Hepatocellular Carcinoma in Non-cirrhotic Liver Arises with a More Advanced Tumoral Appearance: A Single-Center Cohort Study

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Cite this article as: Demirtaş CÖ, Tolu T, Keklikkiran Ç, Özdoğan OC, Gündüz F. Hepatocellular carcinoma in non-cirrhotic liver arises with a more advanced tumoral appearance: A single-center cohort study. *Turk J Gastroenterol.* 2021; 32(8): 685-693.

ABSTRACT

Background: *A small proportion of all hepatocellular carcinomas (HCCs) arise in a non-cirrhotic liver (NCL). However, our knowledge about the HCCs developing in a NCL is scarce. This study was undertaken to investigate the characteristics and survival course of this patient group.*

Methods: *We retrospectively analyzed the database of patients with HCC at a tertiary center during a 10-year period (2009-2019). All demographic, clinical, laboratory, and tumoral features with survival outcomes were compared between the HCC-CL and HCC-NCL groups.*

Results: *Out of 384 HCC cases, 11.2% (n = 43) had no cirrhosis. The dominant etiology in the HCC-NCL group was hepatitis B virus (n = 26, 60.5%), followed by non-alcoholic fatty liver disease (n = 10, 23.2%), and hepatitis C virus (n = 7, 16.3%). The maximum tumor diameter was approximately 2 times larger in the HCC-NCL group (HCC-NCL: 90 mm vs. HCC-CL: 46.5 mm, P < .001). The proportion of patients with vascular (HCC-NCL: 27.9% vs. HCC-CL: 8.6%, P < .001) and extrahepatic invasion (HCC-NCL: 14% vs. HCC-CL: 3%, P = .001) were prominently higher in the HCC-NCL group. Patients with HCC-NCL were less often detected in early-curable stages (BCLC 0-A) than those in the HCC-CL group (HCC-NCL: 16.3% vs. HCC-CL: 34.9%, P = .004). The overall survival was not different between the 2 groups (HCC-NCL: 19.4 ± 9.8 months vs. HCC-CL: 17.5 ± 2.3 months, P = .581).*

Conclusion: *HCC in NCL is diagnosed at more advanced tumoral stages with larger tumor size and more often with vascular and extrahepatic spread. Despite the preserved liver functions, the overall survival is not prolonged in HCCs without cirrhosis, due to the late recognition.*

Keywords: *Non-cirrhotic, hepatocellular carcinoma, liver, cirrhosis*

INTRODUCTION

Hepatocellular carcinoma (HCC) is the fifth most common cancer and the second leading cause of cancer-related deaths globally.[1] Liver cirrhosis is the main risk factor for HCC development, causing necroinflammation and subsequent hepatocellular regeneration. However, a set of HCCs can arise in an underlying solid liver parenchyma without cirrhosis. This unique type of HCC has long been considered as an unusual event, and primarily attributed to chronic hepatitis B virus (HBV) infection. However, evolving data have shown that it can also occur in underlying chronic hepatitis C virus (HCV) and non-alcoholic fatty liver disease (NAFLD), at frequencies that cannot be ignored.[2-5] Besides, some other rare reasons, such as alcohol abuse, hepatic adenoma, dietary exposure to aflatoxin, hereditary hemochromatosis, alpha-1 antitrypsin deficiency, and other factors have been held responsible for some HCCs arising in the non-cirrhotic liver (NCL).[6-9]

The proportion of HCCs in non-cirrhotic liver (HCC-NCL) changes across various geographic regions, from 12% to 50%.[10,11] Till now, the rate of HCCs occurring in the absence of cirrhosis has been reported at around 12% to 20% in the Western countries, whereas it reaches up to 50% in some reports from China and Japan. This increased ratio of HCC-NCL in Asian countries has been attributed to the dominance of HBV etiology. The proportion of HCC-NCL in the Turkish population has been reported as 18.6% in 1 study, but the clinical characteristics and survival outcomes have never been investigated in the Turkish population before.[12]

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Received: ***July 25, 2020*** *Accepted:* ***January 13, 2021*** *Available Online Date:* ***September 8, 2021***

DOI: 10.5152/tjg.2021.20677

The solid structure of the underlying liver parenchyma might make this type of HCC a different entity in terms of etiology, clinical and tumoral presentation, treatment requirements, and prognostic factors. It is generally assumed that HCC in the absence of cirrhosis is usually more suitable for surgical resection, and therefore might have a better prognosis than HCC arising in cirrhotic liver (HCC-CL). Therefore, the purpose of this study is to assess the demographic and clinical features of patients with HCC-NCL, and reveal the disparities with HCC-CL patients, all with Turkish ancestry. Furthermore, we aimed to investigate the specific prognostic factors of patients with HCC-NCL, and compare the survival outcomes with the HCC-CL patients.

MATERIALS AND METHODS

Patient Selection and Data Collection

We retrospectively reviewed the data of 502 patients with HCC at a tertiary center in a 10-year period (February 2009-March 2019). The clinical, demographic, and height/weight measurement data were collected prospectively via paper records. The baseline laboratory results and radiologic data were collected from the hospital's electronic database. Patients with insufficient data at the entry, an uncertain HCC diagnosis, and an eventual diagnosis of cholangiocarcinoma or liver metastasis were excluded. After excluding the ineligible cases, 384 treatment-naive, newly diagnosed patients were enrolled for the study. HCC was diagnosed radiologically and/or histologically using the EASL guidelines.[13] Patients considered initially as non-cirrhotic were confirmed using Mittal's definition of no cirrhosis (Accordingly, patients with histologically proven and/or no features suggestive of cirrhosis on abdominal imaging nearest to HCC diagnosis within the year of HCC diagnosis, and 2 of 3 test values in the normal range based on laboratory results available nearest to HCC diagnosis within 6 months before and 4 weeks after the HCC diagnosis albumin > 3.5 g/L, platelets > 200 000/mL or international normalized < 1.1 was accepted as no cirrhosis).[14]

The Barcelona Clinic Liver Cancer (BCLC) and TNM stages were assigned and confirmed using the collected clinical, radiologic, and laboratory data.[15,16] The initial treatments were recorded and categorized into 4 categories, as follows: (a) curative options, (b) palliative options, (c) combination therapies, and (d) best supportive care. Liver transplantation (LT), resection, and radiofrequency ablation (RFA) were considered curative options, whereas transarterial chemoembolization (TACE), transarterial radioembolization (TARE), and systemic therapies were classified as palliative options.

Survival time was calculated from the date of HCC diagnosis until the date of exact notified death, as retrieved from the hospital records and/or the national death notification system, or censored on March 1, 2020, if alive.

Statistical Analysis

The median and interquartile range (IQR) were used to display continuous skewed data, and mean ± standard deviation (SD) was used if normally distributed. The results of the categorical data were given as absolute numbers with percentage. For the comparison of continuous variables between the HCC-NCL and the HCC-CL group, the Student's *t*-test was used when the data conformed to a normal distribution; otherwise, the Mann–Whitney *U*-test was used. The chi-square test was used to compare categorical parameters. To reveal the parameters influencing survival in the HCC-NCL group, we performed univariate analyses using the log-rank test with Kaplan–Meier curves for categorical variables and Cox-regression analyses for each non-categorical variable. Finally, we performed multivariate analyses with the Cox-regression test, to reveal parameters significantly influencing the survival in the HCC-NCL group. The overall survival rates of the HCC-NCL and the HCC-CL group were compared via the Kaplan–Meier method using the log-rank test. The statistical significance was defined as $P < .05$. All statistical analyses were conducted using the SPSS software Version 20.0 (IBM Corp.; Armonk, NY, USA).

RESULTS

General Comparison of Patients with HCC-NCL and HCC-CL

The demographic and clinical characteristics of patients are exhibited in Table 1. Out of 384 HCC patients analyzed, 43 (11.2%) were confirmed as HCC-NCL. The median age at the time of the diagnosis was 64 (20-89), and approximately every 3 out of 4 (~76%) were men, which did not differ between the HCC-NCL and HCC-CL groups. The 2 groups did not differ with regard to body mass index, concomitant comorbidities, tobacco use, alcohol use, and ECOG performance status. The dominant etiology in the HCC-NCL group was HBV (60.5%, *n* = 26), followed by NASH-cryptogenic (23.2%, *n* = 10),

Table 1. Demographics and Clinical Characteristics

	HCC-NCL (*n* = 43)	HCC-CL (*n* = 341)	*P*
Age, median (IQR), years	64 (20-83)	64 (28-89)	.470
Sex, n (%)			.942
Male	33 (76.7)	260 (76.2)	
Female	10 (23.3)	81 (23.8)	
Body mass index, mean ± SD, kg/m^2	26.9 ± 4.2	27.4 ± 4.9	.590
Obese, n (%)	5 (17.9)	47 (26)	.482
Smoking, n (%)	15 (34.9)	124 (36.4)	.849
Alcohol, n (%)	8 (18.6)	56 (16.4)	.717
Diabetes, n (%)	13 (30.2)	125 (36.7)	.408
Hypertension, n (%)	18 (41.9)	105 (30.8)	.143
Hyperlipidemia, n (%)	12 (27.9)	56 (16.5)	.64
Charlson-comorbidity index, median (IQR)	5 (1-13)	6 (1-13)	.105
ECOG-PS, n (%)			.268
0	36 (83.7)	230 (67.4)	
1	5 (11.6)	69 (20.2)	
2	2 (4.7)	31 (9.1)	
3	-	8 (2.3)	
4	-	3 (0.9)	
Etiology, n (%)			.962
Hepatitis B virus	26 (60.5)	185 (54.3)	
NAFLD/cryptogenic	10 (23.2)	77 (22.5)	
Hepatitis C virus	7 (16.3)	57 (16.7)	
Alcoholic	-	9 (2.6)	
Hepatitis B and hepatitis C virus	-	2 (0.6)	
Hepatitis B and hepatitis D virus	-	7 (2.1)	
Autoimmune hepatitis	-	2 (0.6)	
Primary biliary cholangiopathy	-	1 (0.3)	
Wilson's disease	-	1 (0.3)	
Ascites, n (%)	-	152 (44.6)	-
Hepatic encephalopathy, n (%)	-	23 (6.7)	-
Varices, n (%)	-	199 (60.1)	-
Variceal bleeding, n (%)	-	35 (10.4)	-

ECOG-PS, Eastern Cooperative Oncology Group performance status; HCC-CL, hepatocellular carcinoma with cirrhotic liver; HCC-NCL, hepatocellular carcinoma in non-cirrhotic liver; NAFLD, non-alcoholic fatty liver disease.

and HCV (16.3, *n* = 7), which was similar to the etiologies in the HCC-CL group as well.

The laboratory characteristics of the patients are given in Table 2. Total bilirubin and international normalized ratio (INR) were lower, whereas platelet count and albumin value were higher in the HCC-NCL group, owing to their preserved liver synthesis capacity. Besides, lipid parameters (total cholesterol, low-density lipoprotein, and triglyceride) were detected higher in the HCC-NCL group. Among the calculated scores, AST/PLT, APRI, FIB-4, and ALBI score were found to be lower in the HCC-NCL

Table 2. Laboratory Characteristics

	HCC-NCL median (IQR)	HCC-CL median (IQR)	*P*
Aspartate aminotransferase, U/L	61 (18-636)	53 (13-782)	.635
Alanine aminotransferase, U/L	40 (11-426)	41.5 (7-727)	.715
Alkaline phosphatase, U/L	136 (36-657)	135 (16-661)	.934
Gamma-glutamyl transferase, U/L	102.5 (14-2018)	99.5 (12-1107)	.727
Albumin, g/dL	4 (3.6-4.7)	3.5 (1.3-6.4)	.000*
Total bilirubin, mg/dL	0.83 (0.2-2)	1.23 (0.2-12.8)	.000*
Creatinine, mg/dL	0.83 (0.43-4.7)	0.79 (0.31-7.9)	.665
Sodium, mEq/L	138 (130-142)	137 (121-148)	.540
INR	1.1 (0.9-1.5)	1.24(0.84-3.9)	.000*
Alpha-fetoprotein, ng/mL	25 (1.58-38630)	19.9 (1-371458)	.928
White blood cell, µL/mL	6.900 (3.500-14.400)	5.700 (1.400-25.500)	.002*
Hemoglobin, g/L	13.5 (9.6-17.2)	12.8(6.1-17.8)	.063
Platelet count, $\times 1000/m^3$	227 (141-441)	133.5 (28-538)	.000*
Glucose, mg/dL	117 (74-320)	113 (64-551)	.749
Total cholesterol, mg/dL	170 (118-382)	152 (58-382)	.004*
Low-density lipoprotein, mg/dL	114.8 (65-280)	93 (27-334)	.002*
High-density lipoprotein, mg/dL	38 (17-79)	40 (5-138)	.476
Triglycerides, mg/dL	104 (50-337)	91 (33-356)	.053*
Ferritin, ng/mL	80.8 (3.7-498)	55.4 (3.3-2978)	.615
Uric acid, mg/dL	5.2 (1.6-8.7)	5.1 (2-13.1)	.774
Vitamin B12, pg/mL	295 (50-1500)	418.5 (102-2000)	.084
25-OH vitamin D, ng/mL	15.49 (5.01-85.05)	15.31 (3-71.8)	.623
AST/ALT ratio	1.29 (0.11-3.63)	1.39 (0.26-6.68)	.467
AST/PLT ratio	0.22 (0.05-1.44)	0.44 (0.05-6.05)	.000*
APRI score	0.55 (0.13-3.61)	1.11 (0.12-15.13)	.000*
FIB-4 score	2.58 (0.27-8.99)	4.3 (0.59-37.64)	.000*
ALBI score	−2.64 (−3.57-−2.05)	−2.17 (−4.05-0.02)	.000*
pALBI score	32.92 (−4.2-−2.09)	−2.80 (−4.69-−0.92)	.07
Child–Pugh score	-	6 (5-13)	-
MELD score	-	10.5 (6-21)	-

HCC-CL, hepatocellular carcinoma in cirrhotic liver; HCC-NCL, hepatocellular carcinoma in non-cirrhotic liver; MELD, Model for End-stage Liver Disease; INR, international normalized ratio.
* sign indicates p value <0.05

group, confirming the unimpaired liver functions and the absence of cirrhosis. Other than these, no significant difference was observed in the laboratory parameters between the 2 groups (Table 1).

Tumoral Characteristics of Patients with HCC-NCL and HCC-CL

The tumor-related characteristics are summarized in Table 3. The maximum tumor diameter (MTD) was approximately 2 times larger in the NCL-HCC group (90 mm vs. 46.5 mm, $P < .001$) than the HCC-CL group. The proportion of patients with vascular invasion (27.9% vs. 8.6%, $P < .001$) and extrahepatic metastases (14% vs. 3%, $P = .001$) were prominently higher in the HCC-NCL group as well. Patients with HCC-NCL were less often detected in early stages (BCLC 0-A) than in the HCC-CL group (16.3% vs. 34.9%, $P = .004$). The remaining 83.7% of the HCC-NCL group was beyond candidature for curative

Table 3. Tumor-Related Characteristics

	HCC-NCL (*n* = 43)	HCC-CL (*n* = 341)	*P*
Maximum tumor diameter, median (IQR)	90 (16-200)	46.5 (8-190)	.000*
Number of lesions, n (%)			.842
1	28 (65.1)	208 (61)	
2	6 (14)	43 (12.6)	
3	2 (4.7)	28 (8.2)	
Multiple	7 (16.3)	57 (16.7)	
Diffuse	-	5 (1.3)	
Lobar involvement, n (%)			.409
Unilobar	31 (72.1)	265 (77.7)	
Bilobar	12 (27.9)	76 (22.3)	
Portal vein thrombosis, n (%)	7 (16.3)	79 (23.4)	.295
Lymph node involvement, n (%)	7 (16.3)	62 (18.6)	.715
Vascular invasion, n (%)	12 (27.9)	29 (8.6)	.000*
Extrahepatic metastasis, n (%)	6 (14)	10 (3)	.001*
BCLC staging, n (%)			.04*
0	2 (4.7)	19 (5.6)	
A	5 (11.6)	100 (29.3)	
B	19 (44.2)	113 (33.1)	
C	16 (37.2)	84 (24.6)	
D	1 (2.3)	25 (7.3)	
TNM staging, n (%)			.000*
1	19 (44.2)	161 (47.8)	
2	1 (2.3)	54 (16)	
3A	5 (11.6)	33 (9.8)	
3B	8 (18.6)	21 (6.2)	
3C	4 (9.3)	58 (17.2)	
4	6 (14)	10 (3)	

BCLC, Barcelona clinic liver cancer; HCC-CL, hepatocellular carcinoma with cirrhotic liver; HCC-NCL, hepatocellular carcinoma in non-cirrhotic liver.

treatment options, according to the BCLC algorithm. Similar results were found in the application of the TNM staging system, consistent with the BCLC staging system. The early stages were less common and the advanced stages were more common in the NCL-HCC group (NCL-HCC: TNM I-II, 46.5% and TNM III-IV, 53.5%; vs. CL-HCC: TNM I-II, 63.8% and TNM III-IV, 36.2%; $P < .001$). As a consequence of more advanced tumoral appearance, curative treatment options were less applied to patients with HCC-NCL (19% vs. 33.2%, $P = .05$) despite having preserved liver function. Moreover, approximately two-thirds of the patients with HCC-NCL received palliative treatment options, which was higher than the observed rate in the HCC-CL group (64.3% vs. 42.6%, $P = .008$). The details of initial treatment modalities are presented in Table 4.

Prognostic Factors of Patients with HCC-NCL and Comparison of Survival Outcomes

The factors associated with a higher risk of mortality in the HCC-NCL group were symptomatic presentation at diagnosis ($P = .047$), higher ECOG performance status ($P < .001$), higher MTD ($P < .001$), increased AFP concentration ($P = .044$), presence of extrahepatic metastasis ($P = .018$), and application of curative treatment options ($P = .001$), as seen with univariate analysis. The multivariate

Table 4. Initial Treatment Modalities

	HCC-NCL (n = 43)	HCC-CL (n = 341)	*P*
Curative options, n (%)	8 (19)	110 (33.2)	.05*
Liver transplantation	-	21 (6.3)	
Resection	6 (14.3)	16 (4.8)	
RFA	2 (4.8)	73 (22.1)	
Palliative options, n (%)	27 (64.3)	141 (42.6)	.008*
TACE	19 (45.2)	104 (31.4)	
Systemic therapy	6 (14.3)	21 (6.3)	
TARE	2 (4.8)	16 (4.8)	
Best supportive care, n (%)	5 (11.9)	76 (23)	.102
Combination therapies, n (%)	2 (4.8)	4 (1.2)	-
RFA+TACE	1 (2.4)	2 (0.6)	
TACE+TARE	1 (2.4)	1 (0.3)	
TACE+Sorafenib	-	1 (0.3)	

HCC-CL, hepatocellular carcinoma with cirrhotic liver; HCC-NCL, hepatocellular carcinoma in non-cirrhotic liver; RFA, radiofrequency ablation; TACE, transarterial chemoembolization; TARE, transarterial radioembolization.
*sign indicates p value <0.05

analyses revealed that higher ECOG performance status (0-1 vs 2-4; HR: 12.45, 95% CI 0.92-168.21, *P* = .05) and higher MTD (HR: 1.023, 95% CI 1.023, *P* = 1.008-1.039) are the only parameters influencing the overall survival independently (Table 5).

Both the BCLC and the TNM staging systems were able to discriminate survival outcomes in patients with HCC-NCL (*P* = .019 and *P* = .012, respectively), with an exceptional error in distinguishing TNM stage III and IV (Figure 1). Therefore, the BCLC system was more applicable in discrimination of survival between the stages of patients with HCC-NCL. The overall survival was not different between the 2 groups (HCC-NCL: 19.4 ± 9.8 (0.02-38.78) months vs HCC-CL: 17.5 ± 2.3 (13.02-22.04) months, *P* = .581). The Kaplan–Meier survival curves of the HCC-NCL and HCC-CL groups are exhibited in Figure 2.

DISCUSSION

To the best of our knowledge, this is the first study to characterize patients with HCC-NCL in the Turkish population. In our cohort, patients with HCC-NCL were more commonly diagnosed in the advanced tumoral stages with a larger tumor size that had a higher tendency to invade to extrahepatic veins and organs than patients with HCC-CL. Therefore, patients with HCC-NCL were more prone to crossing the border of resection, and usually were candidates for palliative treatment modalities. Despite the more advanced tumoral appearance in HCC-NCL, the survival outcomes were similar with the HCC-CL group. This can be explained by the equilibrium of liver-related and tumor-related prognostic parameters in HCC prognosis. While the tumoral burden is an important arm for treatment decision and prediction of prognosis, our results showed that the intact liver function in the background seems to equalize the prognostic scale for patients with HCC-NCL.

In our cohort with all Turkish ancestry, 11.2% of the HCCs emerged in an NCL background, which is slightly lower than the previous reports. Two recent large-cohort studies from the Netherlands and Germany revealed that cirrhosis does not appear in 19% of HCC cases, and survival was significantly improved in the patients with HCC-NCL.[17,18] Another large cohort study from Germany, conducted with 571 patients, detected that 14.1% of HCC patients had no underlying cirrhosis. However, they could not demonstrate the survival benefit in the HCC-NCL group, despite the more frequent application of surgical resection in their study.[19] In a multicenter cohort study from Turkey with 1332 patients, Akkiz et al. revealed that

Table 5. Prognostic Factors Associated With Survival for Patients With Hepatocellular Carcinoma Without Cirrhosis

	Univariate *P*	*P*	Multivariate Exp (B)	95% CI
Symptom at presentation	.047	.366	1.752	0.52-5.9
ECOG-PS (0-1 vs. 2-4)	.000	.05*	12.452	0.92-168.21
Extrahepatic metastasis	.018	.167	0.378	0.095-1.503
Treatment category (Curative vs. other)	.001	.967	0.001	0.001-4.136
Maximum tumor diameter	.000	.004*	1.023	1.008-1.039
Alpha-fetoprotein	.044	.885	1.752	0.520-5.900

ECOG-PS, Eastern Cooperative Oncology Group performance status.
*sign indicates p value <0.05

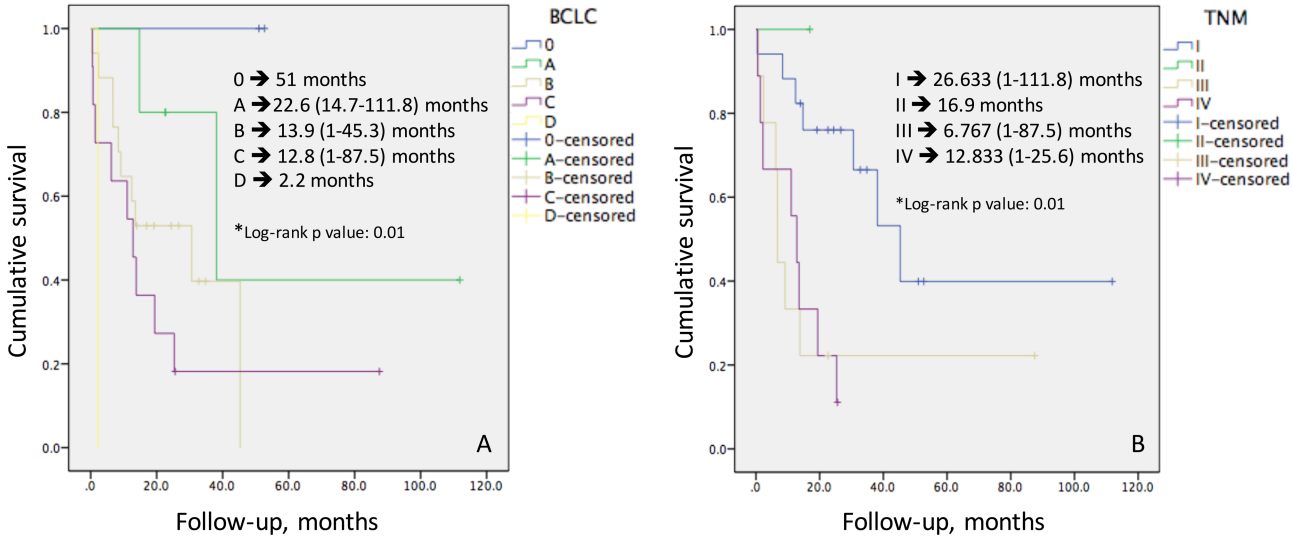

Figure 1. Survival analysis of patients with hepatocellular carcinoma in non-cirrhotic liver according to: (A) Barcelona Clinic Liver Cancer (BCLC) staging system, (B) TNM staging system.

18.6% of HCCs had no underlying cirrhosis.[12] The reason for the slightly lower rate of NCL in our HCC cohort may be the strict criteria we used to confirm NCL in our cohort. In line with the result of our study, a multicenter retrospective cohort study from the United States has detected the rate of HCC-NCLs as 11.7%, using the same criteria to define non-cirrhotic.[20] They found that patients with HCC-NCL more frequently underwent resection, and therefore had better overall survival than cirrhotic HCC patients. Despite the higher implementation of resection in our patients with HCC-NCL (14.3 vs. 4.8), we did not observe an extension in the survival of these patients in out cohort. The most reasonable explanation for this disparity would be the detection of the HCC-NCL cases at more advanced tumoral stages, and the relatively higher application of other curative options (LT and RFA) to patients with HCC-CL.

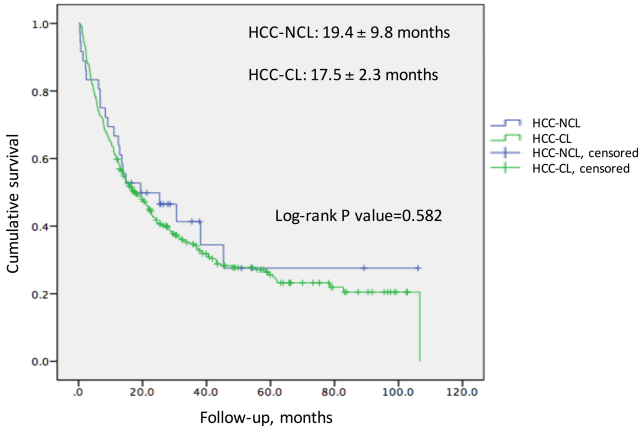

Figure 2. Kaplan–Meier survival curves of patients with hepatocellular carcinoma in non-cirrhotic and cirrhotic liver.

In the present study, HBV was the dominant etiology, followed by NAFLD and HCV in patients with HCC-NCL. The distribution of etiologies in our cohort was more similar to the results reported from the Far East. Two Asian studies from China and Japan, with selected patients who underwent surgical resection, revealed that the majority (approximately 75%) of the non-cirrhotic HCC patients had underlying chronic HBV etiology.[21,22] In 2013, HCV was reported as the most common etiology (46.5%) in 52 HCC-NCL patients from a large Italian unselected cohort study.[23] Although significantly lower than HBV infection, HCV still possesses direct oncogenic potential, with several gene products capable of contributing to carcinogenesis.[24] However, in the most recent cohort studies from Europe and the United States,[17,20] the dominant etiology in HCC-NCL was reported to be NAFLD (26.3-28%). This clear leadership of NAFLD in the Western countries is probably the reflection of the general increasing burden of NAFLD both in cirrhotic and non-cirrhotic HCCs.[20,25,26]

The laboratory disparities between the 2 groups (lower total bilirubin-INR, higher platelet–albumin value and a less altered lipid profile in HCC-NCL) were indicators of preserved liver functions in patients with HCC-NCL.[27] However, none of the laboratory findings were able

to predict survival outcomes in patients with HCC-NCL, including the AFP concentration. It is generally thought that both HCCs with NCL and CL have individual prognostic risk factors. Various studies have shown that a higher TNM stage, hsa-mir-149 overexpression, the presence of extrahepatic vascular invasion and metastasis, increasing alpha-fetoprotein levels, higher ECOG performance status, and selection of liver resection for treatment are independently associated with poor prognosis in HCC-NCL.[19,28-30] Some of these studies had the bias of selecting only resected patients. The present study demonstrated that higher ECOG-PS and MTD are the only independent predictors of mortality in a cohort comprised of unselected HCC-NCL patients.

The lack of HCC surveillance in the majority of patients with HCC-NCL may explain the higher MTD, more common extrahepatic invasion, and advanced tumoral stage detected in this patient group. Nearly half of our patients with HCC-NCL (44.1%) were not aware of any underlying chronic liver disease prior to HCC presentation. From a theoretical standpoint, the absence of cirrhosis is a condition favoring the use of curative treatment, and therefore might improve the survival outcomes of these patients. However, these potential advantages were curbed by the late recognition in our study. Globally, non-cirrhotic patients are less likely to undergo HCC screening and surveillance. In fact, HCC surveillance is probably not even offered to non-cirrhotic patients in non-hepatology clinics, and the clinicians' awareness is still questionable, despite the recommendations of the liver society's guidelines (EASL and American Association for the Study of Liver Diseases). Non-cirrhotic NAFLD and HCV are generally accepted as mild conditions, and despite the general acceptance of increased risk for HCC, the surveillance efficacy has not yet been demonstrated. Nevertheless, all chronic HCV and NAFLD patients with advanced fibrosis stage (F3-4) are also recommended to undergo biannual HCC surveillance with USG ± AFP, according to the prominent liver society guidelines.[13,31] In our opinion, this recommendation is reasonable when considering the distribution of etiologies in patients with HCC-NCL, but should be further tailored to improve the cost-effectiveness and applicability.[32,33] Nevertheless, these suggestions are only valid for those with chronic liver disease and advanced fibrosis. Reasonably practicable community-based intervention strategies might be helpful for HCCs arise even in subjects without any known chronic liver disease and fibrosis.

The present study has several limitations that must be taken into consideration when interpreting the results. Our study was conducted in a single tertiary care center and the results were retrospectively evaluated. Although the data were collected rigorously after the diagnosis of HCC, the retrospective nature of the study has prevented us from collecting some key data about the pre-diagnostic period, especially for those who were referred to our center for suspicion of HCC and were followed-up in another center in the pre-diagnostic period. The lack of data on adherence to the HCC surveillance program prevented us from elucidating the late tumoral recognition in patients with HCC-NCL. Finally, the lack of liver biopsy in all patients prevented us from re-categorizing the heterogeneous non-cirrhotic group, ranging from no fibrosis to stage 3 fibrosis, revealing the proportion of the fibrolamellar type and each HCC histologic grade.

To the best of our knowledge, this is the first study investigating the characteristics and survival outcomes of Turkish patients with HCC and no cirrhosis. Distinct from Western countries, HBV is the dominant etiology in Turkish patients with HCC-NCL. Our study demonstrated that the patients with HCC without cirrhosis are diagnosed at more advanced tumoral stages with larger tumor size, and more often vascular and extrahepatic invasion. Despite the preserved liver functions in patients with HCC-NCL, the overall survival is similar to that of HCC patients with cirrhosis, mainly due to late recognition. Optimized surveillance programs for those without cirrhosis and carrying a high risk for HCC development might improve the prognosis of patients with HCC-NCL.

Ethics Committee Approval: The study followed the tenets of the Declaration of Helsinki and it was approved by the local Ethics Committee of Marmara University, School of Medicine (Approval number: 09.2020.860-861-862-869-870, Approval date: July 24, 2020)

Informed Consent: Informed consent is not necessary due to the retrospective nature of this study.

Peer review: Externally peer-reviewed.

Author Contributions: Concept – C.O.D., F.G.; Design – C.O.D., F.G.; Supervision– F.G., O.C.O.; Resource – T.T.; Materials– T.T.; Data Collection and/or Processing – T.T., C.K.; Analysis and/or Interpretation – C.O.D.; Literature Search – C.O.D.; Writing – C.O.D.; Critical Review – O.C.O., F.G.

Conflict of Interest: The authors have no conflict of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

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