	1	1	1	1	1	0	0	0	0

Fig. 3. Disease-free survival according to Kaplan–Meier curves. DFS rates at 1, 3 and 5 years were 70% for cHCC-CCA group and 93.8%, 93.8% and 85.9% respectively for the HCC group. The censored cases correspond to end of the follow-up period. The log-rank test was used to compare survival between groups, without statistically significant results (p = 0.25)

DISCUSSION

LT provides the most favorable survival outcome for patients with primary liver cancer and even for patients with cHCC-CCA, survival after LT is better than with any other therapeutic modality. Unfortunately, the scarcity of donor liver allografts, historically reported high recurrence rates and inferior survival compared with HCC has put restrictions [19]. Therefore, it is imperative that outcomes for liver transplant for cHCC-CCA are equivalent to patients undergoing transplant for other currently accepted indications for liver transplantation. A study of the SEER and UNOS databases concluded worse outcomes for transplant for patients with cHCC-CCA compared to HCC; however, that study did not differentiate outcomes based on size or pathological evaluation and lacked granular data due to the retrospective use of large and old databases [2]. In our analysis, we performed a simple matching to ensure that the cHCC-CCA and HCC groups were comparable and that the difference in their results was primarily due to the type of tumor.

The number of cases in our series is lower than most of the main publications on the subject, with a total of 9 cases. The percentage of patients diagnosed with cHCC-CCA compared to the total of transplants analyzed was 0.16%. This percentage was lower than the largest series of cases described, between 2.8% [3] and 4.3% [20, 21]. This is probably because it is a single-center study in a tertiary center in a region of Spain.

Because of the low incidence of cHCC-CCA, few studies are available to provide detailed evaluation of outcomes following LT. Moreover, the majority of these studies mix evaluation of CC and cHCC-CCA, are old, have a historical bias and some do not meet the most current classification for cHCC-CCA (WHO 2019). One of the most noteworthy features of our study relates to the matching method we used. While several previous studies have matched HCC controls based on pre-transplant radiographic characteristics or pathological tumor burden at explant [3, 15, 20, 22], none of these studies have matched based on lymphovascular invasion or MELD score, which limits the ability to address whether cHCC-CCA tumors are truly inherently more aggressive. Kim et al. reported on their multivariate analysis that MELD score ≥20 (p = 0.04) was an independent risk factor for poor OS, whereas microvascular invasion (p = 0.01) was

an independent risk factor for poor DFS [16]. Another important issue is that patient overall survival depends not only on oncological prognosis, but also on patient- and transplant-related variables such as MELD score, retransplantation, life support at LT, recipient and donor age, cold ischemia time and donor type. Finally, to avoid historical bias in a database as long as ours, we matched by year of transplantation.

As most of these patients are cirrhotic patients, often with severe liver dysfunction and ascites, a biopsy is not always possible. When performed, the removed fragments may not be representative of the entire lesion or in multinodular tumors, a biopsy of one nodule does not guarantee the diagnosis of others [23]. In fact, only 3 patients in the studied cohort had a previous biopsy, which was compatible with HCC (subsequently one of them was cHCC-CCA). In the large multicenter Spanish cohort of 42 patients, 10 patients underwent pre-LT biopsy, with 7 biopsies incorrectly reporting a diagnosis of HCC and 3 biopsies being inconclusive [3]. Similarly, in the study published by Lunsford et al., only 33% of cHCC-CCA and 36% of HCC were biopsied prior to transplant and none of them tested positive for cHCC-CCA [15]. According to The 2024 ILTS-ILCA consensus recommendations for liver transplantation, «if any atypical imaging features are present, a biopsy should be performed to rule out cholangiocarcinoma or cHCC-CCA tumors, which can impact eligibility, prognosis and optimal treatment» [24].

Patients with cHCC-CCA are usually excluded from listing for LT due to the generally poor outcomes. In this single-center matched cohort with long-term follow-up, we did not identify statistically significant differences in overall or disease-free survival between incidentally diagnosed cHCC-CCA and HCC recipients, but outcomes were numerically inferior in the study group, particularly OS at 5 years (41.7% *vs* 81.5%). The absence of statistical significance must therefore be interpreted in the context of limited sample size and low recurrence number. The results are similar to those described by Sapisochin et al. in 2014 (93%, 78% and 78% *vs* 97%, 86% and 86%; p = 0.9) [3], Lunsford et al. in 2018 (75%, 54% and 42% versus 72%, 60%, and 48%; p = 0.54) [15], Antwi et al. in 2018 (survival of 1 and 3 years 84% and 74% versus 95% and 87%, p = 0.22) [22] and Dageforde et al. in 2021 (89%, 77% and 70% versus 90%, 81% and 73%; p = 0.81) [21], except for the lower survival of the study group in our series. The study reported by De Abreu et al [20]. found statistically significant differences in overall survival between both groups (survival of 1, 3, and 5 years, respectively, 70%, 57.5% and 57.5% study group versus 78.7%, 71.4% and 66.6% control group, p = 0.019), although it should be noted that the study group includes patients with CC. In fact, the same study acknowledges darker outcomes for CC.

cHCC-CCA has been shown to be significantly more likely to have poor differentiation compared with HCC [15, 25]. Recurrent disease appears to be associated more with the tumor grade/differentiation than pathologic size, although this could not be confirmed in our study, due to incomplete records due to retrospective data collection. In a Korean multivariate analysis, frequency of locoregional therapies >3, tumor size >3 cm, and lymph node metastasis were predisposing factors for tumor recurrence [26]. The cases that recurred presented some risk factor: vascular invasion, large size, or poor differentiation (Table 3). Several studies have analyzed the recurrence of cHCC-CCA. One of the earliest studies from Mayo Clinic Jacksonville reported a 58% recurrence rate [12], the group from Mount Sinai reported a recurrence of 44% [17], a Korean study reflected a recurrence rate of 35.1% [27] and a multicenter Spanish study published a recurrence in only 1 of 15 [3]. However, they included both cHCC-CCA patients as well as CC recipients, so the results should be taken with caution. Regarding previous studies, we found a lower recurrence in cHCC-CCA group (22.2%). According to DFS, the results are consistent with those reported by Lunsford et al. (66%, 42% and 42% versus 76%, 67%, and 61%; p = 0.17) [15] and Dageforde et al. (82%, 75% and 70% *vs* 87%, 78% and 70%; p = 0.74) [21], but higher than those reported by Amory et al. (51%, 25% and 17% versus 63%, 35% and 26%: p = 0.19) [28].

Kodali et al. found that both OS (HR, 4.67; 95% CI, 2.07–10.53; p < 0.001) and DFS (HR, 3.65; 95% CI, 1.70–7.82; p < 0.001) [29] were significantly inferior for patients with cHCC-CCA, but in our study we were unable to establish statistically significant differences in the increased risk of death and recurrence in the study group. The study is underpowered and as a result, the confidence intervals are very wide. Moreover, Five-year DFS of 70.0% alongside five-year OS of 41.7% creates an apparent paradox. Overall survival is affected not only by tumor recurrence in a functioning graft (40% in the study group), but also by graft failure (40%) and infections (20%). It is important to note that transplant recipients are immunocompromised and, therefore, more susceptible to infectious diseases, cardiovascular disease, and other tumors [30].

Overall, our study contributes long-term European single-center data to a limited body of literature addressing incidental cHCC-CCA after LT. While it does not demonstrate equivalence to HCC, it could serve as a pilot study to analyze cHCC-CCA subgroups that might benefit from LT or to conduct a more statistically powerful European multicenter study.

LIMITATIONS AND FUTURE DIRECTIONS

There are several limitations to the present study. First, the sample size of the cHCC-CCA group was small (n = 9), resulting in limited statistical power to detect

clinically meaningful differences in survival. Second, the retrospective and single-center design introduces potential selection bias. Only incidentally diagnosed after LT cases were included, which may represent a biologically more favorable subset of cHCC-CCA. Third, the number of recurrence events was low, limiting robust multivariable risk modeling and precluding definitive conclusions regarding prognostic factors. The proportional hazards assumption has not been verified due to the small sample size. Given the survival patterns, the Cox hazard ratio could represent a potentially misleading «time-averaged» effect. These data should be considered within the context of an exploratory and hypothesis-generating analysis of a limited sample of patients at a tertiary center. Fourth, a high proportion of histopathological variables in study group, particularly tumor differentiation and Edmondson–Steiner grading, had missing data due to retrospective data collection, which may limit interpretation of biological aggressiveness. So, oncological biology of the cHCC-CCA cohort remains largely uncharacterized. Finally, the small sample size of the cHCC-CCA group impeded reliable estimation of hazard ratios, resulting in over-inflated risk estimates and wide confidence intervals. Given these limitations, results should be interpreted as exploratory and hypothesis-generating.

It is possible that the small number of cases, even in the most representative series, was responsible for the divergent results found to date. The greatest challenge to any potential prospective trial investigating the benefits of LT for patients with cHCC-CCA is the limited ability to accurately diagnose these cancers in the pre-operative setting. International multicenter collaborations and meta-analyses of available data may help answer this question in the future.

CONCLUSIONS

To date, this 25-year study represents one of the most rigorously matched European analyses, uniquely incorporating lymphovascular invasion and BAR score as matching variables. Although cHCC-CCA did not demonstrate statistically significant differences in post-transplant survival or recurrence compared with HCC, outcomes were numerically inferior. It is consistent with the current non-indication of LT for cHCC-CCA. This study was substantially underpowered (post-hoc power for OS <21%), and the absence of statistical significance should not be interpreted as clinical equivalence. Larger multicenter studies are required.

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