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Hepatectomy for Metabolic Associated Fatty Liver Disease (MAFLD) related HCC: Propensity case-matched analysis with viral- and alcohol-related HCC

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ABSTRACT

Background and aims: We investigated the clinical impact of the newly defined metabolic-associated fatty liver disease (MAFLD) in patients undergoing hepatectomy for HCC (MAFLD-HCC) comparing the characteristics and outcomes of patients with MAFLD-HCC to viral- and alcoholic-related HCC (HCV-HCC, HBV-HCC, A-HCC).

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Methods: A retrospective analysis of patients included in the He.RC.O.Le.S. Group registry was performed. The characteristics, short- and long-term outcomes of 1315 patients included were compared according to the study group before and after an exact propensity score match (PSM).
Results: Among the whole study population, 264 (20.1%) had MAFLD-HCC, 205 (15.6%) had HBV-HCC, 671 (51.0%) had HCV-HCC and 175 (13.3%) had A-HCC. MAFLD-HCC patients had higher BMI ($p < 0.001$), Charlson Comorbidities Index ($p < 0.001$), size of tumour ($p < 0.001$), and presence of cirrhosis ($p < 0.001$). After PSM, the 90-day mortality and severe morbidity rates were 5.9% and 7.1% in MAFLD-HCC, 2.3% and 7.1% in HBV-HCC, 3.5% and 11.7% in HCV-HCC, and 1.2% and 8.2% in A-HCC ($p = 0.061$ and $p = 0.447$, respectively). The 5-year OS and RFS rates were 54.4% and 37.1% in MAFLD-HCC, 64.9% and 32.2% in HBV-HCC, 53.4% and 24.7% in HCV-HCC and 62.0% and 37.8% in A-HCC ($p = 0.345$ and $p = 0.389$, respectively). Cirrhosis, multiple tumours, size and satellitosis seems to be the independent predictors of OS.
Conclusion: Hepatectomy for MAFLD-HCC seems to have a higher but acceptable operative risk. However, long-term outcomes seems to be related to clinical and pathological factors rather than aetiological risk factors.

1. Introduction

Hepatocellular carcinoma (HCC) is the sixth most frequently diagnosed cancer and the fourth leading cause of cancer-related death worldwide [1]. Currently, in Western countries, over 60% of HCCs are related to chronic viral hepatitis infection (HCV and HBV), and nearly 20% are related to alcohol abuse [2]. Recently, due to improvements in the prevention, management and treatment of chronic viral hepatitis infections, the proportion of patients with infection being the determinant of the onset of liver cirrhosis and subsequent HCC carcinogenesis has decreased [3]. Meanwhile, there has been an increase in the prevalence of both cirrhosis and HCC in relation to metabolic disorders (MDs), a spectrum of clinical manifestations including hypertension, dyslipidaemia, obesity, and insulin resistance [4,5]. Metabolic disorders may lead to an abnormal build-up of fat in the liver, the traditionally so-called non-alcoholic fatty liver disease (NAFLD), even in patients without a history of viral hepatitis or alcohol abuse.

In the literature, there is no clear agreement on the impact and results of surgical resection in MD-related HCC. Several surgical series have investigated the short- and long-term outcomes of patients with HCC associated with different MDs, but the results are difficult to decipher due to the great variability of the study designs and the definitions used [6–12].

However, according to these previous studies, the survival results remain controversial; patients with MDs seem to have an increased operative risk, particularly related to higher cardiovascular and infectious complications, and adequate evaluation with tailored perioperative management are recommended [13].

Recently, a group of experts tried to integrate the current understanding of patient differences captured by the acronym NAFLD, proposing metabolic-associated fatty liver disease (MAFLD) as the new definition, with the purpose of more accurately reflecting the pathogenesis and helping classify and manage patients [14,15].

To date, in the literature, there are no specific data regarding the outcomes of surgery in patients with MAFLD-related HCC (MAFLD-HCC).

The aims of this study were: 1) to evaluate and compare the clinical and pathological characteristics of patients with MAFLD-HCC to viral- and alcoholic-related HCC (HCV-HCC, HBV-HCC, A-HCC); 2) to evaluate and compare short- and long-term outcomes according to the different study groups.

2. Patients and methods

2.1. Patients and study design

This study evaluated patients enrolled in a multi-institutional Register of HCC by the He.RC.O.Le.S. Group, which is composed of 30 Italian liver surgery centers [16].

The study protocol was registered at clinicaltrials.gov (ID = NCT04053231) and followed the ethical guidelines of the 1975 Declaration of Helsinki (as revised in Brazil 2013). More information about the He.RC.O.Le.S. Project can be found at http://www.hercolesgroup.eu.

A total of 2410 consecutive adult patients (age ≥18 years) with histologically proven HCC who underwent hepatectomy from January 2008 to December 2018 were enrolled in He.RC.O.Le.S. database and evaluated. The study design and patient selection are summarized in Fig. 1. To avoid bias in the definition of HCC aetiology, patients without sufficient data to define tumour aetiology were excluded. Moreover, patients with known multiple or mixed aetiologies for HCC and patients with cryptogenic HCC or rare disease-related HCC (i.e., Wilson's Disease, Hemochromatosis) were both excluded.

Finally, 1315 (54.6%) patients with only one single known determinant for the development of HCC were included in the study.

According to the new definition given by Eslam et al. in a recent consensus statement [14], metabolic-associated fatty liver disease (MAFLD) is defined by hepatic steatosis (detected by imaging, blood scores/markers, or histology) in association with overweight (BMI ≥25 kg/m^2 in Caucasians or ≥23 in Asians) or type 2 diabetes mellitus (according to international criteria) or normal weight in the presence of two or more metabolic risk abnormalities (high waist circumference, blood hypertension, abnormal levels of plasma triglycerides or cholesterol, insulin resistance or prediabetes and high level of plasma c-reactive protein). All HBV and HCV patients had a serological diagnosis. Alcohol abuse was defined according to ICD-11 [17].

The study population was divided into four groups according to the HCC determinant: MAFLD-related HCC (MAFLD-HCC), HBV-related HCC (HBV-HCC), HCV-related HCC (HCV-HCC), and alcohol-related HCC (A-HCC).

Details on the data collection and other definitions used were

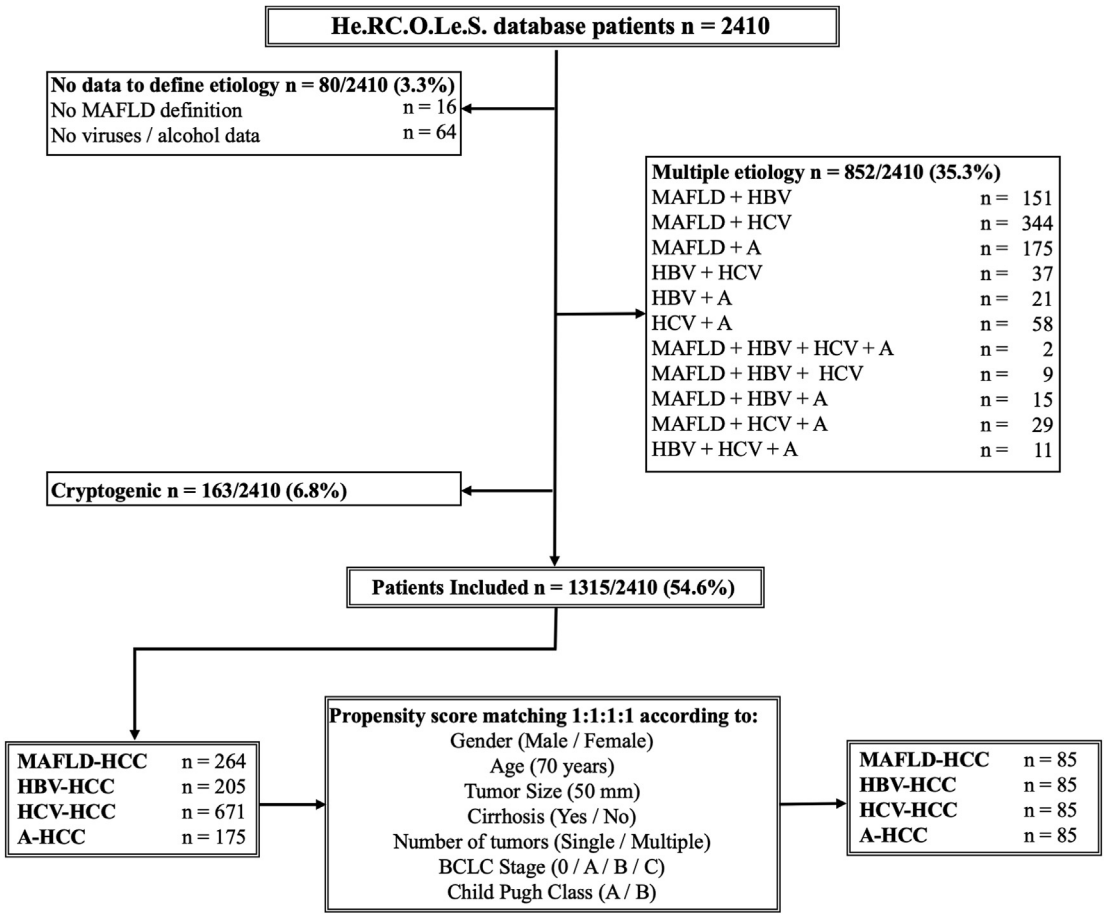


Fig. 1. Study patients selection and matching criteria.

reported previously by He.RC.O.Le.S Group published papers [16,18,19].

Patient surveillance was closed at August 31, 2020. The median follow-up period for surviving patients was 40.0 months.

2.2. Statistical analysis

Statistical analysis was performed using IBM SPSS Statistics version 25.0 (IBM Corp., Armonk, NY). Continuous variables were reported as medians with interquartile ranges (IQRs) and compared among groups using the unpaired *t*-test or Mann-Whitney *U* test as appropriate. Categorical variables were reported as totals and frequencies and compared using the chi-square test or Fisher's exact as appropriate.

The Kaplan-Meier method was used to estimate overall survival and recurrence-free survival probabilities, which were compared using the log-rank test. Univariate analysis was used to compare clinical and pathological features and outcomes among the four groups (overall and propensity score matched patients).

A multivariable Cox regression model was used to identify factors that were independently related to survival (overall and recurrence free) to estimate hazard ratios with 95% confidence intervals (95% C.I.), adjusting for potential confounders.

Propensity exact score matching (PSM) was performed, comparing patients according to the determinant aetiology. Propensity score matching was calculated by multivariable logistic regression including baseline variables: age (<70 or ≥70 years), gender (male or female), cirrhosis (yes or no), tumour size (<50 or ≥50 mm), number of tumours (single or multiple), BCLC stage (0, A, B, C) and Child-Pugh class (A or B). A calliper width of 0.001 SD was used, and nearest neighbours (without replacement) were matched at a 1:1:1:1 ratio, giving a total of 340 patients, 85 per group. A p value < 0.05 was considered significant for all tests.

3. Results

3.1. Clinical and pathological characteristics of the whole study population

The study population included 1315 patients who underwent hepatectomy for HCC (Fig. 1). A total of 264 patients had MAFLD-HCC, 205 had HBV-HCC, 671 had HCV-HCC, and 175 had A-HCC. Nine hundred eighty-five patients (74.9%) were male, and the median age of the whole study population was 71 years. Eight hundred twenty-nine patients had cirrhosis (63.0%), and 331 patients (25.2%) had steatosis. The great majority of patients were Child-Pugh A (1232, 93.7%); 81 (6.1%) were Child-Pugh B, and only 2 (0.2%) were Child-Pugh C.

The median size (IQR) of the tumours was 40 mm (25–60), and a single tumour was found in 851 (64.7%) cases. According to the BCLC staging system, 304 (23.1%) patients were BCLC-0, 570 (43.3%) patients were BCLC-A, 216 (16.4%) patients were BCLC-B, and 225 (17.1%) patients were BCLC-C. On pathology, 172 patients (13.1%) had satellitosis, 192 (14.6%) had macrovascular invasion, and 356 (27.1%) had microvascular invasion.

Laparoscopic hepatectomy was performed in 395 patients

Table 1
Comparison of clinical and pathological characteristics and short-term outcomes between the study groups in the whole study population.

Characteristics		MAFLD-HCC n = 264 n (%)	HBV-HCC n = 205 n (%)	HCV-HCC n = 671 n (%)	A-HCC n = 175 n (%)	*Overall p-values*	*p-values*[a]	*p-values*[b]	*p-values*[c]
CLINICAL									
Gender, male		219 (83.0)	161 (78.5)	447 (66.6)	158 (90.3)	<0.001	0.226	<0.001	0.031
Age, years, median (IQR)		71 (66–76)	68 (60–74)	72 (65–76)	70 (63–75)	<0.001	<0.001	0.706	0.205
BMI, median (IQR)		27.8 (25.0–31.0)	24.0 (22.0–26.3)	24.0 (22.0–26.0)	25.0 (23.0–27.0)	<0.001	<0.001	<0.001	<0.001
BMI	≥30 kg/m2	74 (28.0)	8 (3.9)	9 (1.3)	8 (4.5)	<0.001	<0.001	<0.001	<0.001
CCI, median (IQR)		7 (5–8)	5 (4–6)	6 (5–7)	6 (5–7)	<0.001	<0.001	<0.001	0.011
Diabetes type II		165 (62.5)	5 (2.4)	7 (1.0)	2 (1.1)	<0.001	<0.001	<0.001	<0.001
Cardiovascular diseases		104 (39.4)	14 (6.8)	89 (13.3)	19 (10.9)	<0.001	<0.001	<0.001	<0.001
Pulmonary diseases		41 (15.5)	12 (5.9)	63 (9.4)	20 (11.4)	0.005	0,001	0,007	0.224
Renal diseases		33 (12.5)	2 (1.0)	23 (3.4)	4 (2.3)	<0.001	<0.001	<0.001	<0.001
Metabolic Syndrome		111 (42.0)	0 (0.0)	0 (0.0)	0 (0.0)	<0.001	<0.001	<0.001	<0.001
ASA Score	3–4	127 (48.1)	52 (25.4)	206 (30.7)	45 (25.7)	<0.001	<0.001	<0.001	<0.001
LIVER FUNCTION									
Child Pugh	A	252 (95.5)	193 (94.1)	622 (92.7)	165 (94.3)	0.554	0.524	0.181	0.583
	B	12 (4.5)	12 (5.9)	47 (7.0)	10 (5.7)				
	C	0 (0.0)	0 (0.0)	2 (0.3)	0 (0.0)				
MELD score, median (IQR)		8 (6–9)	8 (7–9)	8 (7–9)	7 (7–9)	0.241	0.313	0.097	0.197
MELD	≥8	129 (48.9)	62 (30.2)	213 (31.7)	60 (34.3)	0.417	0.648	0.694	0.168
Steatosis		239 (90.5)	16 (7.8)	52 (7.7)	24 (13.7)	<0.001	<0.001	<0.001	<0.001
Cirrhosis		101 (38.3)	122 (59.5)	491 (73.2)	115 (65.7)	<0.001	<0.001	<0.001	<0.001
PLTs, 10^9/L, median (IQR)		186 (150–240)	172 (131–244)	163 (116–217)	164 (112–219)	0.068	0.424	<0.001	0.211
Esophageal varices		15 (5.7)	34 (16.6)	128 (19.1)	33 (18.9)	<0.001	<0.001	<0.001	<0.001
Splenomegaly		17 (6.4)	33 (16.1)	119 (17.7)	25 (14.3)	<0.001	0,001	<0.001	0.006
CPH		18 (6.8)	37 (18.0)	148 (22.1)	35 (20.0)	<0.001	<0.001	<0.001	<0.001
TUMOUR									
Size mm, median(IQR)		45 (30–70)	40 (30–70)	35 (24–50)	38 (25–60)	<0.001	0.812	<0.001	0.176
Size	>50 mm	118 (44.7)	83 (40.5)	191 (28.5)	60 (34.3)	<0.001	0.361	<0.001	0.030
Bilobar Disease		31 (9.8)	15 (8.3)	55 (8.9)	17 (8.6)	0.085	0.034	0.022	0.198
Number of tumours, median (IQR)		1 (1–2)	1 (1–2)	1 (1–2)	1 (1–2)	0.211	0.240	0.048	0.520
Number of tumours	Single Multiple	185 (70.1) 79 (29.1)	134 (65.4) 71 (34.6)	418 (62.3) 253 (37.7)	114 (65.1) 61 (34.9)	0.165	0.278	0.025	0.278
BCLC	0	39 (14.8)	40 (19.5)	181 (27.0)	44 (25.1)	<0.001	<0.001	<0.001	0.021
	A	149 (56.4)	78 (38.0)	266 (39.6)	77 (44.0)				
	B	42 (15.9)	31 (15.1)	110 (16.4)	33 (18.9)				
	C	34 (12.9)	56 (27.3)	114 (17.0)	21 (12.0)				
Satellitosis		48 (18.2)	26 (12.7)	76 (11.3)	22 (12.6)	0.048	0.105	0.005	0.116
Macrovascular Invasion		31 (11.7)	53 (25.9)	94 (14.0)	14 (8.0)	<0.001	<0.001	0.359	0.206
Microvascular Invasion		94 (35.6)	63 (30.7)	152 (22.6)	47 (26.8)	<0.001	0.212	<0.001	0.182
SURGERY									
Anatomic Resection		155 (58.7)	140 (68.3)	407 (60.7)	106 (60.6)	0.163	0.033	0.585	0.698
Major Hepatectomy		55 (21.7)	58 (30.4)	117 (19.1)	26 (17.0)	0.005	0.037	0.388	0.254
Laparoscopy		57 (21.6)	66 (32.2)	222 (33.1)	50 (28.6)	0.006	0.010	0.001	0.095
Pedicle Clamping		147 (55.7)	155 (75.6)	486 (72.4)	118 (67.4)	<0.001	<0.001	<0.001	0.011
R0 resection		190 (72.0)	149 (72.7)	504 (75.1)	119 (68.0)	0.249	0.439	0.410	0.506
SHORT TERM OUTCOMES									
Complications		94 (35.6)	67 (32.7)	235 (35.0)	61 (34.9)	0.920	0.508	0.866	0.872
Clavien Dindo > 3		19 (7.2)	17 (8.3)	62 (9.2)	11 (6.3)	0.434	0.439	0.241	0.737
Post-operative Ascites		21 (8.0)	15 (7.3)	63 (9.4)	20 (11.4)	0.488	0.797	0.490	0.221
PHLF		11 (4.2)	13 (6.3)	27 (4.0)	5 (2.9)	0.373	0.289	0.921	0.473
90 days mortality		11 (4.2)	5 (2.4)	21 (3.1)	3 (1.7)	0.485	0.307	0.432	0.152
Hospital stay, days, median (IQR)		8 (7–11)	9 (7–13)	9 (7–12)	9 (7–11)	0.132	0.051	0.010	0.110

IQR, interquartile range; BMI, body mass Index; CCI, charlson comorbidity index; ASA, American Society of Anesthesiologists; MELD, Model For End-Stage Liver Disease; PLTs, platelets; CPH, clinical portal hypertension; AFP, alpha-fetoprotein; BCLC, Barcelona Clinic Liver Cancer staging system; PHLF, Post Hepatectomy Liver Failure.

[a] MALFD-HCC vs HBV-HCC.

[b] MAFLD-HCC vs HCV-HCC.

[c] MAFLD-HCC vs A-HCC.

Table 2
Univariate and multivariate analysis of overall survival (OS) and recurrence free survival (RFS) survival of the whole study population.

VARIABLES		Overall Survival					Recurrence Free Survival				
		Univariate Analysis		Multivariate Analysis			Univariate Analysis		Multivariate Analysis		
		5-years OS rate	p-values	HR	95% CI	p-values	5-years RFS rate	p-values	HR	95% CI	p-values
Study group	MAFLD-HCC	46.0%	0.030			0.014	34.6%	0.403			
	HBV-HCC	67.1%		0.593	0.432–0.815	0.001	37.7%				
	HCV-HCC	57.3%		0.776	0.610–0.987	0.039	39.6%				
	A-HCC	59.6%		0.793	0.574–1.096	0.160	35.3%				
Gender	Female	57.2%	0.833				46.4%	0.006			
	Male	56.9%					35.5%				
Age	<70 years	58.2%	0.276				39.9%	0.260			
	>70 years	55.8%					36.9%				
MELD	<8	56.5%	0.129				36.6%	0.174			
	>8	52.2%					29.8%				
CPH	No	56.9%	0.531				37.9%	0.817			
	Yes	55.8%					39.7%				
Cirrhosis	No	62.0%	0.033	1.562	1.269–1.923	<0.001	42.4%	0.070	1.310	1.117–1.538	0.001
	Yes	53.9%					35.7%				
Number of tumours	Single	61.6%	<0.001	1.262	1.045–1.525	0.016	40.9%	0.003	1.160	0.993–1.354	0.061
	Multiple	48.7%					32.8%				
Tumour size	<50 mm	64.9%	<0.001	2.120	1.740–2.583	<0.001	43.9%	<0.001	1.592	1.357–1.868	<0.001
	>50 mm	40.4%					26.5%				
Macrovascular invasion	No	59.6%	<0.001	1.524	1.195–1.943	0.001	40.4%	<0.001	1.348	1.101–1.651	0.004
	Yes	39.0%					24.0%				
Satellitosis	No	60.3%	<0.001	1.802	1.417–2.291	<0.001	41.6%	<0.001	2.193	1.791–2.686	<0.001
	Yes	33.8%					12.4%				
BCLC	0	73.4%	<0.001				47.9%	<0.001			
	A	58.4%					39.9%				
	B	47.6%					28.8%				
	C	38.5%					27.1%				
Laparoscopy	No	56.2%	0.496				40.0%	0.045			
	Yes	59.0%					35.0%				
Pedicle Clamping	No	52.0%	0.071				38.4%	0.724			
	Yes	58.7%					37.6%				
Anatomic resection	No	57.3%	0.393				35.0%	0.173			
	Yes	56.3%					40.0%				
Major hepatectomy	No	60.1%	<0.001				41.6%	0.024			
	Yes	45.9%					34.8%				
R0 resection	No	44.2%	0.031				41.5%	0.002			
	Yes	56.6%					28.8%				

MELD, Model For End-Stage Liver Disease; CPH, clinical portal hypertension; BCLC, Barcelona Clinic Liver Cancer staging system.

(30.0%), and major hepatectomy was required in 256 patients (19.5%). The overall complication rate was 34.8% (n = 457), and the severe complication rate (Clavien-Dindo ≥3) was 8.3% (n = 109). The 90-day mortality rate was 3.0% (n = 40), and the median (IQR) length of hospital stay was 8 days (7-12).

Baseline clinical and pathological characteristics of the study population are summarized in Supplementary Table 1.

3.2. Comparison of the clinical, pathological and surgical findings according to the study groups

The median age was higher in MAFLD-HCC (71 years) than in HBV-HCC (68 years, p < 0.001) but similar to that in HCV-HCC (72 years, p = 0.706) and A-HCC (70 years, p = 0.205) (overall p < 0.001).

In the underlying liver, there was steatosis in 90.5% of MAFLD-HCC compared with 7.8% of HBV-HCC (p < 0.001), 7.7% of HCV-HCC (p < 0.001), and 13.7% of A-HCC (p < 0.001), and there was cirrhosis in 38.3% of MAFLD-HCC compared with 59.5% of HBV-HCC (p < 0.001), 73.2% of HCV-HCC (p < 0.001), and 65.7% of A-HCC (p < 0.001).

Regarding tumour characteristics, the median size of the tumour nodule was 45 mm in MAFLD-HCC compared with 40 mm in HBV-HCC (p = 0.812), 35 mm in HCV-HCC (p < 0.001), and 38 mm in A-HCC (p = 0.176) (overall p < 0.001). Comparison of the clinical and pathological characteristics, as well as the surgical details and short-term outcomes according to the study groups are fully reported in Table 1.

3.3. Prognostic factors for overall and recurrence-free survival in the whole study population

Uni- and multivariable survival analysis for the whole study population can be found fully reported in Supplementary Fig. 1.

The median and 5-year overall survival (OS) and recurrence-free survival (RFS) rates for the whole population were 82.0 months and 32.0 months and 55.6% and 37.5%, respectively. The 5-year OS rate was 46.0% in MAFLD-HCC compared with 67.1% in HBV-HCC, 57.3% in HCV-HCC and 59.6% in A-HCC (p = 0.030) (Supplementary Fig. 1A). No differences were found in the RFS rate among the study groups: the 5-year RFS rate was 34.6% in MAFLD-HCC compared with 37.7% in HBV-HCC, 39.6% in HCV-HCC and 35.3% in A-HCC (p = 0.403) (Supplementary Fig. 1B).

Multivariable survival analysis identified the following independent prognostic factors for overall survival: study group (aetiology) (MAFLD-HCC ref; HBV-HCC, p = 0.001; HCV-HCC, p = 0.039; A-HCC, p = 0.160), cirrhosis (p < 0.001), number of tumours (single or multiple) (p = 0.016), tumour size ≥50 mm (p < 0.001), macrovascular invasion (p = 0.001) and satellitosis (p < 0.001) (Table 2). We identified the following independent prognostic factors for RFS in the multivariable analysis: cirrhosis (p = 0.001), tumour size ≥50 mm (p < 0.001), macrovascular invasion (p = 0.004) and satellitosis (p < 0.001) (Table 2).

The results of univariable and multivariable subgroup analyses

Table 3
Comparison of clinical, pathological characteristics and short-term outcomes between the study groups in propensity score matched cohort.

Characteristics		MAFLD-HCC n = 85 n (%)	HBV-HCC n = 85 n (%)	HCV-HCC n = 85 n (%)	A-HCC n = 85 n (%)	*Overall p-values*	*p-values*[a]	*p-values*[b]	*p-values*[c]
CLINICAL									
Gender, male		77 (90.6)	77 (90.6)	77 (90.6)	77 (90.6)	1	1	1	1
Age, years, median (IQR)		69 (63–74)	69 (61–75)	69 (61–75)	69 (63–74)	0.536	0.256	0.670	0.916
BMI, median (IQR)		28.0 (26.0–31.1)	24.0 (21.6–26.0)	24.2 (22.6–26.9)	24 (23.0–26.1)	<0.001	<0.001	<0.001	<0.001
BMI	>30 kg/m2	24 (28.2)	2 (2.3)	0 (0.0)	5 (5.9)	<0.001	<0.001	<0.001	0.025
CCI, median (IQR)		7 (6–8)	5 (4–6)	6 (5–7)	6 (5–7)	<0.001	<0.001	0.027	0.028
Diabetes type II		61 (71.8)	1 (1.2)	1 (1.2)	0 (0.0)	<0.001	<0.001	<0.001	<0.001
Cardiovascular diseases		32 (37.6)	8 (9.4)	6 (7.1)	7 (8.2)	<0.001	<0.001	<0.001	<0.001
Pulmonary diseases		16 (18.8)	6 (7.1)	7 (8.2)	14 (16.5)	0.047	0.022	0.044	0.687
Renal diseases		11 (12.9)	1 (1.2)	3 (3.5)	3 (3.5)	0.003	0.003	0.026	0.026
Metabolic Syndrome		41 (48.2)	0 (0.0)	0 (0.0)	0 (0.0)	<0.001	<0.001	<0.001	<0.001
ASA Score	3–4	40 (47.1)	25 (29.4)	21 (24.7)	24 (28.2)	0.109	0.019	0.109	0.114
LIVER FUNCTION									
Child Pugh	A	84 (98.8)	84 (98.8)	84 (98.8)	84 (98.8)	1	1	1	1
	B	1 (1.2)	1 (1.2)	1 (1.2)	1 (1.2)				
	C	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)				
MELD score, median (IQR)		8 (7–9)	8 (6–9)	8 (7–9)	7 (7–9)	0.294	0.187	0.361	0.237
MELD	≥8	41 (48.2)	34 (40.0)	34 (40.0)	29 (34.1)	0.604	0.597	0.975	0.379
Steatosis		73 (85.9)	6 (7.1)	6 (7.1)	12 (14.1)	<0.001	<0.001	<0.001	<0.001
Cirrhosis		56 (65.9)	56 (65.9)	56 (65.9)	56 (65.9)	1	1	1	1
PLTS, 10^9/L, median (IQR)		179 (150–216)	162 (113–227)	157 (102–185)	170 (112–213)	0.052	0.303	0.005	0.198
Esophageal varices		5 (5.9)	16 (18.8)	16 (18.8)	17 (20.0)	0.036	0.007	0.032	0.001
Splenomegaly		6 (7.1)	14 (16.5)	16 (18.8)	12 (14.1)	0.143	0.057	0.022	0.135
CPH		6 (7.1)	17 (20.0)	19 (22.4)	17 (20.0)	0.035	0.014	0.005	0.014
TUMOUR									
Size mm, median (IQR)		38 (25–60)	37 (28–60)	36 (23–60)	40 (25–58)	0.913	0.859	0.595	0.936
Size	>50 mm	28 (32.9)	28 (32.9)	28 (32.9)	28 (32.9)	1	1	1	1
Bilobar Disease		8 (9.4)	6 (7.1)	4 (4.7)	10 (11.8)	0.422	0.309	0.912	0.496
Number of tumours, median (IQR)		1 (1–1)	1 (1–1)	1 (1–1)	1 (1–1)	0.726	0.512	0.704	0.666
Number of tumours	Single	65 (76.5)	65 (76.5)	65 (76.5)	65 (76.5)	1	1	1	1
	Multiple	20 (23.5)	20 (23.5)	20 (23.5)	20 (23.5)				
BCLC	0	21 (24.7)	21 (24.7)	21 (24.7)	21 (24.7)	1	1	1	1
	A	43 (50.6)	43 (50.6)	43 (50.6)	43 (50.6)				
	B	13 (15.3)	13 (15.3)	13 (15.3)	13 (15.3)				
	C	8 (9.4)	8 (9.4)	8 (9.4)	8 (9.4)				
Satellitosis		11 (12.9)	15 (17.6)	11 (12.9)	8 (9.4)	0.469	0.394	1	0.465
Macrovascular Invasion		9 (10.6)	11 (12.9)	8 (9.4)	5 (5.9)	0.472	0.634	0.798	0.264
Microvascular Invasion		21 (24.7)	33 (38.8)	25 (29.4)	19 (22.3)	0.254	0.072	0.254	0.812
SURGERY									
Anatomic Resection		47 (55.3)	54 (63.5)	43 (50.6)	47 (55.3)	0.392	0.274	0.539	1
Major Hepatectomy		18 (21.2)	17 (20.0)	14 (16.5)	13 (15.3)	0.719	0.955	0.828	0.692
Laparoscopy		16 (18.8)	27 (31.8)	17 (20.0)	22 (25.9)	0.176	0.052	0.846	0.269
Pedicle Clamping		43 (50.6)	61 (71.8)	64 (75.3)	58 (68.2)	0.005	0.010	0.001	0.022
R0 resection		68 (80.0)	60 (70.6)	50 (58.8)	58 (68.2)	0.595	0.167	0.428	0.429
SHORT TERM OUTCOMES									
Complications		35 (41.2)	35 (41.2)	42 (49.4)	41 (48.2)	0.542	1	0.674	0.355
Clavien Dindo > 3		6 (7.1)	6 (7.1)	10 (11.7)	7 (8.2)	0.447	1	0.329	0.833
Postoperative Ascites		9 (10.6)	7 (8.2)	6 (7.1)	6 (7.1)	0.817	0.599	0.272	0.417
PHLF		4 (4.7)	4 (4.7)	7 (8.2)	3 (3.5)	0.550	1	0.350	0.699
90 days mortality		5 (5.9)	2 (2.3)	3 (3.5)	1 (1.2)	0.061	0.044	0.107	0.038
Hospital stay, days, median (IQR)		8 (7–12)	9 (8–13)	10 (8–18)	9 (7–13)	0.017	0.156	0.001	0.076

IQR, interquartile range; BMI, body mass Index; CCI, charlson comorbidity index; ASA, American Society of Anesthesiologists; MELD, Model For End-Stage Liver Disease; PLTs, platelets; CPH, clinical portal hypertension; AFP, alpha-fetoprotein; BCLC, Barcelona Clinic Liver Cancer staging system; PHLF, Post Hepatectomy Liver Failure.
[a] MALFD-HCC vs HBV-HCC.
[b] MAFLD-HCC vs HCV-HCC.
[c] MAFLD-HCC vs A-HCC.

of prognostic factors for OS and RFS of MAFLD-HCC are presented in Supplementary Table 2.

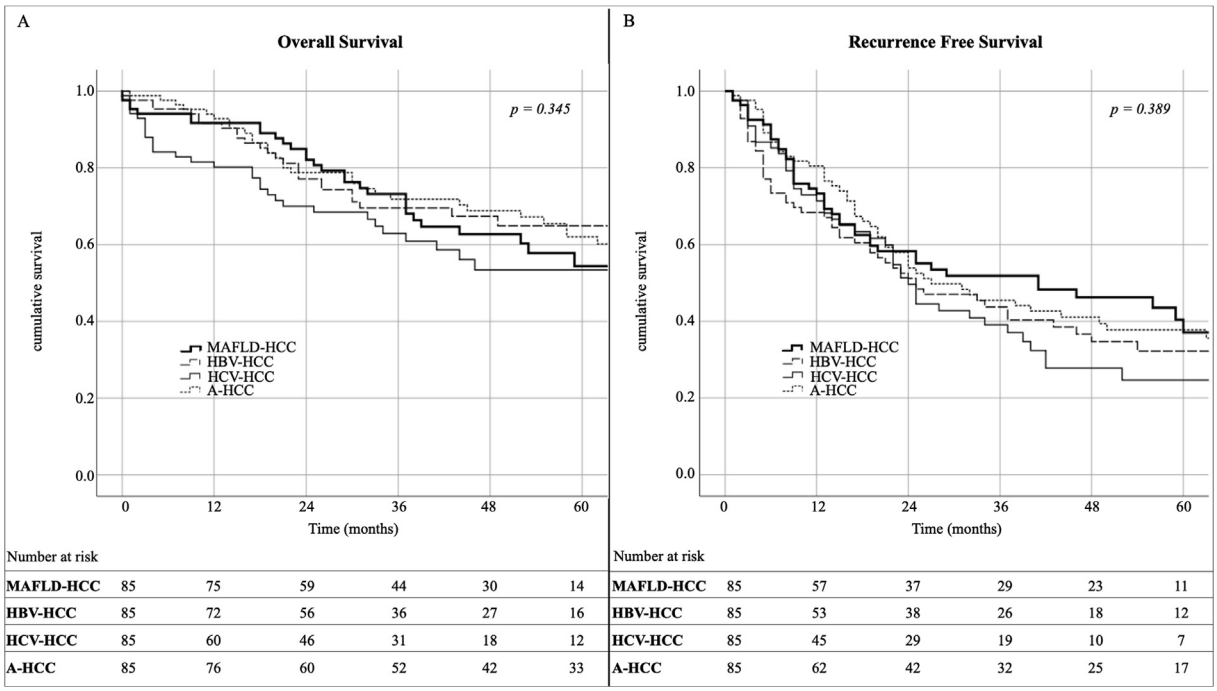
3.4. Comparison of the clinical, pathological and surgical findings according to the study groups in the propensity score matched cohort

After PSM, we obtained 340 patients, 85 per study group. Even in the matched cohort, some of the differences identified between the study groups in the whole population were maintained. (see Table 3).

Major hepatectomy was performed in 21.2% of MAFLD-HCC compared with 20.0% of HBV-HCC (p = 0.955), 16.5% of HCV-HCC (p = 0.828), and 15.3% of A-HCC (p = 0.692) (overall p = 0.719). Post hepatectomy liver failure occurred in 4.7% of MAFLD-HCC compared with 4.7% of HBV-HCC (p = 1.000), 8.2% of HCV-HCC (p = 0.350), and 3.5% of A-HCC (p = 0.699). The 90-day mortality rate was 5.9% in MAFLD-HCC, 2.3% in HBV-HCC (p = 0.044), 3.5% in HCV-HCC (p = 0.107), and 1.2% in A-HCC (p = 0.038) (overall p = 0.061) (Table 3).

3.5. Prognostic factors for overall and recurrence-free survival in the propensity score matched cohort

The median and 5-year OS and RFS rates for the matched cohort were 80.0 months and 26.0 months and 58.3% and 33.7%,



Number at risk

MAFLD-HCC	85	75	59	44	30	14
HBV-HCC	85	72	56	36	27	16
HCV-HCC	85	60	46	31	18	12
A-HCC	85	76	60	52	42	33

Number at risk

MAFLD-HCC	85	57	37	29	23	11
HBV-HCC	85	53	38	26	18	12
HCV-HCC	85	45	29	19	10	7
A-HCC	85	62	42	32	25	17

Fig. 2. Survival curves of the propensity score matched cohort according to the study group: A) Overall survival curves; B) Recurrence free survival curves. MAFLD-HCC, Metabolic Associated Fatty Liver Disease (MAFLD) related HCC; HBV-HCC, HBV related HCC; HCV-HCC, HCV related HCC; A-HCC, Alcohol related HCC.

respectively. The 5-year OS rate was 54.4% in MAFLD-HCC compared with 64.9% in HBV-HCC, 53.4% in HCV-HCC and 62.0% in A-HCC (p = 0.345) (Fig. 2A). The 5-year RFS rate was 37.1% in MAFLD-HCC compared with 32.2% in HBV-HCC, 24.7% in HCV-HCC and 37.8% in A-HCC (p = 0.389) (Fig. 2B).

Multivariable survival analysis identified the following independent prognostic factors for overall survival: cirrhosis (p = 0.004), number of tumours (single or multiple) (p = 0.047), tumour size ≥50 mm (p < 0.001) and satellitosis (p = 0.012). We identified the following independent prognostic factors for RFS in the multivariable analysis: number of tumours (single or multiple) (p = 0.010), tumour size ≥50 mm (p < 0.001) and satellitosis (p < 0.001) (Table 4).

4. Discussion

In Western countries, the incidence of MD-related HCC is continually increasing. In previously published studies, these patients were classified according to underlying liver characteristics (i.e., NAFLD-HCC) or the presence of metabolic syndrome (MS-HCC). In both of these populations, the strict classification criteria led to the exclusion of patients with HCC and MDs who did not fall exactly within the definitions used.

In 2015, Mittal et al. showed that in a US cohort of over 1500 patients with HCC, 8% had NAFLD-HCC [20]. In the same year, a study based on a multi-institutional Italian surgical cohort reported that metabolic syndrome could be identified as a unique risk factor for HCC in 6% of patients [12]. Moreover, in recent surgical series, the rate of cryptogenic HCC ranges between 13 and 18% [21,22].

The new MAFLD definition and classification used seems to be more inclusive and thus probably captures more patients with MD-related HCC. In fact, in the current study, MAFLD was recognized in 41.0% (989/2410) of the whole population and in 10.9% (264/2410) if we considered MAFLD to be the unique determinant for HCC (MAFLD-HCC), while cryptogenic HCC patients accounted for less than 7.0% (Fig. 1). Moreover, among the MAFLD-HCC patients, only 42.0% fulfilled the criteria of metabolic syndrome (Table 1).

As reported for NAFLD-HCC [23,24] or MS-HCC [25], MAFLD-HCC was confirmed to have specific clinical and pathological features that differed from the other groups. MAFLD-HCC patients were mostly overweight elderly males with solitary large tumours (27.8 kg/m^2 median BMI, 83.0% male, 71 years median age, 70.1% single tumour and 44.7% > 50 mm).

Although some authors assumed that the development of HCC in patients with MDs is related to the onset of cirrhosis [25], other studies clearly showed that HCC may also occur in noncirrhotic livers [12,26,27]. The current study confirmed this statement, as cirrhosis occurred in 38.3% of MAFLD-HCC patients.

Given the clinical and pathological differences between MAFLD-HCC and the other study groups (Table 1), we decided to compare the short- and long-term results of the surgery in the whole study population (Table 2) and after a PSM analysis (Tables 3–4).

Unfortunately, there are no specific data available in the literature regarding the surgical outcomes in MAFLD-HCC; consequently, we compared our results with surgical series on MS-HCC and NAFLD-HCC.

In the PSM cohort, MAFLD-HCC showed a nearly doubled postoperative mortality rate (overall p = 0.061) compared with the other groups, despite similar rates of severe complications and PHLF (Table 3). In one of the first series on this topic, Cauchy et al. reported a higher mortality rate (18%) after liver resection in MS-HCC with abnormal liver parenchyma (NAFLD or fibrosis) [28]. Further studies yielded similar results. In 2018, Tian et al. reported worse severe morbidity (grade 3–5) in 81 MS–HCC patients (33.3%) than in 1154 HBV-HCC patients (15.7%) (p < 0.001) [29]. Moreover, in another large eastern cohort of patients, Koh et al. comparing the surgical outcomes of 152 NAFLD-HCC patients with 844 non-NAFLD-HCC patients (including HCV-HCC and HBV-HCC), confirmed a higher major complication rate in NAFLD-HCC (16.2% vs 8.1%, p < 0.001), despite similar 90-day mortality rates (2.0% vs 2.5%) [30]. However, the high number of comorbidities (higher CCI and ASA scores), need for major hepatectomy due to a larger

Table 4
Univariate and multivariate analysis of overall survival (OS) and recurrence free survival (RFS) survival in the propensity score matched cohort.

		Overall Survival					Recurrence Free Survival				
VARIABLES		Univariate Analysis		Multivariate Analysis			Univariate Analysis		Multivariate Analysis		
		5-years OS rate	p-values	HR	95% CI	p-values	5-years RFS rate	p-values	HR	95% CI	p-values
Study group	MAFLD-HCC	54.4%	0.345				37.1%	0.389			
	HBV-HCC	64.9%					32.2%				
	HCV-HCC	53.4%					24.7%				
	A-HCC	62.0%					37.8%				
Gender	Female	44.9%	0.089				49.2%	0.140			
	Male	59.8%					32.3%				
Age	<70 years	59.9%	0.245				32.7%	0.536			
	>70 years	56.5%					35.4%				
MELD	<8	61.8%	0.212				35.0%	0.744			
	>8	52.8%					27.2%				
CPH	No	61.6%	0.158				34.4%	0.258			
	Yes	43.2%					30.4%				
Cirrhosis	No	71.2%	0.030	1.936	1.234–3.036	0.004	36.9%	0.448			
	Yes	53.4%					32.3%				
Number of tumours	Single	61.3%	0.044	1.486	1.005–2.198	0.047	37.1%	0.075	1.535	1.109–2.125	0.010
	Multiple	49.7%					24.6%				
Tumour size	<50 mm	64.9%	<0.001	2.719	1.853–3.990	<0.001	38.3%	<0.001	1.812	1.323–2.482	<0.001
	>50 mm	45.1%					23.4%				
Macrovasc invasion	No	60.5%	0.011				35.8%	<0.001			
	Yes	39.8%					8.0%				
Satellitosis	No	62.1%	<0.001	1.839	1.144–2.955	0.012	37.3%	<0.001	2.850	1.914–4.245	<0.001
	Yes	32.8%					10.3%				
BCLC	0	75.4%	<0.001				48.6%	0.001			
	A	59.1%					32.5%				
	B	47.3%					23.8%				
	C	34.7%					10.1%				
Laparoscopy	No	57.6%	0.260				31.7%	0.373			
	Yes	59.9%					40.7%				
Pedicle Clamping	No	56.2%	0.295				37.6%	0.579			
	Yes	58.9%					31.2%				
Anatomic resection	No	64.6%	0.018				33.3%	0.286			
	Yes	53.0%					34.2%				
Major hepatectomy	No	62.1%	0.003				41.1%	0.005			
	Yes	44.3%					16.7%				
R0 resection	No	64.7%	0.296				20.5%	0.034			
	Yes	55.8%					38.4%				

MELD, Model For End-Stage Liver Disease; CPH, clinical portal hypertension; BCLC, Barcelona Clinic Liver Cancer staging system.

tumour and underlying abnormal liver (steatosis, steatohepatitis and cirrhosis) could justify these results.

The long-term results after surgery in MD-related HCC are still controversial. In the survival analysis before PSM, MAFLD-HCC had a significantly worse OS than the other groups (Table 2 and Supplementary Fig. 1), and the determinant aetiology seemed to be an independent prognostic factor for OS. However, after PSM, the OS was similar to that of the other groups (Fig. 2), and the multivariable analysis showed that clinical and pathological factors such as cirrhosis, number and size of tumours and satellitosis were the main independent predictors of OS (Table 4).

Recently, Yang et al. compared the survival after surgery of NAFLD-HCC and HBV-HCC before and after PSM, showing similar OS among the study groups in both matched and unmatched cohorts [31]. Conversely, in the study by Koh et al., NAFLD-HCC had a significantly better OS than non-NAFLD-HCC (5-year OS, 70.1% vs 60.9%, $p = 0.004$, respectively); however, the study groups were not matched or homogeneous. In particular, NAFLD-HCC had a surprisingly smaller lesion than non-NAFLD-HCC (median size, 7 mm vs 40 mm, respectively) [30]. Furthermore, in the study of Viganò et al., MS-HCC seemed to have a slightly better prognosis than a matched cohort of HCV-HCC (5-year OS, 65.6% vs 61.4%, $p = 0.023$, respectively) [12].

Wakai et al. reported, in a small sample size study, that NAFLD-HCC had better RFS than HCV-HCC and HBV-HCC, supporting the hypothesis that late carcinogenesis and consequent recurrence could be less frequent in NAFLD-HCC [32]. However, subsequent and larger studies showed no differences in RFS between NAFLD-HCC and viral-HCC [31,33]. Even in the current study, there were no differences among the groups in terms of RFS.

The present study had several limitations. First, the retrospective design, the long period of inclusion and the multi-institutional nature of He.RC.O.Le.S registry could lead to missed data and to selection bias due to differences in surgical policy among the centers. Second, since the enrolled patients had resectable tumours with good liver function, the results could not be generalized to all patients with MALFD-HCC. Third, although PSM analysis was performed, the relatively small sample size of the matched groups limited the statistical power of the current study. Nonetheless, it represents the first large surgical series that analysed the clinical impact of the new MAFLD definition in comparison with all three main and most frequent HCC aetiologies. External validation and further studies are needed to confirm our results.

In conclusion, MAFLD-HCC shows unique clinical and pathological characteristics and represents an emerging and challenging issue for liver surgeons. Surgical treatment for MAFLD-HCC seems to have a higher but acceptable operative risk and similar long-term results to viral- and alcohol-related HCC. Survival seems to be related to clinical and pathological factors rather than determinant aetiology. Surveillance programs should be recommended to

MALFD patients for earlier detection of HCC, which could lead to favourable effects on outcomes.

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Declaration of competing interest

The Authors declare that there are no conflicts of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejso.2021.07.015.

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