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Clinical Patterns of Hepatocellular Carcinoma in Nonalcoholic Fatty Liver Disease: A Multicenter Prospective Study

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Nonalcoholic fatty liver disease (NAFLD) represents the hepatic manifestation of metabolic syndrome and may evolve into hepatocellular carcinoma (HCC). Only scanty clinical information is available on HCC in NAFLD. The aim of this multicenter observational prospective study was to assess the clinical features of patients with NAFLD-related HCC (NAFLD-HCC) and to compare them to those of hepatitis C virus (HCV)-related HCC. A total of 756 patients with either NAFLD (145) or HCV-related chronic liver disease (611) were enrolled in secondary care Italian centers. Survival was modeled according to clinical parameters, lead-time bias, and propensity analysis. Compared to HCV, HCC in NAFLD patients had a larger volume, showed more often an infiltrative pattern, and was detected outside specific surveillance. Cirrhosis was present in only about 50% of NAFLD-HCC patients, in contrast to the near totality of HCV-HCC. Regardless of tumor stage, survival was significantly shorter ($P = 0.017$) in patients with NAFLD-HCC, 25.5 months (95% confidence interval 21.9-29.1), than in those with HCV-HCC, 33.7 months (95% confidence interval 31.9-35.4). To eliminate possible confounders, a propensity score analysis was performed, which showed no more significant difference between the two groups. Additionally, analysis of patients within Milan criteria submitted to curative treatments did not show any difference in survival between NAFLD-HCC and HCV-HCC (respectively, 38.6 versus 41.0 months, P = nonsignificant) *Conclusions:* NAFLD-HCC is more often detected at a later tumor stage and could arise also in the absence of cirrhosis, but after patient matching, it has a similar survival rate compared to HCV infection; a future challenge will be to identify patients with NAFLD who require more stringent surveillance in order to offer the most timely and effective treatment. (HEPATOLOGY 2016;63:827-838)

Hepatocellular carcinoma (HCC) is among the five top-ranking causes of cancer death worldwide.[1] Its occurrence is frequently associated with fibrotic or cirrhotic chronic liver disease whose main etiology is either viral infection, hepatitis B virus or hepatitis C virus (HCV), or alcohol abuse.[2-4] Autoimmune and biliary diseases account for a lower number of cases.

In recent years, an emerging role has been recognized for nonalcoholic fatty liver disease (NAFLD) as a cause of chronic liver disease progressing to nonalcoholic steatohepatitis (NASH) and cirrhosis. NAFLD encompasses a large spectrum of features, ranging from simple reversible steatosis to the presence of inflammation and/or fibrosis, which can progress to cirrhosis and HCC.[5] NAFLD represents the hepatic manifestation of the metabolic syndrome, and its prevalence is growing rapidly, especially in Western countries in parallel with the epidemic proportions of obesity and type 2 diabetes mellitus. NAFLD is almost always associated with the presence of insulin resistance and type 2 diabetes mellitus.[6-8] On the other hand, the

Abbreviations: APRI, aspartate aminotransferase-to-platelet ratio index; CI, confidence interval; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis.

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**The names and affiliations of all members of the HCC-NAFLD Italian Study Group are listed as an appendix.*

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most frequent type of cancer in type 2 diabetes has been shown to be HCC,[9] and obesity almost doubles the risk of HCC.[10,11] Therefore, a rapidly increasing incidence of NAFLD-HCC may be expected in the coming years.[12]

Only scant information exists about the clinical features and survival outcome of HCC on NAFLD, and a comparison with the features of HCC in viral hepatitis has not been satisfactorily addressed. Hence, whether HCC on NAFLD follows a similar outcome course to HCC on HCV is still a matter of debate. The aim of the present study was to assess the survival outcomes of patients with NAFLD-HCC and to compare them to those of patients having HCV-related HCC, all enrolled in the same period.

Patients and Methods

This is a prospective, multicenter, comparative observational study of consecutive patients with HCC enrolled in secondary care Italian centers, between 2010 and the end of 2012. The majority of the participating centers belong to the ITA.LI.CA. Study Group,[13] but the study was not restricted as other centers were invited to participate. The ethical committees of the participating hospitals approved the study. The protocol is consistent with the principles of the Declaration of Helsinki and was approved by the Fatty Liver Inhibition of Progression Consortium Board of Review (see http://www.flip-fp7.eu).

Enrollment in each study center took place when a patient with HCC was seen at the center between January 1, 2010, and December 31, 2012, either at the first HCC diagnosis or at any time during the course of the neoplastic disease. The inclusion criterion was the presence of HCC diagnosed according to the latest international guidelines in connection with the time of patient observation.[14,15] These guidelines foresee the possibility of an imaging diagnosis in patients with cirrhosis and the need for histological confirmation only in those without cirrhosis (or those with an uncertain diagnosis after imaging procedures).

Patients were classified as having NAFLD if all other known etiologies of liver disease could be ruled out and if consistent present or past histological or ultrasonographic features of fatty liver and alcohol intake <30 g/day were present.[16] Fibrosis in NAFLD patients was categorized according to the Kleiner classification.[17]

Patients with a history of alcohol abuse (defined as a chronic alcohol intake exceeding 30 g/day) as well as those with hepatitis B surface antigen positivity, antibody to hepatitis B core antigen positivity, or antibody to hepatitis B surface antigen positivity in the absence of a history of vaccination or with chronic intake of fatty liver-inducing drugs were excluded from the study. Patients with concurrent active non-HCC liver cancer, either primary or metastatic, were also excluded.

The diagnosis of cirrhosis was based either on histology or on clinical, ultrasound, endoscopic, and/or laboratory assessment.

Metabolic syndrome was diagnosed if at least three of the following five criteria were present[18]:

- Body mass index ≥25, with waist circumference ≥94 cm in men and ≥88 cm in women
- Fasting glucose 110 mg/dL or a diagnosis of type 2 diabetes
- Triglycerides 1.7 mmol/L (150 mg/dL)
- High-density lipoprotein cholesterol <1.0 mmol/L (40 mg/dL; men) or <1.3 mmol/L (50 mg/dL; women)
- Blood pressure ≥130/85 mm Hg or ongoing antihypertensive therapy

The final study group consisted of 145 patients with NAFLD-HCC. The control group consisted of 611

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patients with purely HCV-related HCC and was obtained from the ITA.LI.CA centers database. The enrollment period of the control groups was the same (2010-2012) as that of NAFLD-HCC.

Information regarding the metabolic profile (including diabetes, arterial hypertension, triglyceridemia, cholesterolemia, signs of atherosclerosis), tumor burden (number and size of the largest nodule, infiltrative forms), liver function tests, alpha-fetoprotein level, and type of treatment was recorded at the time of observation in the study center, while age and type of HCC detection were recorded at the time of the first HCC diagnosis.

We considered as the first treatment the one performed at the entry into the study when also the demographic and clinical variables were collected. Survival was calculated accordingly. Treatment was selected in line with the current guidelines[15] and according to the clinical, biochemical, and oncologic characteristics of the patients. Liver function tests, serum virological markers, metabolic profile, and alpha-fetoprotein were measured by conventional methods, using commercial kits.

Treatment was categorized as "best supportive care" when no oncologic treatment was used, when patients were enrolled in randomized controlled trials including a placebo, or when patients received oncologic treatment different from sorafenib (as either a hormonal or a chemotherapeutic first-line or second-line treatment). When combined locoregional treatments were used, the patient was classified according to the most radical treatment.

STATISTICAL ANALYSIS

Continuous variables are expressed as means and standard deviations or medians and interquartile ranges as appropriate after testing for normal distribution using the Kolmogorov-Smirnov test and categorical variables, as the number of cases and proportions. Quantitative variables were compared using the Student *t* test, and categorical variables were compared using the Fisher's exact test, as appropriate. For the present study liver function was categorized according to the Child-Pugh classification[19] also in patients without a clear demonstration of cirrhosis.

Survival was measured as the interval between the first visit to the referral center and the last follow-up visit or death. It was calculated using the Kaplan-Meier method, reported as mean (95% confidence interval [CI]) and compared by means of the log-rank test.

Lead-time bias is the bias caused by the amount of time by which the diagnosis is advanced because of the surveillance program. To minimize this effect, which could possibly be the result of an unbalance in the number of cases with a diagnosis of HCC under surveillance in the two groups, we calculated the lead time, using the formula $E(s) = (1\text{-}e\lambda t)/\lambda$, as explained in detail elsewhere.[20]

Propensity analysis was carried out using logistic regression in order to create a propensity score for NAFLD and HCV patients. The variables entered into the propensity model were age, sex, surveillance, size of the largest nodule, number of nodules, Child-Pugh score, and type of treatment. This model was then used to provide a one-to-one match between NAFLD-HCC and HCV-HCC patients using the nearest-neighbor matching method. The survival analysis was repeated in each matched subgroup in order to assess the impact of etiology on mortality due to confounding factors.

Missing values were extremely limited and were replaced by means or median values. Survival information was retrieved by enquiring about the living status or date of death from the municipality offices of the towns of residence.

A two-tailed P value <0.05 was considered statistically significant. All statistical analyses were carried out using the SPSS 13.0 statistical package (SPSS Inc., Chicago, IL). Cumulative incidence rates of competing events were calculated using the Fine and Gray method. Competing risk analysis was done using the package "cmprsk" for R (v2.13.0; R Foundation for Statistical Computing, Vienna, Austria).

Results

PATIENT CHARACTERISTICS

The demographic and clinical characteristics of patients are reported in Tables 1 and 2. NAFLD was confirmed by histology in 40 of the 145 patients (27.6%). Cirrhosis was detected in 78 of 145 NAFLD patients (53.8%); 24 (17%) were histologically confirmed (including 21 patients with established cirrhosis and three patients with bridging fibrosis) and in 594 HCV patients (97.2%; 52 of the 594 [9%] were histologically confirmed). The remaining 16 NAFLD patients without cirrhosis, as proven by histology, showed the absence of any fibrosis in three (7.5% of

TABLE 1. Demographic, Clinical, and Liver Function Characteristics of the Study Populations

Variable	HCC on NAFLD (n = 145)	HCC on HCV (n = 611)	*P**
Demographic and clinical			
Age in years (mean, SD)	67.8 (9.0)	71.1 (9.5)	<0.0001
Male gender (n and percent of patients)	115 (79.3%)	374 (61.2%)	<0.0001
Body mass index (mean, SD)	29.1 (5.0)	27.6 (4.4)	0.430
Alcohol (n and percent of drinkers)	66 (45.5%)	41(8.6%)	<0.0001
Tobacco (n and percent of smokers)	84 (60.9%)	108 (23.8%)	<0.0001
Metabolic risk factors†			
Diabetes (n and percent of patients)	106 (73.1%)	148 (24.9%)	<0.0001
Hypertension (n and percent of patients)	106 (73.1%)	204 (37.1%)	<0.0001
Hypertriglyceridemia (n and percent of patients)	37 (25.7%)	17 (3.8%)	<0.0001
Hypercholesterolemia (n and percent of patients)	47 (32.9%)	34 (7.3%)	<0.0001
Atherosclerosis (n and percent of patients)	44 (31.0%)	89 (19.1%)	0.004
Ischemic cardiomyopathy (n and percent of patients)	18 (12.4%)	47 (8.5%)	0.151
Blood glucose (mg/dL; mean and SD)	124.3 (61.2)	108.0 (39.6)	<0.0001
LDL cholesterol (mg/dL; mean and SD)	90.1 (44.79)	94.5 (43.0)	0.516
HDL cholesterol (mg/dL; mean and SD)	46.9 (24.9)	43.3 (16.5)	0.204
Triglycerides (mg/dL; mean and SD)	150.3 (163.2)	104.4 (48.5)	<0.0001
Liver function			
Bilirubin (mg/dL; mean and SD)	1.1 (0.7)	1.6 (2.2)	0.013
Albumin (g/dL; mean and SD)	4.8 (6.4)	3.9 (3.6)	0.015
International normalized ratio (mean and SD)	1.2 (0.4)	1.0 (0.5)	<0.0001
Child-Pugh score (median and range)‡	5.6 (5-11)	5.8 (5-12)	0.154
MELD score (median and range)	8.3 (3-28)	9.0 (3-24)	0.136
ECOG PS ≥2 (n and percent of patients)	22 (16.9%)	90 (16.8%)	1.000
Clinical hepatic encephalopathy (n and percent of patients)	7 (4.9%)	31 (5.1%)	1.000
Ascites (n and percent of patients)	32 (22.2%)	196 (36.7%)	0.009
CTP 5-6 (n and percent of patients)	107 (82.3%)	366 (68.1%)	0.001
CTP 7-9 (n and percent of patients)	20 (13.8%)	151 (24.7%)	0.002
CTP ≥10 (n and percent of patients)	3 (2.3%)	20 (3.7%)	0.595

*P value was assumed to be significant when <0.05.
†Hypertriglyceridemia was assigned if plasma triglycerides >150 mg/dL. Hypercholesterolemia was assigned if total cholesterol >200 mg/dL. Atherosclerosis was assigned if any imaging technique detected arterial atherosclerotic plaques. Ischemic cardiomyopathy was assigned if clinical history comprised one or more episodes of documented ischemic cardiomyopathy.
‡Among patients in Child-Pugh B class, nine of 20 NAFLD and 71 of 151 HCV patients had a specific score of B7.
Abbreviations: CTP, Child-Turcotte-Pugh score; ECOG PS, Eastern Cooperative Oncology Group Performance Status; HDL, high-density lipoprotein; LDL, low-density lipoprotein; MELD, Model for End-Stage Liver Disease; SD, standard deviation.

total NAFLD with histology), mild to minimal fibrosis in two (5.0%), and moderate fibrosis in 11 (27.5% of histologically confirmed NAFLD patients). In the remaining cases of NAFLD, the diagnosis of cirrhosis was reached by clinical, ultrasonographic, elastographic, and laboratory findings as accepted by the American Association for the Study of Liver Diseases guidelines.[16] In order to confirm that the 51 patients without histology-proven cirrhosis were free from an advanced fibrotic stage, we calculated the aspartate aminotransferase-to-platelet ratio index (APRI) score.[20] A total of 36 of 51 (71%) patients showed an APRI score <0.7, confirming nonsevere fibrosis; four (8%) showed an APRI score between 0.7 and 1.0, consistent with less certainty about the severity of fibrosis, whereas only 14 (27%) showed an APRI score >1.0, which would suggest severe fibrosis or cirrhosis, especially for scores >2.[20]

In summary, the absence of cirrhosis could be clearly proven by either histology or APRI score <0.7 in 47 (70%) of the 67 NAFLD-HCC patients judged as not having cirrhosis by the enrolling investigator based on clinical criteria, confirming the reliability of clinical judgment.

Patients with NAFLD-HCC were significantly ($P < 0.0001$) younger (67.8 ± 9.0 versus 71.1 ± 9.5 years) and were more often male than patients with HCV-related HCC (Table 1). They were also more often smokers and alcohol (<30 g/day) drinkers. As expected, the metabolic risk factors were more often present in NAFLD patients than in those with HCV-related HCC (Table 1), and liver function tests were significantly less severe in NAFLD patients than in HCV patients (Table 1). In HCV-related HCC patients, HCC was diagnosed more frequently during surveillance (Table 2) than in

TABLE 2. Tumor Characteristics of the Study Population

Variable	HCC on NAFLD (n = 145)	HCC on HCV (n = 611)	*P*
Modality of initial tumor detection			
Surveillance (n and percent of patients)	69 (47.6%)	387 (63.3%)	0.001
Case findings (n and percent of patients)	56 (38.6%)	150 (24.6%)	0.001
Symptomatic (n and percent of patients)	20 (13.8%)	45 (7.4%)	0.056
Not specified	0	29 (4.7%)	
Tumor characteristics at observation in the study center			
Size of largest tumor (cm; mean and SD)	4.1 (2.6)	3.3 (2.9)	0.003
Number of nodules (mean and SD)	1.8 (1.6)	1.6 (1.5)	0.080
Milan In (n and percentage of patients)	80 (55.2%)	418 (68.4%)	0.005
Milan Out (n and percentage of patients)	65 (44.8%)	193 (31.6%)	0.005
Barcelona Clinic Liver Cancer			
Stage 0	0	68 (11.1%)	<0.0001
Stage A	62 (42.8%)	256 (42.9%)	0.925
Stage B	28 (19.3%)	89 (14.6%)	0.201
Stage C	48 (33.1%)	146 (23.9%)	0.033
Stage D	3 (2.1%)	30 (4.9%)	0.174
Infiltrative (n and percent of patients)*	21 (15.4%)	21 (4.0%)	<0.0001
Extrahepatic metastasis (n and percent of patients)*	13 (9.3%)	105 (17.2%)	0.020
Macrovascular infiltration (n and percent of patients)*	25 (17.5%)	87 (14.7%)	0.436
Alpha-fetoprotein (ng/dL; median and range)	7.13 (1.5-83110.2)	20.4 (1-267912)	0.001

*These patients might belong to more than one group (infiltrative and/or extrahepatic spread and/or macrovascular infiltration but all out of Milan criteria).
P value was assumed to be significant when <0.05.
Abbreviation: Milan In, inside Milan criteria; Milan Out, outside Milan criteria; SD, standard deviation.

those with NAFLD, in whom HCC was detected either at the appearance of symptoms or by hepatic ultrasound performed without previous history or clinical signs of chronic liver disease. Thus, HCC was diagnosed during specific surveillance or periodic ultrasound in 387 (63.3%) HCV patients versus 69 (47.7%) NAFLD patients, $P < 0.0001$. A total of 14.9% of HCV patients had experienced at least one attempt at treatment with antivirals (interferon-based regimens).

Small HCC (i.e., single HCC <5 cm or two or three nodules all <3 cm) and Barcelona Clinic Liver Cancer 0[15] were less frequent in NAFLD-HCC than in HCV-related HCC patients (Table 2). Conversely, advanced-stage Barcelona Clinic Liver Cancer C HCC or infiltrative HCC was significantly ($P < 0.0001$) more common in NAFLD patients (infiltrative HCC: 21% versus 4% in NAFLD and HCV, respectively).

Patients with HCV infection had worse liver function in comparison to NAFLD patients; in particular, Child-Pugh class A, with a score of either 5 or 6, was observed in 366 (68.1%) HCV versus 107 (82.3%) NAFLD patients ($P = 0.001$; Table 1).

Different patterns of tumor burden and liver function led to partially different treatment allocations in the two groups (Table 3). More patients with NAFLD-HCC than HCV-HCC were eligible for liver resection (19.3% versus 10.6%, $P = 0.002$), but more also underwent only supportive care/unproven

TABLE 3. Treatment Strategy in Patients With HCC According to Underlying Etiology

Variable	HCC on NAFLD (n = 145)	HCC on HCV (n = 611)	*P*
Treatment			
Liver transplantation	1 (0.7%)	10 (1.6%)	0.700
Surgical resection	28 (19.3%)	65 (10.6%)	0.002
PEI	2 (1.4%)	57 (9.3 %)	0.002
Thermal ablation*	35 (24.1%)	169 (27.6%)	0.915
TACE†	37 (25.5%)	182 (29.8%)	0.606
Sorafenib	4 (2.8%)	53 (8.7%)	0.028
BSC or trials‡	38 (26.2%)	75 (12.3%)	<0.0001

Data are reported as absolute number of patients and percentage of patients of the total series for each etiology.
*Thermal ablation was carried out in the large majority of cases by the radiofrequency modality. Very few cases underwent microwave ablation.
†TACE also includes very few patients who underwent yttrium-90 radiometabolization (four patients withHCV, one patient with NAFLD).
‡The term "trials" include phase 2 and phase 3 randomized trials of systemic drug treatments as well as off-label chemotherapeutic treatments as either first-line or second-line. BSC includes hormonal therapy or other therapies of unproven efficacy.
Abbreviations: BSC, best supportive care (could be adopted in either first-line or second-line treatment for advanced HCC); PEI, percutaneous ethanol injection; TACE, transarterial chemoembolization.

TABLE 4. Baseline General, Liver, and Tumor Characteristics of the Study Populations After Propensity Score Match Analysis

Variable	HCC on NAFLD (n = 64)	HCC on HCV (n = 64)	*P*
Demographic			
Age (years; mean and SD)	68.9 (8.4)	69.3 (9.4)	0.83
Male gender (n and percent)	50 (78.1%)	49 (76.6%)	1
Liver function			
CTP 5-6 (n and percent)	47 (73.4%)	51 (79.7%)	0.53
CTP 7 (n and percent)	7 (10.9%)	4 (6.2%)	0.53
CTP 8-9 (n and percent)	7 (10.9%)	9 (14.1%)	0.79
CTP ≥10 (n and percent)	3 (4.7%)	0	0.24
Tumor characteristics			
Size largest nodule (cm; mean and SD)	3.2 (1.9)	3.4 (2.0)	0.58
Size ≤2 cm (n and percent)	24 (37.5%)	23 (35.9%)	1
Size 2.1-3 cm (n and percent)	17 (26.6%)	16 (25.0%)	1
Size 3.1-5 cm (n and percent)	15 (23.4%)	15 (23.4%)	1
Size ≥5 cm (n and percent)	8 (12.5%)	10 (15.6%)	0.8
Number of nodules: 1 (n and percent)	44 (68.7%)	43 (67.2%)	1
Number of nodules: 2-3 (n and percent)	15 (23.4%)	15 (23.4%)	1
Number of nodules: >3 (n and percent)	5 (7.8%)	4 (6.2%)	1
Infiltrative (n and percent)	1 (1.6%)	3 (4.7%)	0.62
Detection on surveillance (n and percent)	29 (45.3%)	44 (68.7%)	0.12
Treatments			
Liver transplantation (n and percent)	1 (1.6%)	1 (1.6%)	1
Surgical resection (n and percent)	14 (21.9%)	17(26.6%)	0.68
PEI (n and percent)	2 (3.1%)	3 (4.7%)	1
Thermal ablation (n and percent)	21 (32.8%)	19 (29.7%)	0.85
TACE (n and percent)	23 (35.9%)	20 (31.2%)	0.71
Sorafenib (n and percent)	0	0	
BSC or trials (n and percent)	0	0	

Data are reported as absolute number of patients (n) and percentage of patients of the total series for each etiology.
Abbreviations: BSC, best supportive care (could be adopted in either in first-line or second-line treatment for advanced HCC); CTP, Child-Turcotte-Pugh score; LT, liver transplantation; PEI, percutaneous ethanol injection; SD, standard deviation; TACE, transarterial chemoembolization,

therapies (26.2% versus 12.3%, $P < 0.001$). Percutaneous ethanol injection was adopted more often in HCV patients (9.3 versus 1.4%, $P = 0.002$). However, the overall rate of patients submitted to curative treatments (surgical resection, transplantation, or percutaneous ablation) was similar in the two populations (45.5% versus 49.1% in HCV-HCC, $P =$ nonsignificant).

SURVIVAL OUTCOMES

Over a median follow-up of 13 months (interquartile range 5-47), 188 patients died (24.9%), of whom 38 had NAFLD-HCC (26.2% of HCC in NAFLD) and 150 had HCV-related HCC (24.5%). Crude mean survival differed statistically between the two groups, being 27.2 months (95% CI 23.5-30.9) in the NAFLD patients and 34.4 months (95% CI 32.7-36.0) in the HCV patients ($P = 0.015$). Survival rates at 1 year and 3 years were 76.4% and 48.7% versus 84.2% and 61.1%, respectively.

These outcomes might theoretically result only from a later diagnosis in patients not under surveillance or a later referral of NAFLD-HCC patients to the study centers with a more advanced tumor stage rather than to a more aggressive tumor biology.

Because this is a relevant and yet unsolved question, we adjusted survival for the lead time in patients who were under surveillance.[13] Mean survival differed statistically between the two groups even after the adjustment, being 25.5 months (95% CI 21.9-29.1) in the NAFLD patients and 33.7 months (95% CI 31.9-35.4) in the HCV patients ($P = 0.017$). The survival rate at 1 year and 3 years was 74.7% and 48.3% in the NAFLD-HCC patients versus 81.5% and 59.5% in the HCV-HCC patients, respectively.

To clarify further the intrinsic tumor aggressiveness in the two etiologies, we tried to eliminate possible confounders such as differences in age, liver function, and tumor burden, which indeed differed in the two groups. We therefore ran a propensity score analysis taking into consideration the main variables with

TABLE 5. Baseline Characteristics of the Population Treated With Curative Approaches

Variable	NASH (n = 66)	HCV (n = 269)	*P*
Demographic and clinical			
Age (years; SD)	66.4 (10.3)	71.4 (8.8)	<0.0001
Male gender	54 (81.8%)	162 (60.2%)	0.001
Surveillance	39 (59.1%)	195 (72.5%)	0.037
Case findings	22 (33.3%)	55 (20.4%)	0.033
Symptomatic	5 (7.6%)	12 (4.5%)	0.345
Body mass index	29.2 (4.5)	28.2 (36.6)	0.723
Alcohol intake	30 (45.4%)	22 (8.2%)	<0.0001
Tobacco	34 (51.5%)	54 (20.1%)	<0.0001
Metabolic risk factors			
Diabetes	48 (72.7%)	60 (22.3%)	<0.0001
Hypertension	44 (66.7%)	87 (32.3%)	<0.0001
Hypertriglyceridemia	19 (28.8%)	6 (2.2%)	<0.0001
Hypercholesterolemia	22 (33.3%)	11 (4.1%)	<0.0001
Atherosclerosis	18 (27.3%)	34 (12.6%)	0.001
Ischemic cardiomyopathy	4 (6.1%)	9 (3.3%)	0.043
Glycemia	127.6 (51.6)	101.2 (38.2)	<0.0001
LDL cholesterol	88.2 (42.3)	106.6 (41.6)	0.059
HDL cholesterol	51.8 (27.3)	49.1 (16.3)	0.563
Triglyceride	165.6 (203.4)	106.8 (57.3)	0.007
Tumor characteristics			
Size of largest tumor (cm)	3.4 (1.7)	2.9 (2.8)	0.135
Size ≤2 cm	20 (30.3%)	112 (41.6%)	0.049
Size 2.1-3 cm	15 (22.7%)	82 (30.5%)	0.136
Size 3.1-5 cm	22 (33.3%)	36 (13.4%)	0.001
Size ≥5 cm	9 (13.6%)	23 (8.5%)	0.259
Number of nodules: 1	51 (77.3%)	210 (78.1%)	0.486
Number of nodules: 2-3	14 (21.2%)	43 (16.0%)	0.371
Number of nodules: > 3	1 (1.5%)	5 (1.8%)	1
Milan In	49 (74.2%)	217 (80.7%)	0.010
Milan Out	17 (25.7%)	29 (10.8%)	0.010
Infiltrative	5 (7.6%)	2 (0.7%)	0.005
Metastasis	2 (3.0%)	2 (0.7%)	0.194
Thrombosis	4 (6.1%)	8 (3.0%)	0.265
Liver function			
Bilirubin (SD)	0.9 (0.6)	1.2 (0.9)	0.017
Albumin (SD)	4.8 (5.0)	3.8 (2.8)	0.171
INR (SD)	1.3 (0.4)	1.0 (0.5)	<0.0001
Alpha-fetoprotein (SD)	371.5 (1601.7)	242.6 (1925.6)	0.634
CTP	5.6 (1.2)	5.5 (1.9)	0.536
ECOG ≥2	5 (7.6%)	17 (6.3%)	0.783
Encephalopathy	1 (1.5%)	8 (3.0%)	1
Ascites	10 (15.1%)	57 (21.2%)	0.224

Abbreviations: CTP, Child-Turcotte-Pugh score; ECOG, Eastern Cooperative Oncology Group; HDL, high-density lipoprotein; INR, international normalized ratio; LDL, low-density lipoprotein; Milan In, inside Milan criteria; Milan Out, outside Milan criteria; SD, standard deviation.

clinically known impact on survival and showing statistical differences between the two groups (Table 4). Patients submitted to only supportive care were not included in this propensity score comparison because they were few and the reasons for the choice of the supportive care were most likely heterogenous.

After matching according to the propensity analysis, there was a smaller, nonsignificant difference in mean survival between the two groups (30.2 months, 95% CI 25.3-35.2) in patients with NAFLD-HCC and 36.9 (95% CI 32.6-41.1) in patients with HCV-related HCC liver-related disease ($P = 0.330$). The survival rates at 1 year and 3 years were 91.9% and 63.3% versus 87.4% and 72.6%, respectively. Because matching could not include the variable of detection under surveillance and this was insufficiently represented in NAFLD patients, we corrected this possible source of bias by considering the lead time. After adjustment for lead time, the difference in survival remained nonsignificant between the two groups: 28.5 months (95% CI 23.7-33.4) in the NAFLD patients and 35.0 months (95% CI 30.8-39.1) in the HCV

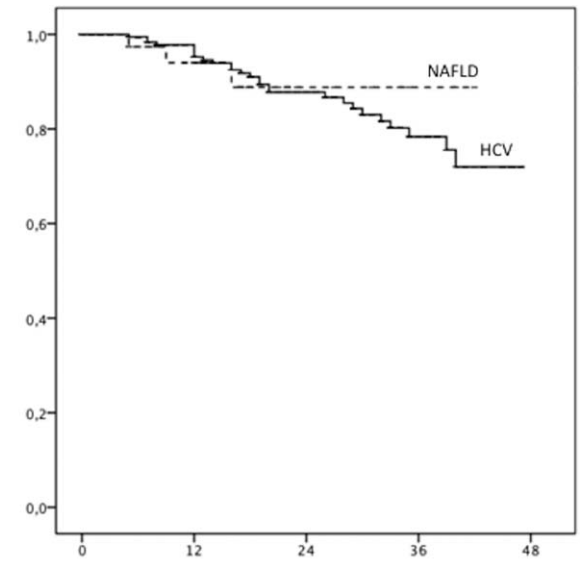
TABLE 6. Baseline Characteristics of the Population Treated With Curative Approaches and Selected to Be Within the Milan HCC Criteria

Variable	NAFLD (n = 49)	HCV (n = 217)	P*
Demographic and clinical			
Age (years; SD)	65.6 (9.2)	71.4 (9.1)	<0.0001
Male gender	41 (83.7%)	129 (59.4%)	0.002
Surveillance	32 (65.3%)	166 (76.5%)	0.146
Case findings	14 (28.6%)	40 (18.4%)	0.119
Symptomatic	3 (6.1%)	5 (2.3%)	0.167
Body mass index	29.3 (4.6)	27.0 (30.0)	0.368
Alcohol consumption	24 (49.0%)	18 (8.3%)	<0.0001
Tobacco	24 (49.0%)	42 (19.3%)	<0.0001
Metabolic risk factors†			
Diabetes	36 (73.5%)	48 (22.1%)	<0.0001
Hypertension	31 (63.3%)	64 (29.5%)	<0.0001
Hypertriglyceridemia	13 (26.5%)	4 (1.8%)	<0.0001
Hypercholesterolemia	16 (32.6%)	8 (3.7%)	<0.0001
Atherosclerosis	13 (26.5%)	25 (11.5%)	0.004
Ischemic cardiomyopathy	3 (6.1%)	8 (3.7%)	0.117
Glycemia	127.5 (54.9)	99.9 (36.0)	0.001
LDL cholesterol	84.6 (45.4)	96.4 (35.2)	0.285
HDL cholesterol	54.3 (31.0)	50.9 (14.3)	0.577
Triglycerides	185.1 (240.8)	106.2 (61.1)	0.054
Tumor burden			
Size of largest tumor (cm)	2.6 (0.9)	2.4 (0.9)	0.136
Size ≤2 cm	20 (40.8%)	107 (49.3%)	0.342
Size 2.1-3 cm	15 (30.6%)	79 (36.4%)	0.509
Size 3.1-5 cm	14 (28.6%)	30 (13.8%)	0.019
Size ≥5 cm	0	0	
Number of nodules: 1	43 (87.7%)	184 (84.8%)	0.823
Number of nodules: 2-3	6 (12.2%)	33 (15.2%)	0.823
Number of nodules: > 3	0	0	
Liver function			
Bilirubin (SD)	0.9 (0.6)	1.1 (0.8)	0.075
Albumin (SD)	4.6 (4.8)	3.9 (3.1)	0.185
INR (SD)	1.3 (0.5)	1.0 (0.5)	0.001
Alpha-fetoprotein (SD)	9.1 (11.3)	63.7 (226.7)	0.002
CTP	5.6 (1.3)	5.5 (1.8)	0.727
ECOG ≥2	4 (8.2%)	9 (4.1%)	0.264
Encephalopathy	1 (2.0%)	5 (2.3%)	1
Ascites	6 (12.2%)	48 (22.1%)	0.289
Survival (months)	38.6	41.0	0.839

*P value was assumed to be significant when <0.05.
†Hypertriglyceridemia was assigned if plasma triglycerides >150 mg/dL. Hypercholesterolemia was assigned if total cholesterol >200 mg/dL. Atherosclerosis was assigned if any imaging technique detected arterial atherosclerotic plaques. Ischemic cardiomyopathy was assigned if clinical history comprised one or more episodes of documented ischemic cardiomyopathy.
Abbreviations: CTP, Child-Turcotte-Pugh score; ECOG, Eastern Cooperative Oncology Group; HDL, high-density lipoprotein; INR, international normalized ratio; LDL, low-density lipoprotein; SD, standard deviation.

patients ($P = 0.344$). The survival rates at 1 year and 3 years were 85.4% and 63.9% versus 92.2% and 63.7%, respectively, which were also not statistically significant.

However, a trend toward longer survival in HCV-HCC remained present in all the analyses, which did not clarify the question of a potentially greater tumor aggressiveness of HCC on NAFLD. We therefore performed an additional analysis selecting comparable patient populations. We selected patients from the two HCC groups submitted to curative treatments (surgical resection, transplantation, percutaneous ablation). For these patients no difference in survival related to etiology was observed (34.2 versus 40.8 months, NAFLD and HCV-HCC, respectively; $P = 0.073$). However, the two patient populations differed regarding the tumor burden as NAFLD-HCC patients showed a higher percentage of tumors 3-5 cm (Table 5) in spite of no difference in liver function assessed as Child-Pugh and Model for End-Stage Liver Disease scores (Table 1). Consequently, we further restricted the survival analysis to patients submitted to curative



Patients at risk

Months	0	12	24	36	48
NAFLD	49	25	6	2	0
HCV	217	145	86	38	0

FIG. 1. Survival curves of patients with HCC in the early stage (inside Milan criteria) submitted to curative treatments subgrouped according to background liver disease (NAFLD or HCV).

treatments but who also had tumors within the Milan criteria, encompassing 74% in the NAFLD-HCC group and 81% in the HCV-HCC group. This analysis confirmed the absence of any survival differences between the two groups (Table 6 and Fig. 1) (38.6 months in NAFLD-HCC versus 41.0 months in HCV-HCC, P = nonsignificant).

Finally, we aimed to verify whether other causes of death besides those related to the liver might have an impact on the trend toward crude higher mortality in NAFLD patients. We performed a competitive risk analysis (Table 7), which confirmed that tumor and liver-related causes of death were similarly represented in the two groups, confirming that HCC in NAFLD is intrinsically not more aggressive than that in HCV patients. Interestingly, however, NAFLD patients were more likely to die from either cardiovascular events, although this cause was altogether marginally responsible for death (4% versus 1% at 3 years), or other non-liver-related, noncardiovascular causes categorized in the database under "other" (11% versus 5.5% at 3 years) (Table 7).

To understand whether the absence of cirrhosis might have an impact on survival in NAFLD patients, we compared the survival of NAFLD patients with and without cirrhosis. Survival curves did not show a significant difference, with overall rates of 28.5 months and 34.9 months in HCC patients with and without cirrhosis, respectively. To verify whether the better liver function in NALFD without cirrhosis may have counterbalanced the larger tumor burden, leading to survival similar to HCC on NAFLD without cirrhosis, we assessed both tumor burden and survival in NAFLD-HCC patients who received curative therapies (surgery or ablation). Tumor size and survival appeared comparable in the two groups (survival 28.5 months in those with cirrhosis versus 34.5 in those without, P = nonsignificant).

Discussion

The natural history of NAFLD-HCC is still poorly understood. In particular, comparison of NAFLD-HCC to HCC related to other etiologies has not been satisfactorily studied. Comparison with historical series of patients with underlying viral cirrhosis is not suitable to provide solid data because diagnostic imaging and treatment modalities were much poorer in the past.

In the present study based on two series of patients collected in a recent period of time, we demonstrated that patients with NAFLD-HCC have a shorter

TABLE 7. Competing Risk Analysis of 1-Year, 2-Year, and 3-Year Cumulative Incidence of Death Rates From Enrollment Subgrouped by Cause

Cause of Death	NAFLD (145 patients) 1-; 2-; 3-year	Gruppo HCV (611 patients) 1-; 2-; 3-year	P
HCC	10.7%; 17.1%; 25.7%	10.3%; 16.0%; 22.0%	0.772
Liver failure	4.0%; 9.6% 9.6%	3.4%; 6.5%; 9.2%	0.481
Gastrointestinal bleeding	0.0%; 0.0%; 0.0%	1.0%; 1.2%; 1.2%	0.258
Liver transplantation	1.4%; 1.4%; 1.4%	0.4%; 1.1%; 2.0%	0.900
Cardiovascular events	0.9%; 4.0%; 4.0%	0.0%; 1.0%; 1.0%	0.008
Others	7.9%; 11.6%; 11.6%	3.0%; 3.9%; 5.5%	0.003

survival than patients with HCV-HCC, mainly because the former combination is usually detected at a later stage and with a greater tumor burden and not because NAFLD-HCC is more aggressive. In fact, when confounding factors were eliminated, NAFLD-HCC showed a survival fully comparable to that of HCV-HCC.

More specifically, tumor burden significantly differs among the two groups (Table 2), suggesting that the crude figure of shorter overall survival in NAFLD-HCC (Fig. 1) should not be regarded as a greater aggressiveness of the tumor but most likely only a delayed diagnosis. The later diagnosis could be caused by the absence of recognized risk factors (absence or unrecognized cirrhosis), which results in the lack of any surveillance program in many NAFLD-HCC patients and consequently to a delayed diagnosis prolonged beyond the lead-time bias. We believe this is the most likely explanation for the shorter overall survival observed in patients with NAFLD-HCC. In line with this conclusion is the observation that when patients were matched according to a propensity score analysis based on tumor burden and liver function or when patients at the early tumor stage (Milan In, inside Milan criteria) were analyzed, the difference in survival disappeared.

The number of NAFLD patients with infiltrative HCC was higher than that of HCV patients (15% versus 2%), but this figure is comparable to previous findings reported in patients with viral hepatitis or with mixed etiologies not systematically enrolled in HCC surveillance programs.[21,22] This further suggests late diagnosis, and hence lack of surveillance strategies, in patients with NASH, metabolic syndrome, or type 2 diabetes without cirrhosis as the most likely cause for our findings.[23]

Our data also showed that in almost 50% of cases HCC arose in the absence of frank cirrhosis, in agreement with previous smaller studies including fewer than 100 NAFLD-HCC patients.[24-26] The large majority of cases where histology was available confirmed that NAFLD was not simple fatty liver but rather NASH with moderate fibrosis. However, limitations of our data are that (1) histology was available only in nearly 30% of NAFLD patients, but unfortunately this limitation can hardly be solved because in nonsurgical patients a biopsy of nontumoral liver is often not justified or accepted, and (2) a referral bias could be present because some of the study centers are tertiary centers, which, in addition to their own patients with HCC emerging on surveillance, also receive patients (either HCV or NAFLD) referred from other centers, and whether the referral of the two etiologies is similar cannot be established from our data.

The prevalence of social alcohol drinkers (>0-30 g/day) was higher among our NAFLD patients than among HCV patients (45.5% versus 8.6%). This finding is not surprising as the prevalence of social alcohol drinkers was estimated to be about 40% worldwide and around 60%-70% in Western Europe including Italy.[27] Because most NAFLD patients were presumably not aware of an ongoing liver disease risk (as suggested by HCC detected as an incidental finding in 38% and only 48% of them being under any type of surveillance), they most likely behaved as social drinkers, differently from HCV patients, who usually stop drinking alcohol because they are very concerned about their liver disease only in consideration of having chronic hepatitis viral infection, regardless of the stage.

On the basis of our data, we conclude that NAFLD-HCC is more often found at a later tumor stage than HCV-related HCC, ending with an overall worse prognosis. However, this difference disappears when patients with NAFLD and HCV are matched for tumor stage, suggesting that the natural history is unrelated to the background etiology of liver disease. These results highlight the need to focus future research on identifying those patients with NAFLD who require surveillance in order to establish earlier diagnosis and offer them treatment, which in our series appeared to be as effective as that provided for patients with HCV at an early stage.

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Appendix

The following institutions and related physicians have cooperated to collect and clinically manage the study cases: Dipartimento di Scienze Mediche e Chirurgiche, Alma Mater Studiorum-Università di Bologna, Bologna, Italy: Mauro Bernardi, Maurizio Biselli, Paolo Caraceni, Marco Domenicali, Francesca Garuti, Annagiulia Gramenzi, Barbara Lenzi, Donatella Magalotti, Matteo Cescon, Matteo Ravaioli; Unità Operativa di Chirurgia, Policlinico S. Marco, Zingonia, Italy: Paolo Del Poggio, Stefano Olmi; Unità di Medicina Interna e Gastroenterologia, Complesso

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