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# Hepatocellular carcinoma in cirrhotic versus noncirrhotic livers: results from a large cohort in the Netherlands

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**Objectives** Hepatocellular carcinoma (HCC) usually occurs in patients with cirrhosis, but can also develop in noncirrhotic livers. In the present study we explored associated risk factors for HCC without cirrhosis and compared patient and tumor characteristics and outcomes in HCC patients with and without underlying cirrhosis.

**Methods** Patients with HCC diagnosed in the period 2005–2012 in five Dutch academic centers were evaluated. Patients were categorized according to the presence of cirrhosis on the basis of histology or combined radiological and laboratory features.

**Results** In total, 19% of the 1221 HCC patients had no underlying cirrhosis. Noncirrhotic HCC patients were more likely to be female and to have nonalcoholic fatty liver disease or no risk factors for underlying liver disease, and less likely to have hepatitis C virus or alcohol-related liver disease than did cirrhotic HCC patients. HCCs in noncirrhotic livers were more often unifocal (67 vs. 48%), but tumor size was significantly larger (8 vs. 4 cm). Despite the larger tumors, more patients underwent resection (50 vs. 10%) and overall survival was significantly better than in cirrhotics. In multivariate analyses, absence of cirrhosis [hazard ratio (HR) 0.49, 95% confidence interval (CI) 0.38–0.63] and presence of hepatitis B (HR 0.68, 95% CI 0.51–0.91) were independent predictors for lower mortality, whereas hepatitis C virus was associated with higher mortality (HR 1.32, 95% CI 1.01–1.65).

**Conclusion** HCC without cirrhosis was strongly associated with female sex and presence of nonalcoholic fatty liver disease or no risk factors for underlying liver disease. In absence of cirrhosis, resections were more often performed, with better survival despite larger tumor size. *Eur J Gastroenterol Hepatol* 28:352–359

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## Introduction

Primary liver cancer is the sixth most common cancer in the world and the second cause of cancer-related death [1]. Hepatocellular carcinoma (HCC) represents more than 90% of all primary liver cancers and typically occurs in patients with underlying cirrhosis. Nevertheless, HCC can also develop in noncirrhotic livers. On the basis of previous studies, the proportion of HCC in the absence of cirrhosis varied widely (from 2 to 54%) between various geographical regions [2–7]. This may be the consequence

of different patterns of underlying risk factors, such as viral hepatitis, alcohol abuse, and nonalcoholic fatty liver disease (NAFLD).

Currently, NAFLD is a leading cause of chronic liver disease in the Western countries and its prevalence is expected to increase further [8,9]. There is emerging evidence that presence of NAFLD and features of metabolic syndrome are associated with HCC [10–15]. Increased HCC risk seems to affect especially those with cirrhosis. Nevertheless, it has recently been demonstrated that in noncirrhotic livers, presence of NAFLD, and especially nonalcoholic steatohepatitis, is strongly associated with HCC [13,16–18]. Furthermore, steatosis is often present as a cofactor in patients with other risk factors for underlying liver disease [19].

The severity of the underlying liver disease has a great impact on treatment decisions and prognosis in HCC patients: presence of cirrhosis and resulting impaired liver function may limit surgical and nonsurgical options. In contrast, absence of cirrhosis could favor use of surgical treatment with curative intent [6,20,21]. Available data also suggest that etiology of underlying liver disease in HCC patients may influence outcomes [22].

In the present study we explored the prevalence of HCC in absence of cirrhosis and investigated associated risk factors in a large cohort of HCC patients. Furthermore, we compared patient and tumor characteristics as well as outcomes in HCC patients with and without underlying

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cirrhosis and with various causes of underlying liver disease.

## Methods

All patients with an HCC diagnosis in the period 2005–2012 in five major Dutch academic centers were evaluated. Diagnosis of HCC was based on AASLD 2005 and 2011 guideline criteria [23,24]. Data on the influence of HCC surveillance in the same cohort have recently been reported [25]. Collected data were obtained from (electronic) medical records. Extensive efforts were made to clarify all missing data – for example, by contacting patients, or referring hospitals or general practitioners.

Patients were categorized according to the presence or absence of cirrhosis. Patients were included in the ‘no cirrhosis’ group on the basis of the following criteria as essentially proposed by El-Serag *et al.* [26]: (A) histology without cirrhosis either in biopsy within 1 year of HCC diagnosis or in a resection specimen in combination with absence of radiological features of cirrhosis, or (B) (in absence of liver histology) all three of the following criteria: (1) an aspartate aminotransferase to platelet ratio index less than or equal to 1, (2) two of the following three laboratory tests within normal range: (a) albumin greater than 35 g/l, (b) platelet counts greater than  $200 \times 10^9/l$ , (c) international normalized ratio less than 1.1, and (3) absence of radiological features of cirrhosis. The aspartate aminotransferase to platelet ratio index score was calculated using the following formula: (aspartate aminotransferase/upper limit of normal)/(platelet count  $\times 100$ ) [27]. Patients who had histology demonstrating cirrhosis or (in absence of histology) clear radiological features of cirrhosis and/or did not fulfill the above mentioned criteria for the ‘no cirrhosis’ group were included in the ‘cirrhosis’ group.

Information was collected on the cause of underlying liver disease: (a) alcohol-related liver disease (defined as a history of average alcohol use more than or equal to three alcoholic drinks/day [28]), (b) hepatitis B virus (HBV), (c) hepatitis C virus (HCV), (d) hemochromatosis, (e) NAFLD (defined as steatosis greater than 5%, steatohepatitis on liver biopsy, or presence of metabolic syndrome in the absence of other risk factors for chronic liver disease, such as alcohol abuse), (f) others, or (g) absence of any risk factors for underlying liver disease. Finally, data on tumor characteristics [e.g. number of tumor lesions, maximum diameter of the largest tumor lesion, and tumor stage according to Barcelona Clinic Liver Cancer (BCLC) staging system], laboratory values at time of diagnosis, applied treatment(s), and survival data were obtained for each patient. Patients were categorized into treatment groups on the basis of application of surgical therapy (resection or transplantation), radiofrequency ablation (RFA), transcatheter arterial chemoembolization (TACE) or transarterial radioembolization (TARE), systemic therapy (sorafenib) or best supportive care. Patients undergoing sequential therapy appertaining to two or more treatment groups were included in the treatment group that was presumed to have most impact on outcome. In case of RFA and subsequently TACE with at least a 1 month interval, patients were included in the RFA group. When a combination of RFA and TACE was performed

within a 1 month interval, patients were included in the TACE group.

This study was conducted in agreement with the ethical guidelines of the Declaration of Helsinki, and analyses were carried out with institutional medical ethical consent, in an anonymized database.

## Statistical analysis

Continuous data were expressed as means and SDs or, in case of a nonparametric distribution, as medians and ranges, and discrete variables were expressed as absolute and relative frequencies. Independent samples *t*-test, one-way analysis of variance, Mann–Whitney *U* or Kruskal–Wallis tests were applied to compare continuous data in the ‘cirrhosis’ versus ‘no cirrhosis’ groups. Post-hoc analyses using analysis of variance with Bonferroni correction were performed to compare the five major etiology groups. Categorical variables were compared with Pearson’s  $\chi^2$  or Fisher’s exact tests.

Univariate and multivariate logistic regression analyses were performed to evaluate patient characteristics (i.e. sex, age, and etiology of underlying liver disease) associated with risk of HCC in absence of cirrhosis.

Survival time was calculated from date of diagnosis to date of death or end of follow-up (latest: end of study 1 January 2013). The Kaplan–Meier survival curves and log-rank tests were used to compare survival rates between the cirrhotic and noncirrhotic patients in the total group and between the five major etiology groups: HBV, HCV, alcohol-related liver disease, NAFLD, and absence of risk factors for underlying liver disease. Survival between cirrhotic and noncirrhotic patients was also evaluated separately in the different treatment groups, except for RFA as this treatment was almost exclusively performed in cirrhotic patients. Possible predictors for overall mortality were tested using univariate and multivariate Cox proportional hazard regression. Besides the presence of cirrhosis and etiology of underlying liver disease, sex, age, tumor size, number of tumor lesions, BCLC stage, and year of HCC diagnosis were included. Factors with a *P*-value of less than 0.1 in univariate analyses were included in subsequent multivariate analyses. A two-sided *P*-value of less than 0.05 was considered statistically significant. Statistical analysis was performed using IBM SPSS statistics (version 20.0; IBM Corp., Armonk, New York, USA).

## Results

In the period January 2005–December 2012, 1290 HCC patients were under care in five academic hospitals (i.e. ~60% of all Dutch HCC patients in this period [29]). After the exclusion of 69 patients because of missing data, 1221 patients (95%) were included in this study.

### Patient and clinical characteristics in the ‘cirrhosis’ versus ‘no cirrhosis’ groups

In total, 983 of the 1221 included patients (81%) had underlying cirrhosis, without change during the study period. In 238 patients (19%) no cirrhosis was present: fibrosis grade was less than or equal to F2 in 148 patients (62% of all noncirrhotic patients), F3 in 19 (8%), and unknown in 71 (30%). Patient characteristics of all HCC

**Table 1.** Patient characteristics of 1221 cases with hepatocellular carcinoma subdivided according to presence or absence of cirrhosis

	Total group	Cirrhosis	No cirrhosis	<i>P</i> -value <sup>a</sup>
Patient number	1221 (100)	983 (81)	238 (19)	
Male sex	936 (77)	779 (79)	157 (66)	<b>&lt; 0.001</b>
Age at HCC diagnosis	63 (8–91)	63 (8–91)	65 (11–88)	0.514
BMI [mean (SD)]	26.7 (5.0)	27.1 (5.0)	25.4 (4.7)	<b>&lt; 0.001</b>
Etiology				<b>&lt; 0.001</b>
Alcohol	349 (29)	312 (32)	37 (16)	
Chronic viral hepatitis				
HBV	197 (16)	162 (16)	35 (15)	
HCV	249 (20)	236 (24)	13 (6)	
Coinfection	19 (2)	18 (2)	1 (< 1)	
Hemochromatosis	37 (3)	29 (3)	8 (3)	
NAFLD	181 (15)	114 (12)	67 (28)	
Others	43 (3)	39 (4)	4 (2)	
No risk factors known	146 (12)	73 (7)	73 (30)	
ALT (U/l)	47 (4–1193)	49 (4–1193)	39 (8–712)	<b>&lt; 0.001</b>
AST (U/l)	66 (14–8678)	71 (15–8678)	46 (14–1344)	<b>&lt; 0.001</b>
Albumin	38 (13–62)	37 (13–58)	43 (16–62)	<b>&lt; 0.001</b>
Platelets	146 (8–985)	125 (8–985)	259 (62–724)	<b>&lt; 0.001</b>
INR	1.1 (0.8–2.9)	1.2 (0.8–2.9)	1.0 (0.8–1.8)	<b>&lt; 0.001</b>
PT	13.9 (9.7–36.7)	14.3 (10.0–36.2)	12.3 (9.7–36.7)	<b>&lt; 0.001</b>
APRI	1.6 (0.1–304)	2.0 (0.1–304)	0.6 (0.1–32)	<b>&lt; 0.001</b>
MELD score	9 (6–33)	10 (6–33)	7 (6–29)	<b>&lt; 0.001</b>

Results indicate numbers and, between brackets, percentages. Continuous variables reported as medians and, between brackets, ranges unless otherwise indicated.

Significant *P*-values are in bold.

ALT, alanine transaminase; APRI, aspartate aminotransferase to platelet ratio index; AST, aspartate aminotransaminase; coinfection, HBV + HCV infection; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; INR, international normalized ratio; MELD, Model For End-Stage Liver Disease; NAFLD, nonalcoholic fatty liver disease; PT, prothrombin time.

<sup>a</sup>*P*-value applies to the 'cirrhosis' versus 'no cirrhosis' groups.

patients, and separately for the 'cirrhosis' and 'no cirrhosis' groups, are given in Table 1. Median age at the time of HCC diagnosis was 63 years (range: 8–91 years) and did not differ between the two groups. Proportion of men was significantly lower in noncirrhotic patients than in cirrhotic patients (66 vs. 79%;  $P < 0.001$ ). BMI was also significantly lower in noncirrhotic than in cirrhotic patients (25.4 vs. 27.1 kg/m<sup>2</sup>,  $P < 0.001$ ). Furthermore, presence of NAFLD (12 vs. 28%) and absence of risk factors for underlying liver disease (idiopathic HCC; 7 vs. 30%) were more common in patients without cirrhosis than in those with cirrhosis. On the other hand, cirrhotic HCC patients were more likely to have alcohol-related liver disease (32 vs. 16%) and HCV (24 vs. 6%). The contribution of HBV-related HCC was similar in the 'cirrhosis' and 'no cirrhosis' groups (16 vs. 15%) (Table 1). Of the 37 patients with hemochromatosis (29 and eight in the 'cirrhosis' and 'no cirrhosis' groups, respectively), diagnosis was based on positive genetic testing in 41%, whereas in 59% of patients diagnosis was based on laboratory features (i.e. highly increased ferritin and high iron saturation) and typical histopathological characteristics of hemochromatosis.

#### Risk factors for HCC in absence of cirrhosis

In multivariate analysis, absence of risk factors for underlying chronic liver disease [odds ratio (OR): 4.28, 95% confidence interval (CI) 2.58–7.10], presence of NAFLD (OR: 2.59, 95% CI 1.58–4.26), and female sex (OR: 1.44, 95% CI 1.01–2.05) were independent risk factors for HCC in absence of cirrhosis. In contrast, presence of alcohol-related liver disease (OR: 0.56, 95% CI 0.33–0.93) and HCV (OR: 0.25, 95% CI 0.13–0.48) were less often present in HCC patients with noncirrhotic livers (Table 2).

#### Tumor characteristics in the 'cirrhosis' versus 'no cirrhosis' groups

Number of tumor lesions differed significantly between the cirrhotic and noncirrhotic patients: unifocal HCC was significantly more common in patients without cirrhosis (48 vs. 67%), whereas proportion of multifocal or diffuse HCC was higher in patients with cirrhosis (32 vs. 23%) ( $P < 0.001$ ) (Table 3). Nevertheless, tumor size was significantly larger in noncirrhotic patients than in cirrhotic patients (median tumor size: 8 vs. 4 cm;  $P < 0.001$ ). In patients with cirrhosis, HCC was detected at an earlier tumor stage (BCLC 0 and A combined: 38 vs. 19%) than in patients without cirrhosis.  $\alpha$ -Fetoprotein level was significantly higher in patients with cirrhosis than in those without cirrhosis (35 vs. 10  $\mu$ g/l;  $P < 0.001$ ) (Table 3).

#### Treatment in the 'cirrhosis' versus 'no cirrhosis' groups

Despite the larger tumor size in patients without cirrhosis, overall proportion of patients who received surgical therapy was higher than in cirrhotic patients (53 vs. 22%): resection was more often performed in patients without cirrhosis (50 vs. 10%), whereas more patients with cirrhosis underwent transplantation (12 vs. 2%) (Table 3). RFA (15 vs. 2%) and TACE/TARE (18 vs. 13%) were also more often performed in cirrhotic patients. Proportion of patients who received sorafenib was higher in patients without cirrhosis (14 vs. 8%). Almost one-third of the cirrhotic patients received only best supportive care, whereas this was the case only in 15% of the noncirrhotic patients (Table 3).

#### Survival in 'cirrhosis' versus 'no cirrhosis' groups

Data on vital status at the end of the study were available in 1148 patients (94% of all included patients). Median

**Table 2.** Association between patient characteristics and the occurrence of hepatocellular carcinoma in absence of cirrhosis: univariate and multivariate logistic regression analysis

Variables	Patients (n = 1221)	Univariate analysis			Multivariate analysis	
		OR	95% CI	P-value	OR	95% CI
Sex						
Male	936 (77)	Ref.	–	<b>&lt; 0.001</b>	Ref.	–
Female	285 (23)	<b>1.97</b>	<b>1.45–2.68</b>		<b>1.44</b>	<b>1.01–2.05</b>
Age at HCC diagnosis (years)						
≤ 62	585 (48)	0.81	0.61–1.08	0.137	1.05	0.75–1.45
> 62	636 (52)	Ref.	–		Ref.	–
Etiology						
Alcohol	349 (29)	<b>0.55</b>	<b>0.33–0.91</b>	<b>&lt; 0.001</b>	<b>0.56</b>	<b>0.33–0.93</b>
Hepatitis B	197 (16)	Ref.	–		Ref.	–
Hepatitis C	249 (20)	<b>0.26</b>	<b>0.13–0.50</b>		<b>0.25</b>	<b>0.13–0.48</b>
Coinfection	19 (2)	0.26	0.03–1.99		0.26	0.03–2.03
Hemochromatosis	37 (3)	1.28	0.54–3.03		1.34	0.56–3.24
NAFLD	181 (15)	<b>2.72</b>	<b>1.69–4.37</b>		<b>2.59</b>	<b>1.58–4.26</b>
Other	43 (3)	0.48	0.16–1.42		0.41	0.14–1.24
No risk factors known	146 (12)	<b>4.63</b>	<b>2.84–7.55</b>		<b>4.28</b>	<b>2.58–7.10</b>

Values in parentheses are percentages.

Significant odds ratios, 95% CIs and P-values are in bold.

CI, confidence interval; coinfection, hepatitis B + hepatitis C infection; HCC, hepatocellular carcinoma; NAFLD, nonalcoholic fatty liver disease; OR, odds ratio.

**Table 3.** Tumor characteristics of 1221 patients with hepatocellular carcinoma subdivided according to presence or absence of cirrhosis

	Total group	Cirrhosis	No cirrhosis	P-value <sup>a</sup>
Patient number	1221 (100)	983 (81)	238 (19)	
Number of lesions				<b>&lt; 0.001</b>
1	632 (52)	473 (48)	159 (67)	
2	152 (12)	132 (14)	20 (8)	
3	68 (6)	63 (6)	5 (2)	
Multifocal/diffuse	369 (30)	315 (32)	54 (23)	
Tumor size (cm)	5 (1–26)	4 (1–26)	8 (1–26)	<b>&lt; 0.001</b>
BCLC stage				<b>&lt; 0.001</b>
0	75 (6)	72 (7)	3 (1)	
A	345 (28)	301 (31)	44 (18)	
B	406 (33)	274 (28)	132 (56)	
C	299 (25)	247 (25)	52 (22)	
D	96 (8)	89 (9)	7 (3)	
α-Fetoprotein (μg/l)	29 (1–2.7 × 10 <sup>6</sup> )	35 (1–1.8 × 10 <sup>6</sup> )	10 (1–2.7 × 10 <sup>6</sup> )	<b>&lt; 0.001</b>
Treatments				<b>&lt; 0.001</b>
Surgical therapy	341 (28)	215 (22)	126 (53)	
Resection	214 (18)	95 (10)	119 (50)	
Transplantation	120 (10)	116 (12)	4 (2)	
Both	6 (< 1)	4 (< 1)	2 (1)	
RFA <sup>b</sup>	149 (12)	145 (15)	4 (2)	
TACE/TARE <sup>c</sup>	207 (17)	176 (18)	31 (13)	
Systemic therapy	118 (10)	85 (8)	33 (14)	
Best supportive care	351 (29)	314 (32)	36 (15)	
Unknown	55 (4)	48 (5)	8 (3)	

Results indicate numbers and, between brackets, percentages. Continuous variables reported as medians and, between brackets, ranges.

Significant P-values are in bold.

BCLC stage, tumor stage according Barcelona Clinic Liver Cancer staging system; RFA, radiofrequency ablation; TACE, transcatheter arterial chemoembolization; TARE, transarterial radioembolization.

<sup>a</sup>P-value applies to 'cirrhosis' versus 'no cirrhosis' groups.

<sup>b</sup>Thirteen patients received RFA and subsequently TACE with more than 1 month interval.

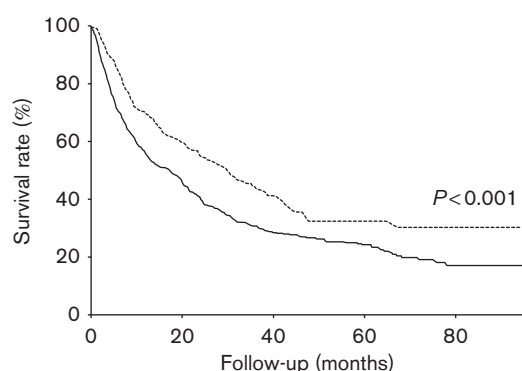
<sup>c</sup>In 31 patients a combination of TACE and RFA within a 1 month interval was performed as initial therapy.

follow-up for both groups was 12 months (range 0.1–95 months). Follow-up time was significantly longer in noncirrhotics than in cirrhotics (15 vs. 11 months;  $P = 0.001$ ). The 1-, 3-, and 5-year survival rates were significantly higher in noncirrhotic patients than in cirrhotic patients (72, 49, and 43% vs. 56, 33, and 29%, respectively) (Fig. 1, log-rank test  $P < 0.001$ ). In multivariate analysis, absence of cirrhosis was an independent predictor for lower overall mortality [hazard ratio (HR) 0.49, 95% CI 0.38–0.63], after adjusting for age, etiology of underlying liver disease, tumor size, number of tumor lesions,

and BCLC stage (Table 4). An age of less than or equal to 62 years (HR 0.76, 95% CI 0.63–0.91) and presence of HBV (HR 0.68, 95% CI 0.51–0.91) were also associated with lower mortality. In contrast, presence of HCV (HR 1.32, 95% CI 1.01–1.65), larger tumor size (HR 1.07, 95% CI 1.04–1.09), multifocal or diffuse HCC (HR 1.64, 95% CI 1.31–2.05), and a more advanced BCLC stage were independent predictors for higher overall mortality (Table 4).

In patients who underwent surgical treatment, absence of cirrhosis (HR 0.38, 95% CI 0.21–0.71) and treatment





**Fig. 1.** Observed survival of patients with hepatocellular carcinoma in the 'cirrhosis' group (solid line) and 'no cirrhosis' group (dotted line) (Kaplan-Meier survival curve; log-rank  $P < 0.001$ ).

with transplantation instead of resection (HR 0.24, 95% CI 0.13–0.42) were both independently associated with

lower overall mortality, after adjustment for etiology of underlying liver disease, tumor size, number of tumor lesions, and BCLC stage. In patients who received TACE or sorafenib treatment, survival was not different between cirrhotic and noncirrhotic patients (results not shown). RFA was almost exclusively performed in cirrhotic patients and therefore impact of cirrhosis could not be evaluated.

#### Patient and clinical characteristics and outcome in relation to etiology of underlying liver disease

Of all the included patients ( $n = 1221$ ), 29% had underlying alcohol-related liver disease, 20% had HCV, 16% had HBV, 15% had NAFLD, and 12% had no risk factors. Patient characteristics were significantly different between the five major etiology groups (in total 1122 patients, included in the following analyses) (Supplementary Table 1, Supplemental digital content 1, <http://links.lww.com/EJGH/A61>). Patients with HBV or HCV who developed HCC were significantly younger than patients with alcohol-related liver disease, NAFLD, or absence of risk factors (median

**Table 4.** Relation between patient/tumor characteristics and mortality in 1148 patients with hepatocellular carcinoma: univariate and multivariate Cox proportional hazard regression analyses

Variables	Patients ( $n = 1148$ )	Univariate analysis			Multivariate analysis	
		HR	95% CI	P-value	HR	95% CI
Presence of cirrhosis						
Yes	919 (80)	Ref.	–	< 0.001	Ref.	–
No	229 (20)	<b>0.67</b>	<b>0.55–0.82</b>		<b>0.49</b>	<b>0.38–0.63</b>
Sex						
Male	879 (77)	Ref.	–	0.46		
Female	269 (23)	0.94	0.79–1.12			
Age at HCC diagnosis (years)						
≤ 62	543 (47)	<b>0.77</b>	<b>0.67–0.90</b>	<b>0.001</b>	<b>0.76</b>	<b>0.63–0.91</b>
> 62	605 (53)	Ref.	–		Ref.	–
Etiology						
Alcohol	334 (29)	Ref.	–	<b>0.001</b>	Ref.	–
Hepatitis B	179 (16)	<b>0.59</b>	<b>0.46–0.75</b>		<b>0.68</b>	<b>0.51–0.91</b>
Hepatitis C	232 (20)	0.84	0.68–1.03		<b>1.32</b>	<b>1.01–1.65</b>
Coinfection	18 (2)	<b>0.44</b>	<b>0.22–0.89</b>		0.71	0.33–1.52
Hemochromatosis	36 (3)	0.96	0.63–1.47		0.94	0.57–1.56
NAFLD	175 (15)	0.90	0.71–1.13		0.92	0.70–1.21
Other	40 (3)	0.81	0.53–1.25		1.30	0.79–2.12
No risk factors known	134 (12)	<b>0.44</b>	<b>0.22–0.89</b>		0.70	0.32–1.49
Tumor size <sup>a</sup>	1008 (88)	<b>1.08</b>	<b>1.06–1.09</b>		<b>1.07</b>	<b>1.04–1.09</b>
Number of tumor lesions						
1	602 (53)	Ref.	–	< 0.001	Ref.	–
2	142 (12)	1.24	0.97–1.59		1.27	0.98–1.65
3	66 (6)	<b>1.55</b>	<b>1.12–2.15</b>		1.29	0.92–1.83
Multifocal (>3)/diffuse	338 (29)	<b>3.93</b>	<b>3.31–4.66</b>		<b>1.64</b>	<b>1.31–2.05</b>
BCLC stage						
0	73 (7)	Ref.	–	< 0.001	Ref.	–
A	334 (29)	1.18	0.77–1.82		1.09	0.70–1.71
B	389 (34)	<b>2.79</b>	<b>1.85–4.22</b>		<b>1.98</b>	<b>1.24–3.17</b>
C	268 (23)	<b>8.07</b>	<b>5.32–12.24</b>		<b>4.46</b>	<b>2.71–7.34</b>
D	84 (7)	<b>10.08</b>	<b>6.38–15.94</b>		<b>7.87</b>	<b>4.75–13.06</b>
Year of HCC diagnosis						
2005	78 (7)	1.06	0.72–1.57	0.15		
2006	81 (7)	0.81	0.54–1.21			
2007	107 (9)	0.83	0.56–1.21			
2008	155 (14)	1.08	0.76–1.54			
2009	170 (15)	1.10	0.77–1.55			
2010	187 (16)	1.21	0.86–1.71			
2011	197 (17)	1.11	0.78–1.59			
2012	173 (15)	Ref.	–			

Values in parentheses are percentages.

Significant hazard ratios, 95% CIs and P-values are in bold.

CI, confidence interval; BCLC stage, tumor stage according Barcelona Clinic Liver Cancer staging system; coinfection, hepatitis B + hepatitis C infection; HR, hazard ratio; NAFLD, nonalcoholic fatty liver disease.

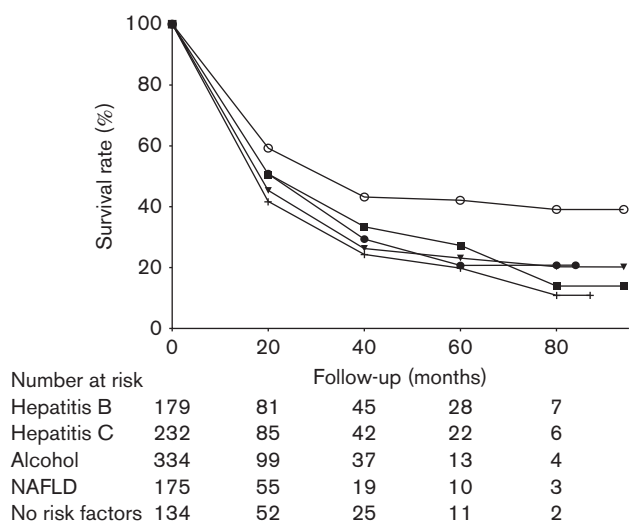
<sup>a</sup>Missing values:  $n = 140$ .

age: 57 and 59 years vs. 65, 67, and 68 years, respectively). Furthermore, female sex was significantly more frequent in patients with NAFLD (34%) or with no risk factors (42%) than in patients with HBV (15%), HCV (21%), or alcohol-related liver disease (15%). BMI was significantly higher in patients with alcohol-related or NAFLD-related HCC (mean BMI 27.8 and 28.9 kg/m<sup>2</sup>, respectively) than in patients with HBV (25.8 kg/m<sup>2</sup>), HCV (26.4 kg/m<sup>2</sup>), or absence of risk factors (24.2 kg/m<sup>2</sup>) (Supplementary Table 1, Supplemental digital content 1, <http://links.lww.com/EJGH/A61>).

Alcohol-related HCCs were significantly more often multifocal or diffuse (38%) than HCCs in patients with HCV, HBV, NAFLD, or no risk factors (range: 24–30%). Furthermore, tumor size was significantly larger in absence of risk factors (9 cm) and smaller in HCV patients (3 cm) than in patients with HBV (4 cm), alcohol-related liver disease (5 cm), or NAFLD (6 cm). BCLC tumor stage was also significantly more advanced in absence of risk factors (BCLC 0 and A combined: 12%) than in HCC patients with other disease etiology (for HBV-related, HCV-related, alcohol-related, or NAFLD-related HCC: BCLC 0 and A combined in 42, 50, 31, and 25%, respectively). Median  $\alpha$ -fetoprotein levels were not significantly different in the various etiology groups (Supplementary Table 2, Supplemental digital content 2, <http://links.lww.com/EJGH/A62>).

Applied treatments differed significantly between the various etiology groups ( $P < 0.001$ ) (Supplementary Table 2, Supplemental digital content 2, <http://links.lww.com/EJGH/A62>). The proportion of patients who received (potentially curative) surgical therapy in general was significantly lower in HCC patients with alcohol-related liver disease (18%) than in patients with HBV, HCV, NAFLD, or absence or risk factors who were treated with surgical therapy in 34, 30, 31, and 33% of cases, respectively. Proportion of patients who underwent resection was significantly higher in case of HBV (22%), NAFLD (25%), or absence of risk factors (27%) than in patients with HCV (14%) or alcohol-related liver disease (8%). In addition, patients with HBV, HCV, or alcohol-related liver disease received significantly more often a liver transplant (11, 15, and 10%, respectively) than did patients with NAFLD or no risk factors (6 and 5%, respectively). RFA was most frequently applied in HCV-related HCC (20%), whereas only 3% of patients without risk factors and 8% of patients with NAFLD received RFA. Proportion of patients who received TACE/TARE ranged between 12 and 20% in the different etiology groups. Furthermore, HCV patients were significantly less often treated with sorafenib (4%) than were patients with HBV, NAFLD, alcohol-related liver disease, or absence of risk factors (9, 11, 12, and 16%, respectively) (Supplementary Table 2, Supplemental digital content 2, <http://links.lww.com/EJGH/A62>).

Survival rates differed significantly between the five major etiology groups (Fig. 2, log-rank test  $P < 0.001$ ). In univariate analysis, survival was significantly longer in HCC patients with HBV (HR 0.59, 95% CI 0.46–0.75, reference group: patients with alcohol-related liver disease) than in the other four etiology groups. Survival rates between the other etiology groups did not differ. As mentioned earlier, in multivariate analyses, presence of HBV (HR 0.68, 95% CI 0.51–0.91) was associated with



**Fig. 2.** Observed survival of patients with hepatocellular carcinoma with underlying hepatitis B (line with open circles), NAFLD (line with solid triangles), hepatitis C (line with solid squares), absence of risk factors (line with solid circles), or alcohol-related liver disease (line with crosses) (Kaplan–Meier survival curve; log-rank  $P < 0.001$ ). NAFLD, nonalcoholic fatty liver disease.

lower mortality. In contrast, presence of HCV (HR 1.32, 95% CI 1.01–1.65) was an independent predictor for higher overall mortality (Table 4).

## Discussion

This study showed that absence of risk factors for underlying liver disease, presence of NAFLD, and female sex were independently associated with HCC in noncirrhotic livers. It has previously been reported that patients who develop HCC in a noncirrhotic liver are younger and that there is a female predominance, although this was not confirmed in other studies [3,6,17]. Despite the larger tumor size and more advanced BCLC tumor stage in HCC patients without cirrhosis, resections were more often performed and survival was significantly better than in cirrhotic patients. In addition, in multivariate analyses, absence of cirrhosis was an independent predictor of longer survival. To the best of our knowledge, the current work represents the largest study assessing the impact of cirrhosis on outcome in an unselected group of cirrhotic and noncirrhotic HCC patients.

Recently, a large cohort study of HCC patients from Germany was published [30]. In line with the results of the current study, cirrhosis was present in 81% of cases and survival was significantly better in noncirrhotic patients. Survival benefit in HCC patients with noncirrhotic livers was also reported in two older studies with cohorts of unselected HCC patients [31,32]. Another study, published in 2005, reported only significant survival differences between patients with compensated liver disease and those with decompensated cirrhosis (Child–Pugh B or C) [33]. Finally, two other recent studies did not find differences in survival rates between cirrhotic and noncirrhotic HCC patients, despite the fact that presence of liver cirrhosis strongly affected HCC treatment choices [17,34]. Consistent with our findings, resection was more often applied in noncirrhotic patients, whereas cirrhotic patients

more often received other treatment modalities. In addition, several studies comparing survival between cirrhotics and noncirrhotics in specific subgroups – for example, after HCC resection – reported that overall and disease-free survivals were significantly better in noncirrhotics [6]. Survival benefit in the total group of noncirrhotic patients may be related to the fact that (potentially curative) surgical therapy was more frequently performed leading to a better outcome. Interestingly, in the current report, transplantation appeared to be associated with better outcome than resection, although patient numbers in the transplantation group were rather small and definite conclusions could not be drawn.

In line with results of previous studies [4,6,17,30,35], causes for underlying liver disease in cirrhotic and noncirrhotic HCC patients were different in our study. Alcohol abuse and viral hepatitis were the most important underlying causes in cirrhotic patients, whereas NAFLD was often present in HCC patients with a noncirrhotic liver. Furthermore, a significant number of noncirrhotic HCC patients proved to have no underlying risk factors despite extensive analyses. The hepatocarcinogenetic pathway of HCC might differ between cirrhotic and noncirrhotic livers, but exact mechanisms are still unclear. In patients with HCV or alcohol-related liver disease, cirrhosis appears to be a prerequisite for HCC development. HBV, on the other hand, could also exert a direct oncogenic effect regardless of presence of cirrhosis. HBV genome integration can lead to host DNA microdeletions and aberrant function of growth regulatory genes in the hepatocyte. In patients with NAFLD, it is thought that oxidative stress (as a result of increased intrahepatic fatty acid levels) may play an important role in the development of hepatocellular damage and HCC development [36].

One interesting finding of the current study is that there are significant differences in applied treatment modalities between patients with various etiologies of underlying liver disease with potential impact on survival. Some previous studies have suggested that cause of underlying liver disease could affect survival, but other studies were not able to confirm this [22,37–39]. In our study, resection was more often applied in patients with HBV, NAFLD, or absence of underlying risk factors for chronic liver disease. In contrast, RFA was most often performed in case of HCV. Moreover, presence of HBV was an independent predictor for lower mortality, whereas presence of HCV was associated with higher mortality. A potential explanation for these findings could be that patients with HBV more often developed HCC before progression to cirrhosis, with a large proportion of solitary lesions. In addition, differences in efficacy of prior antiviral treatment for HBV and HCV could have contributed to these results obtained in a period before introduction of direct-acting anti-HCV agents.

An earlier cross-sectional study in the USA veterans showed that NAFLD and features of metabolic syndrome (hypertension and diabetes) were strongly associated with HCC development in absence of cirrhosis, whereas noncirrhotic HCC patients were less likely to have HCV or alcohol-related liver disease [26]. These results are in line with our findings, although the proportion of noncirrhotic patients was lower in that study (between 3 and 16%) than in our study. A potential explanation for this difference

could be the fact that almost exclusively males were included in the USA veterans study. Unfortunately, details of metabolic syndrome, except BMI values, were not available in the current study. Furthermore, BMI values in our study were not corrected for presence of ascites [40].

Findings of our study are inherently limited by the retrospective study design. In addition, only patients who were diagnosed or referred to one of the five major Dutch academic centers were included. HCC patients with a very poor prognosis were possibly not referred and thus not included in the current cohort. Furthermore, the term ‘noncirrhotic’ involves a heterogeneous group of conditions ranging from chronic hepatitis with stage III fibrosis to a morphologically healthy liver. Moreover, it may also be difficult to differentiate F3 and F4 on the basis of liver biopsy, especially in case of macronodular cirrhosis.

### Conclusion

In this large cohort of HCC patients in the Netherlands, presence of HCC without cirrhosis was strongly associated with absence of risk factors for underlying liver disease, presence of NAFLD, and female sex. In absence of cirrhosis, resections were more often performed, despite larger tumor size. Survival in noncirrhotic patients was significantly better compared with those with liver cirrhosis.

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### Conflicts of interest

There are no conflicts of interest.

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