Liver Cancer

Liver Cancer 2020;9:455–467
DOI: 10.1159/000507397
Received: November 20, 2019
Accepted: February 17, 2020
Published online: May 12, 2020

Original Paper

Mortality after Transplantation for Hepatocellular Carcinoma: A Study from the European Liver Transplant Registry

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Keywords
Hepatocellular carcinoma · Liver transplantation · Prognosis · Propensity score calibration · Unmeasured confounding · Non-cirrhotic liver · Cirrhosis

Abstract
Background and Aims: Prognosis after liver transplantation differs between hepatocellular carcinoma (HCC) arising in cirrhotic and non-cirrhotic livers and aetiology is poorly under-

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Liver Cancer 2020;9:455–467
DOI: 10.1159/000507397

stood. The aim was to investigate differences in mortality after liver transplantation between these patients. ***Methods:*** We included patients from the European Liver Transplant Registry transplanted due to HCC from 1990 to November 2016 and compared cirrhotic and non-cirrhotic patients using propensity score (PS) calibration of Cox regression estimates to adjust for unmeasured confounding. ***Results:*** We included 22,787 patients, of whom 96.5% had cirrhosis. In the unadjusted analysis, non-cirrhotic patients had an increased risk of overall mortality with a hazard ratio (HR) of 1.37 (95% confidence interval [CI] 1.23–1.52). However, the HR approached unity with increasing adjustment and was 1.11 (95% CI 0.99–1.25) when adjusted for unmeasured confounding. Unadjusted, non-cirrhotic patients had an increased risk of HCC-specific mortality (HR 2.62, 95% CI 2.21–3.12). After adjustment for unmeasured confounding, the risk remained significantly increased (HR 1.62, 95% CI 1.31–2.00). ***Conclusions:*** Using PS calibration, we showed that HCC in non-cirrhotic liver has similar overall mortality, but higher HCC-specific mortality. This may be a result of a more aggressive cancer form in the non-cirrhotic liver as higher mortality could not be explained by tumour characteristics or other prognostic variables.

Introduction

Hepatocellular carcinoma (HCC) represents one of the major cancers worldwide with more than 700,000 cases diagnosed annually [1]. The majority of HCC (70–90%) develops as a result of underlying chronic liver disease, with the remaining cases arising in non-cirrhotic livers [1, 2].

In cirrhotic patients, the Milan criteria were introduced in 1996 including size and number of HCC tumours to select patients for transplantation [3]. However, regarding patients with non-cirrhotic livers, macrovascular invasion and extrahepatic spread are the only recommended exclusion criteria for transplantation [4]. Upon diagnosis, HCC in non-cirrhotic livers has been reported to be fewer in number, larger, less differentiated, and more commonly with vascular invasion compared with HCC in cirrhotic livers [5, 6].

Earlier studies from the European Liver Transplant Registry (ELTR) reported a 5-year overall survival of 49% in patients undergoing liver transplantation for non-cirrhotic HCC compared with 75% in patients with cirrhotic livers inside the Milan criteria [7, 8]. Whether this difference is purely a result of different disease stage due to less strict selection criteria for non-cirrhotic patients is unknown.

Regarding all surgically treated HCC, a higher recurrence rate for non-cirrhotic disease may reflect more advanced tumours [5, 9]. Generally, due to underlying liver disease, recurrence risk may persist in cirrhotic patients due to sustained generation of new primary tumours [6]. Conversely, the vast majority of non-cirrhotic patients with recurrence present within 5 years, presumably reflecting recurrence of the primary tumour [10].

Observational studies may be limited due to unmeasured confounding from incomplete information regarding important prognostic variables [11, 12]. By using propensity score (PS) calibration [13–17], data available for a subset of patients with complete information on all confounding variables may be used to correct for unmeasured confounding in the full cohort. Furthermore, in contrast to studies in resected patients, data from transplanted patients eliminate background liver disease in cirrhotic patients, making cirrhotic and non-cirrhotic patients more comparable.

The hypothesis of the present study was that HCC arising in non-cirrhotic livers may be diagnosed later due to lack of surveillance, resulting in more advanced tumours with higher risk of recurrence. Thus, differences in recurrence may be related to disease stage and not tumour biological behaviour. Conversely, a lower overall mortality in non-cirrhotic patients

may be related to lack of comorbidity from the underlying liver disease. Therefore, we hypothesize that overall, HCC-specific and non-HCC-specific mortality are comparable between patients with non-cirrhotic and cirrhotic livers when investigated in a transplant setting using PS calibration where differences in prognostic confounding variables, including tumour characteristics, can be adjusted for.

The aim of the present study was to investigate differences in overall, HCC-specific, and non-HCC-specific mortality for patients liver transplanted for HCC with or without cirrhosis using PS calibration to adjust for unmeasured confounding.

Methods

The study was reported according to the STROBE guideline [18]. A protocol was registered at ClinicalTrials.gov (ID NCT02995096). The study was approved by the Danish Data Protection Agency (RH-2018-70, I-Suite number 6610).

This study is a register-based observational study with prospectively recorded data from the ELTR. The ELTR is a pan-European database including pretransplant and follow-up data from 172 liver transplantation centres. Patients are treated and followed up locally at each centre. The database comprises information on donor, recipient, locoregional treatments, immunosuppression, pathology from explanted liver (tumour size, tumour number, and vascular invasion), underlying liver disease, cirrhosis, time of death, and cause of death.

We included all patients in the ELTR undergoing liver transplantation due to HCC from 1990 to November 2016. Patients with fibrolamellar HCC were excluded (n = 57, 0.2%). The primary exposure variable was cirrhosis in the explanted liver based on pretransplant evaluation. The gold standard for the diagnosis of cirrhosis is liver biopsy evaluated with the METAVIR score [19]. However, for some patients the diagnosis may have been based on pretransplant imaging with an inhomogeneous hepatic surface, an enlarged caudate lobe, splenomegaly, ascites or collateral veins together with elevated Child-Pugh score or Model for End-Stage Liver Disease (MELD) score, and a clinical history of decompensated cirrhosis [20, 21]. Commonly, patients with cirrhosis were selected for liver transplantation based on the Milan criteria [3] or similar, whereas patients without cirrhosis were selected for liver transplantation primarily due to unresectability of the tumour without extrahepatic disease [7]. The criteria for cirrhosis and selection for transplantation were not dictated by the ELTR and may vary between centres. Outcomes were overall mortality, HCC-specific mortality (death due to HCC recurrence), and non-HCC-specific mortality (death due to other causes than HCC recurrence). As confounder variables, we included number of HCC tumours, year of transplantation, size of largest tumour, vascular invasion (micro- or macrovascular), time on waiting list, centre volume, age, sex, locoregional treatment before transplantation, and MELD score [8, 22].

We estimated the association between cirrhosis and mortality using a Cox regression model. We estimated an unadjusted model, an age- and sex-adjusted model, and a model adjusted for variables in the large dataset without any missing data (age, sex, year of surgery, and size of centre). We performed PS calibration to adjust hazard ratios (HRs) from the model adjusted for variables in the large dataset by including additional information from a subset of the dataset with complete data on other confounding variables (time on waiting list, number of HCC tumours, vascular invasion, size of largest tumour, locoregional treatment before transplantation, and MELD score). We calculated two PS in the subset with complete information. The first PS was the error-prone PS (X_{EP}), where we estimated the probability of cirrhosis conditional on confounders measured in the whole dataset. The second PS was the corrected PS (X_{corr}), where we estimated the probability of cirrhosis conditional on all confounders measured in the subset with complete information. Both PS models were estimated using multivariable logistic regression. We then estimated a linear measurement error model by regressing the corrected PS on the error-prone PS and cirrhosis (C):

$$E(X_{corr} \mid C, X_{EP}) = \lambda_0 + \lambda_C C + \lambda_{EP} X_{EP},$$

where λ_0, λ_C, and λ_{EP} are regression estimates. From the estimated coefficient for cirrhosis and mortality from the whole population adjusted for the error-prone PS, we subtracted the estimated coefficient for the error-prone PS (β_X) multiplied by the ratio of the parameter for cirrhosis and the error-prone PS estimated in the measurement model [15, 23]:

Table 1. Baseline patient characteristics

	Main study		Data source with all confounders	
	cirrhosis	no cirrhosis	cirrhosis	no cirrhosis
Number of patients	21,995	792	2,425	103
Female	3,710 (17%)	249 (31%)	355 (15%)	15 (15%)
Age				
Min–max, years	0–79	0–73	0–77	4–67
Mean (SD), years	56.2 (8.8)	47.5 (16.5)	55.6 (9.4)	50.4 (14.4)
Operation year				
1990–1996	1,478 (7%)	197 (25%)	3 (0%)	0 (0%)
1997–2000	1,437 (7%)	69 (9%)	4 (0%)	0 (0%)
2001–2002	2,114 (10%)	66 (9%)	17 (1%)	0 (0%)
2003–2004	1,817 (8%)	60 (8%)	91 (4%)	2 (2%)
2005–2006	2,202 (10%)	53 (7%)	172 (7%)	6 (6%)
2007	1,354 (6%)	35 (5%)	172 (7%)	10 (10%)
2008	1,480 (7%)	33 (4%)	285 (12%)	9 (9%)
2009	1,506 (7%)	47 (6%)	284 (12%)	15 (15%)
2010	1,570 (7%)	49 (6%)	280 (12%)	12 (12%)
2011	1,629 (7%)	52 (7%)	291 (12%)	13 (13%)
2012	1,579 (7%)	49 (6%)	328 (14%)	18 (17%)
2013	1,570 (7%)	45 (6%)	220 (9%)	11 (11%)
2014	1,247 (6%)	21 (3%)	164 (7%)	4 (4%)
2015–2016	1,012 (5%)	16 (2%)	114 (5%)	3 (3%)
Surgeries in centre				
1–10	63 (0%)	21 (3%)	12 (0%)	3 (3%)
11–25	207 (1%)	17 (2%)	53 (2%)	1 (1%)
26–50	469 (2%)	24 (3%)	52 (2%)	1 (1%)
51–100	1,468 (7%)	64 (8%)	250 (10%)	4 (4%)
101–250	10,227 (47%)	459 (58%)	1,189 (49%)	81 (79%)
>250	9,561 (43%)	207 (26%)	869 (36%)	13 (13%)
Waiting time				
Min–max, days	0–4073	0–1563	0–4060	0–1544
Mean (SD), days	186.4 (264.4)	124.0 (185.1)	180.9 (299.8)	169.5 (238.1)
0–26 days	2,859 (13)	185 (23)	602 (25)	27 (26)
27–80 days	3,211 (15)	153 (19)	608 (25)	24 (23)
81–208 days	3,912 (18)	146 (18)	609 (25)	24 (23)
>208 days	4,318 (20)	103 (13)	606 (25)	28 (27)
Missing	7,695 (35)	205 (26)	0	0
Size of largest HCC tumour				
Min–max, mm	1–700	4–600	2–350	9–235
Mean (SD), mm	33.6 (34.4)	48.2 (56.6)	33.8 (22.9)	35.6 (33.8)
Missing	13,109	568	0	0
MELD score				
Min–max	6.4–49.6	6.4–45.6	6.4–49.6	6.4–40.4
Mean (SD)	13.0 (5.9)	12.0 (5.9)	12.3 (5.5)	11.1 (5.5)
Missing	12,545	479	0	0
Number of HCC tumours				
1	3,980 (18%)	117 (15%)	1,062 (44%)	52 (50%)
2–3	3,508 (16%)	58 (7%)	932 (38%)	29 (28%)
4–5	949 (4%)	25 (3%)	240 (10%)	14 (14%)
6–9	427 (2%)	6 (1%)	105 (4%)	3 (3%)
>9	422 (2%)	14 (2%)	86 (4%)	5 (5%)
Missing	12,709 (58%)	572 (72%)	0	0
Vascular invasion				
No vascular invasion	5,986 (27%)	160 (20%)	1,848 (76%)	77 (75%)
Macrovascular invasion	237 (1%)	9 (1%)	92 (4%)	2 (2%)
Microvascular invasion	1,341 (6%)	47 (6%)	485 (20%)	24 (23%)
Missing	14,431 (66%)	576 (73%)	0	0

Table 1 (continued)

	Main study		Data source with all confounders	
	cirrhosis	no cirrhosis	cirrhosis	no cirrhosis
Locoregional treatment				
No treatment	1,350 (6%)	40 (5%)	836 (34%)	19 (19%)
RFA	579 (3%)	62 (8%)	321 (13%)	29 (28%)
TACE	2,028 (9%)	65 (8%)	930 (38%)	33 (32%)
Resection	152 (1%)	16 (2%)	56 (2%)	7 (7%)
Other	114 (1%)	6 (1%)	28 (1%)	5 (5%)
RFA + TACE	266 (1%)	14 (2%)	144 (6%)	3 (3%)
RFA + TACE + other	47 (0%)	2 (0%)	29 (1%)	1 (1%)
Other combinations	184 (1%)	14 (2%)	81 (3%)	6 (6%)
Missing	17,275 (79%)	573 (72%)	0	
Mortality	7,375 (34%)	378 (48%)	500 (21%)	25 (25%)
HCC-specific mortality	1,448 (7%)	141 (18%)	134 (6%)	10 (10%)

Values are presented as *n* (%) unless indicated otherwise. HCC, hepatocellular carcinoma; MELD, Model for End-Stage Liver Disease; RFA, radiofrequency ablation; SD, standard deviation; TACE, transarterial chemoembolization.

$$\beta^*_E = \beta_E - \beta_X \lambda_C / \lambda_{EP},$$

where β^*_E was the calibrated coefficient estimate for cirrhosis and mortality. We used the %blinplus macro [24] to include information on parameter estimates and error-prone and corrected PS models to correct the estimates from the whole population. The %blinplus macro provided the adjusted HR estimates, including 95% confidence intervals (CIs) adjusted for additional uncertainty from the estimation of the measurement error model in the subset data. Mortality was illustrated using Kaplan-Meier plots with 95% CIs including numbers at risk. The analyses were performed using SAS version 9.4 (SAS Institute, Cary, North Carolina, USA) and R version 3.5.1 (R Core Team, Vienna, Austria).

Results

We included 22,787 patients, of whom 21,995 (96.5%) had cirrhosis. Among the patients with cirrhotic livers, 41.2% had hepatitis C-related cirrhosis, 23.9% had alcoholic cirrhosis, and 14.4% had hepatitis B-related cirrhosis. Among the patients without cirrhosis, 23.4% had hepatitis C virus, 11.7% had hepatitis B virus, 9.4% had other hepatitis viruses, and 7% had hemochromatosis. The subset of patients with data on all variables included 2,528, of whom 2,425 (95.9%) had cirrhosis. These patients were comparable to those of the whole dataset regarding baseline characteristics (Table 1). However, the subset patients were more likely to be transplanted in the later part of the period. Patient characteristics were largely comparable between cirrhotic and non-cirrhotic patients except for age and locoregional treatment while on the waiting list. Cirrhotic patients were older and less frequently underwent locoregional treatment (Table 1).

Median survival was 10.7 years (5-year survival 65.5%) for cirrhotic patients and 6.8 years (5-year survival 56.4%) for non-cirrhotic patients. In the unadjusted analysis, non-cirrhotic patients had an increased overall mortality risk with a HR of 1.37 (95% CI 1.23–1.52). Overall mortality is illustrated with a Kaplan-Meier plot in Figure 1. The HR approached unity with increasing adjustment and lastly the CIs included 1 in the PS-calibrated model (Table 2).

In the unadjusted analysis, non-cirrhotic patients had an increased risk of HCC-specific mortality with a HR of 2.62 (95% CI 2.21–3.12). HCC-specific mortality is illustrated in

Liver Cancer 2020;9:455–467
DOI: 10.1159/000507397

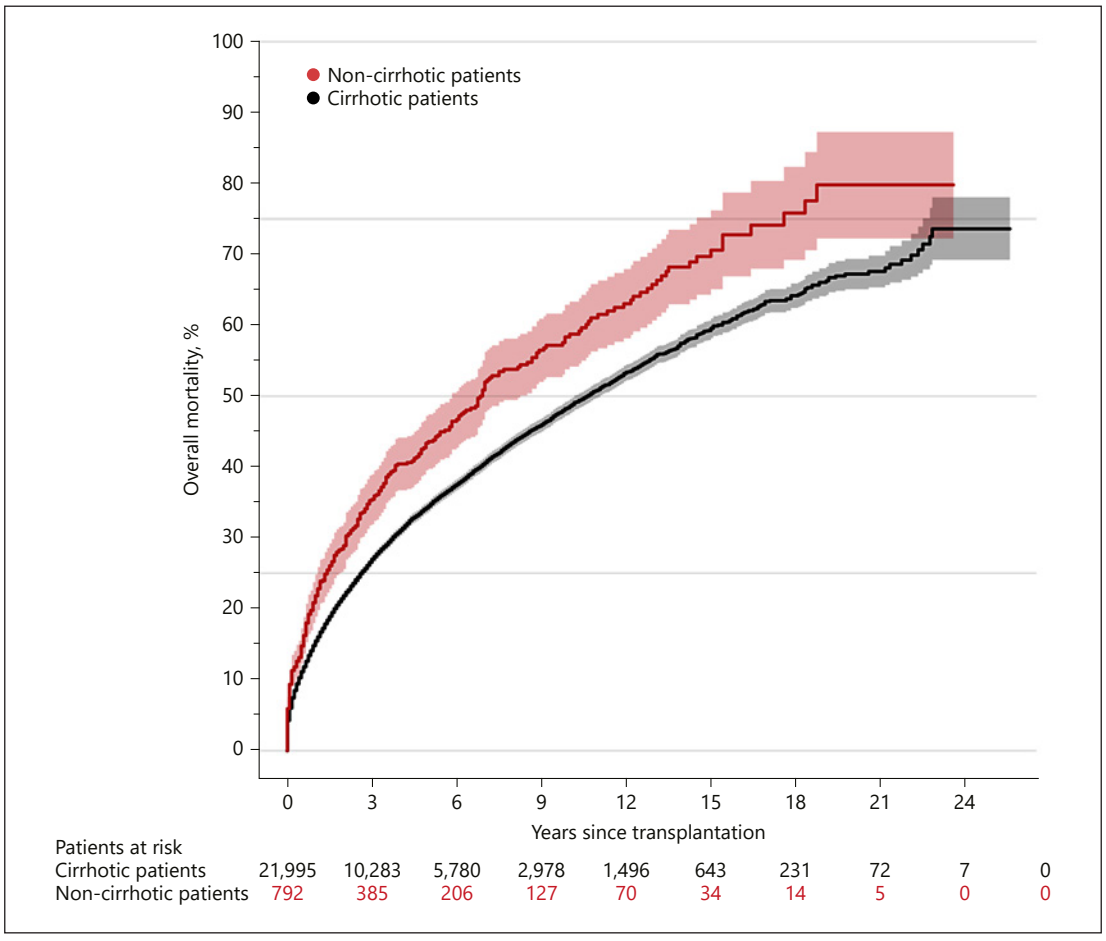

Fig. 1. Kaplan-Meier plot illustrating overall mortality with 95% confidence intervals.

Figure 2. The magnitude of the HR estimate decreased with increasing adjustment. However, the HR remained 1.62 (95% CI 1.31–2.00) in the PS-calibrated model. There was no difference in HR of non-HCC-specific mortality regardless of adjustment between cirrhotic and non-cirrhotic patients (Table 3). Non-HCC-specific mortality is illustrated in Figure 3.

As shown in Table 4, lower age, locoregional treatment, microvascular invasion, and lower MELD score were associated with non-cirrhosis. In addition, the number of surgeries per centre was different between cirrhotic and non-cirrhotic patients, but with no clear pattern.

Discussion

In this study, we showed that differences in overall mortality between cirrhotic and non-cirrhotic patients approached unity when adjusting for unmeasured confounding in the PS-calibrated model. In contrast, HCC-specific mortality remained increased among non-cirrhotic patients in the PS-calibrated model. Furthermore, we showed that patients with non-cirrhotic HCC were younger, had lower MELD scores and a higher risk of microvascular invasion, and received more locoregional treatment.

In a previous study from the ELTR, 105 patients with HCC in non-cirrhotic livers were investigated [7]. Pathological reports were obtained for all patients to confirm absence of

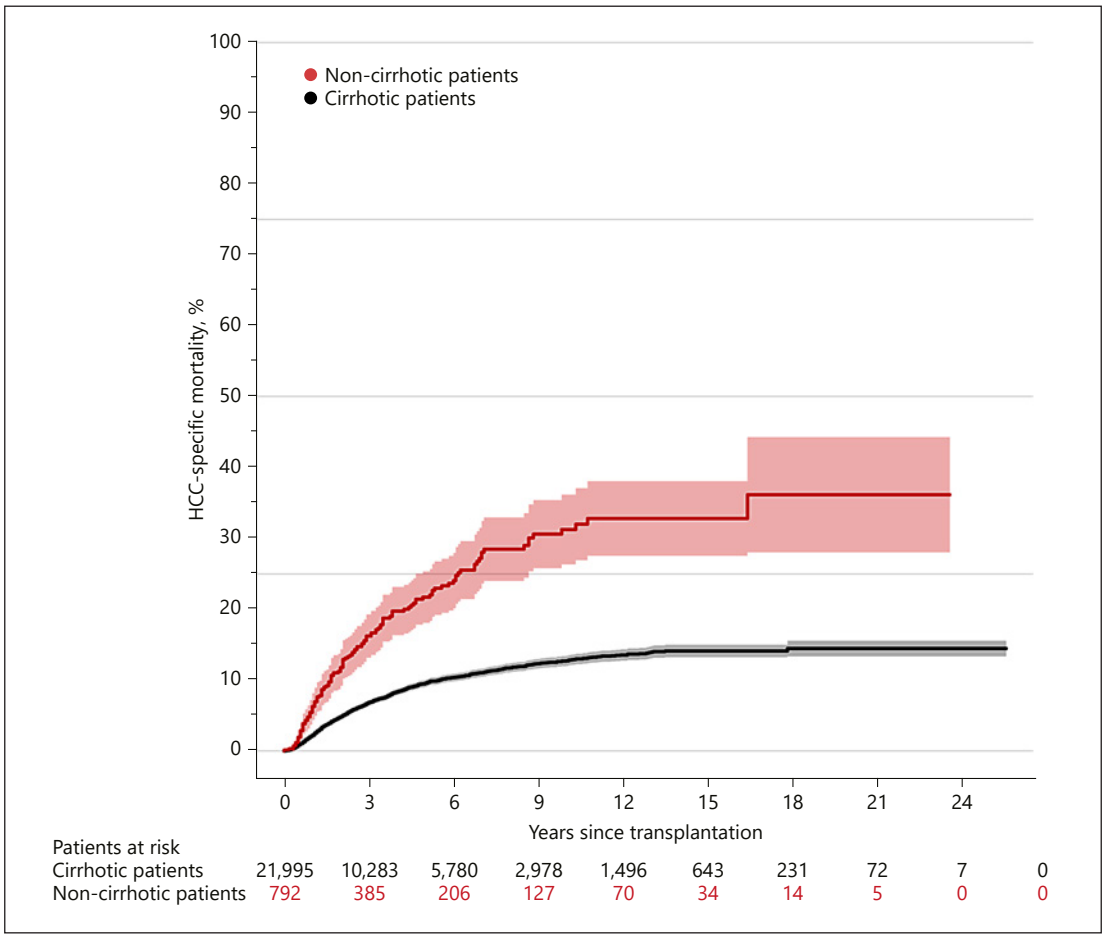

Fig. 2. Kaplan-Meier plot illustrating HCC-specific mortality with 95% confidence intervals. HCC, hepatocellular carcinoma.

underlying liver disease, such as histological signs of inflammation, fibrosis, or cirrhosis. Moreover, patients were to have negative serology testing for hepatitis B and C virus infection. The 5-year overall survival rate was 49% for all patients. However, it increased to 59% in patients without macrovascular invasion or hilar lymph node involvement regardless of tumour size. This is comparable to the results found in the present study and indicates poorer survival after transplantation for non-cirrhotic HCC compared with a 5-year overall survival rate of 75% for cirrhotic patients inside the Milan criteria from the ELTR [8].

In a study combining resected and transplanted patients, 138 cirrhotic and 50 non-cirrhotic patients were compared with a mean follow-up of 39 months [5]. Vascular invasion, larger tumour size, advanced stage, and less differentiated tumours were more frequent for non-cirrhotic patients. Overall survival was similar. However, recurrence was more common in non-cirrhotic patients (36 vs. 18%, $p = 0.008$). Another study evaluated 127 non-cirrhotic, 129 Child-Pugh A cirrhotic, and 37 Child-Pugh B cirrhotic patients inside the Milan criteria undergoing liver resection [9]. The 5-year overall survival was 80 and 47% for non-cirrhotic and cirrhotic patients, respectively ($p < 0.0001$), whereas the 5-year recurrence rate was 54 and 81% for non-cirrhotic and cirrhotic patients, respectively ($p < 0.0001$). The authors speculated that recurrence in cirrhotic patients may be a result of multicentric carcinogenesis limiting the usefulness of resection in cirrhotic patients.

Liver Cancer 2020;9:455–467
DOI: 10.1159/000507397
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Table 2. Cox regression model of the effect of cirrhosis on mortality

	Cases with event	IR[1]	Unadjusted	Age- and sex-adjusted	Adjusted[2]	PS-adjusted[3]	PS-calibrated[4]
Cirrhosis	7,375	68.5	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
No cirrhosis	378	91.7	1.37 (1.23–1.52)	1.48 (1.33–1.65)	1.27 (1.14–1.42)	1.23 (1.11–1.37)	1.11 (0.99–1.25)

IR, incidence rate; PS, propensity score. [1] IR per 10,000 person-years. [2] Adjusted for age, sex, year of, surgery and size of centre (variables without missing). [3] Adjusted for crude PS based on sex, age, sex-age interaction, year of surgery, and size of centre. [4] PS calibrated with crude PS as note (2) and corrected PS model including sex, age, sex-age interaction, year of surgery, size of centre, time on waiting list, number of nodules, vascular invasion, maximum tumour size, locoregional treatment, and Model for End-Stage Liver Disease score.

Table 3. Cox regression model of the effect of cirrhosis on HCC- and non-HCC-specific mortality

	Cases with event	IR[1]	Unadjusted	Age- and sex-adjusted	Adjusted[2]	PS-adjusted[3]	PS-calibrated[4]
HCC-specific mortality							
Cirrhosis	1,448	13.4	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
No cirrhosis	141	34.2	2.62 (2.21–3.12)	2.64 (2.20–3.16)	2.08 (1.73–2.50)	2.03 (1.68–2.44)	1.62 (1.31–2.00)
Non-HCC-specific mortality							
Cirrhosis	5,927	55.0	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
No cirrhosis	237	57.5	1.06 (0.93–1.21)	1.18 (1.03–1.34)	1.03 (0.91–1.18)	1.01 (0.88–1.16)	0.96 (0.83–1.11)

HCC, hepatocellular carcinoma; IR, incidence rate; PS, propensity score. [1] IR per 10,000 person-years. [2] Adjusted for age, sex, year of surgery, and size of centre (variables without missing). [3] Adjusted for crude PS based on sex, age, sex-age interaction, year of surgery, and size of centre. [4] PS calibrated with crude PS as note (2) and corrected PS model including sex, age, sex-age interaction, year of surgery, size of centre, time on waiting list, number of nodules, vascular invasion, maximum tumour size, locoregional treatment, and Model for End-Stage Liver Disease score.

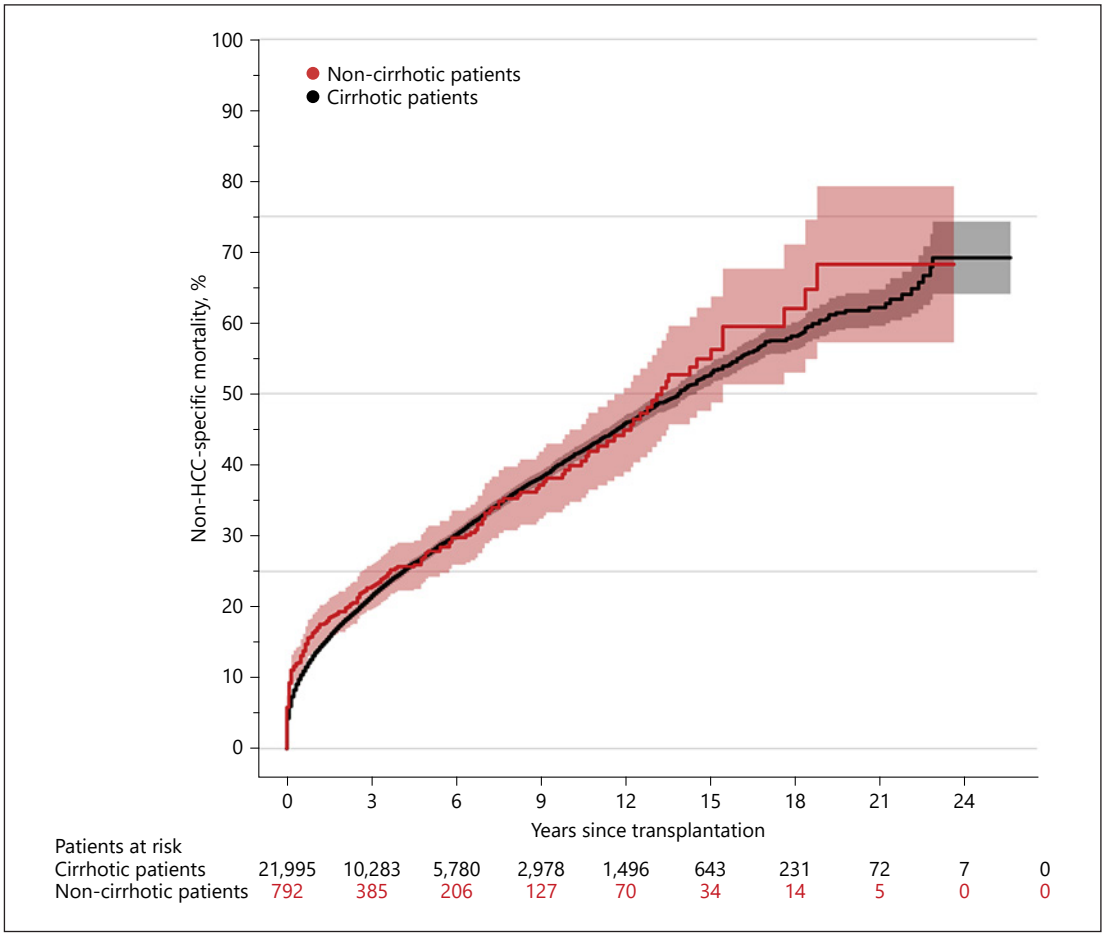

Fig. 3. Kaplan-Meier plot illustrating non-HCC-specific mortality with 95% confidence intervals. HCC, hepatocellular carcinoma.

In a study investigating genetic changes in HCC tumours with comparative genomic hybridization, a marked difference in genomic alterations between non-cirrhotic and cirrhotic HCC was found [25]. Non-cirrhotic HCC exhibited more genomic variants, in particular copy number gain on chromosome 8q, thus supporting a separate tumour biology for non-cirrhotic HCC.

The present study is the largest to date to investigate transplantation in non-cirrhotic patients with HCC. Moreover, the study is the first of its kind to use PS calibration to adjust for unmeasured confounding, which may be a major issue in database studies [11, 12]. Included patients were comparable with respect to background liver disease and accompanying comorbidity, which strongly affects outcome. However, non-cirrhotic patients are generally younger and may be treated differently. Closer follow-up and more focus on recurrence may lead to bias in reporting of HCC-specific mortality. The present study was based on a pretransplant diagnosis of non-cirrhosis, which may be inaccurate. However, it represents the scenario on which the clinical decision to select patients for transplantation is taken. Furthermore, studies have indicated that immunosuppression with the mammalian target of rapamycin inhibitor sirolimus improved prognosis in patients transplanted for HCC [26, 27]. Variables regarding immunosuppression are included in the ELTR database. However, due to the quality and structure of available data, meaningful analyses were not possible. Thus, we

Table 4. Logistic regression model of association between variables included in corrected PS model and OR of non-cirrhotic HCC; data source with all confounders (n = 2,528)

	OR (95% CI)	p value
Female	1.00 (0.55–1.83)	0.98
Male	1.00 (ref.)	
Age (per 10 years)	0.62 (0.52–0.73)	<0.0001
Operation year		0.33
1991–2004	1.24 (0.25–6.29)	
2005–2006	1.70 (0.56–5.20)	
2007	1.86 (0.70–4.94)	
2008	1.00 (ref.)	
2009	1.87 (0.77–4.57)	
2010	1.57 (0.62–3.99)	
2011	1.28 (0.52–3.17)	
2012	1.82 (0.77–4.31)	
2013	1.59 (0.61–4.16)	
2014	0.59 (0.17–2.11)	
2015–2016	0.50 (0.13–1.96)	
Number of surgeries in centre		<0.0001
1–10	0.44 (0.06–3.19)	
11–25	0.34 (0.04–2.58)	
26–50	0.33 (0.04–2.64)	
51–100	0.16 (0.06–0.49)	
101–250	1.00 (ref.)	
>250	0.10 (0.05–0.19)	
Waiting time		0.87
0–26 days	1.00 (ref.)	
27–80 days	1.00 (0.54–1.85)	
81–208 days	0.80 (0.43–1.49)	
>208 days	0.90 (0.49–1.68)	
Size of largest HCC tumour, mm	1.00 (0.99–1.01)	0.85
MELD score	0.95 (0.91–0.99)	0.01
Number of HCC tumours	1.01 (0.91–1.11)	0.91
Vascular invasion		0.08
No vascular invasion	1.00 (ref.)	
Macrovascular invasion	0.77 (0.17–3.43)	
Microvascular invasion	1.81 (1.07–3.06)	
Locoregional treatment		<0.0001
No treatment	1.00 (ref.)	
RFA + TACE	2.16 (0.59–7.86)	
TACE	2.99 (1.58–5.67)	
RFA + TACE + other	3.74 (0.44–31.46)	
Other combinations	6.51 (2.28–18.61)	
Resection	8.78 (3.26–23.68)	
RFA	10.87 (5.46–21.66)	
Other	11.25 (2.90–43.72)	

CI, confidence interval; HCC, hepatocellular carcinoma; MELD, Model for End-Stage Liver Disease; OR, odds ratio; PS, propensity score; RFA, radiofrequency ablation; TACE, transarterial chemoembolization.

could not account for the fact that some patients were treated with sirolimus. Lastly, additional confounding from variables not available in the ELTR database could not be corrected for. Among these, pretransplant alpha-fetoprotein is considered an important prognostic variable [28–30], and sarcopenia has been associated with lower survival after living donor liver transplantation for any indication [31, 32] and higher recurrence risk after living donor liver transplantation for HCC [33].

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DOI: 10.1159/000507397

The implication of the present study may be more strict transplantation selection criteria for non-cirrhotic patients in the future. Promising new methods to include alpha-fetoprotein [28–30] in transplantation criteria need to be validated for non-cirrhotic patients. Positron emission tomography/computed tomography may be used for staging of non-cirrhotic patients as it provides accuracy superior to that of conventional imaging [34]. Locoregional treatment before transplantation may be considered standard regardless of tumour characteristics. Thus, response to such treatment could be used to select patients with acceptable prognosis [35].

In conclusion, using a method to account for unmeasured confounding in the large ELTR database, this study showed that HCC in non-cirrhotic livers may represent a more aggressive cancer form with different tumour biology. Thus, differences in recurrence rates could not be explained by differences in patient and tumour characteristics registered in the ELTR database. However, the magnitude of the estimates decreased after adjusting for unmeasured confounding, indicating that HCC in non-cirrhotic patients shares risk factors with HCC in cirrhotic patients.

Acknowledgements

Thanks to all the centres that contribute to the ELTR. The Organ Sharing Organizations the French ABM (Sami Djabbour and Alain Jolly), the Dutch NTS (Cynthia Konijn), the Eurotransplant Foundation (Undine Samuel and Marieke Van Meel), the Spanish ONT (Gloria de la Rosa), and the UK-Ireland NHSBT (Mike Chilton and Julia Micciche) are acknowledged for data cross-check and sharing with the ELTR.

Statement of Ethics

This study was based solely on registry data. Thus, ethics approval was not required.

Disclosure Statement

The authors have no conflicts of interest to declare.

Funding Sources

The ELTR is supported by grants from Astellas, Novartis, Institut Georges Lopez, and Sandoz and logistic support from the Paul Brousse Hospital (Assistance Publique – Hôpitaux de Paris).

Author Contributions

H.-C. Pommergaard: conception and design, data analysis and interpretation of results, writing of the first draft, critical revision, final approval. A.A. Rostved and L.C. Thygesen: conception and design, interpretation of results, critical revision, final approval. R. Adam, V. Karam, and C. Duvoux: conception and design, acquisition of data, critical revision, final approval. A. Rasmussen: conception and design, interpretation of results, acquisition of data, critical revision, final approval. M. Salizzoni, M.A.G. Bravo, D. Cherqui, P. De Simone, P. Houssel-Debry, V. Mazzaferro, O. Soubrane, J.C. García-Valdecasas, J.F. Prous, A.D. Pinna, and J. O'Grady: acquisition of data, critical revision, final approval.

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