Original research

Epidemiological trends and trajectories of MAFLD-associated hepatocellular carcinoma 2002–2033: the ITA.LI.CA database

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ABSTRACT

Background Metabolic dysfunction-associated fatty liver disease (MAFLD) represents a new inclusive definition of the whole spectrum of liver diseases associated to metabolic disorders. The main objective of this study was to compare patients with MAFLD and non-MAFLD with hepatocellular carcinoma (HCC) included in a nationally representative cohort.

Methods We analysed 6882 consecutive patients with HCC enrolled from 2002 to 2019 by 23 Italian Liver Cancer centres to compare epidemiological and future trends in three subgroups: pure, single aetiology MAFLD (S-MAFLD); mixed aetiology MAFLD (metabolic and others, M-MAFLD); and non-MAFLD HCC.

Results MAFLD was diagnosed in the majority of patients with HCC (68.4%). The proportion of both total MAFLD and S-MAFLD HCC significantly increased over time (from 50.4% and 3.6% in 2002–2003, to 77.3% and 28.9% in 2018–2019, respectively, p<0.001). In Italy S-MAFLD HCC is expected to overcome M-MAFLD HCC in about 6 years. Patients with S-MAFLD HCC were older, more frequently men and less frequently cirrhotic with clinically relevant portal hypertension and a surveillance-related diagnosis. They had more frequently large tumours and extrahepatic metastases. After weighting, and compared with patients with non-MAFLD, S-MAFLD and M-MAFLD HCC showed a significantly lower overall (p=0.026, p=0.004) and HCC-related (p<0.001, for both) risk of death. Patients with S-MAFLD HCC showed a significantly higher risk of non-HCC-related death (p=0.006).

Conclusions The prevalence of MAFLD HCC in Italy is rapidly increasing to cover the majority of patients with HCC. Despite a less favourable cancer stage at diagnosis, patients with MAFLD HCC have a lower risk of HCC-related death, suggesting reduced cancer aggressiveness.

Significance of this study

What is already known on this subject?

⇒ Metabolic dysfunction-associated fatty liver disease (MAFLD) represents a new inclusive definition of the whole spectrum of liver diseases associated to metabolic disorders. Hepatocellular carcinoma (HCC) is the most common type of primary liver cancer in adults. Data on the prevalence of the previously called non-alcoholic fatty liver disease in patients with HCC are not recent and controversial, while studies evaluating the prevalence of MAFLD (based on the new definition and diagnostic criteria) in patients with HCC are lacking.

What are the new findings?

⇒ MAFLD was diagnosed in the majority of Italian patients with HCC (68.4%). MAFLD HCC is expected to become the only form of HCC in Italy in about 10–12 years. Pure MAFLD HCC (in the absence of any additional aetiology, single aetiology MAFLD (S-MAFLD)) had advanced fibrosis/cirrhosis in 90% of cases and a lower surveillance-related diagnosis. Despite tumours being larger, more frequently multinodular, metastatic and with higher α-fetoprotein levels, S-MAFLD was characterised by a significantly lower overall and HCC-related risk of death and higher non-HCC related death risk, suggesting reduced cancer aggressiveness.

INTRODUCTION

Hepatocellular carcinoma (HCC) accounts for more than 80% of primary liver cancer and is the leading cause of mortality in patients with cirrhosis.[1 2]

How might it impact on clinical practice in the foreseeable future?

The new MAFLD diagnostic criteria allow for a better definition of the prevalence of metabolic comorbidities in HCC. MAFLD HCC, the most common form of liver cancer, may be driven by the sole metabolic factors, sometimes in the absence of cirrhosis, or in association with virus or alcohol, with differences in tumour stage, aggressiveness and risk of death. This evidence opens a new scenario for treatment, where obesity, diabetes and other comorbidities need to be carefully considered to reduce the pending, competing risk of cardiovascular outcome. Scientific societies of diabetes and obesity should encourage the evaluation of fibrosis, either by surrogate biomarkers or by transient elastography, in all patients with evidence of hepatic abnormalities, considering the high risk of HCC.

Worldwide, the main causes of this cancer remain chronic hepatitis B virus (HBV) and hepatitis C virus (HCV) infections and alcohol abuse, but over the last two decades a growing proportion of HCCs has been associated to metabolic disorders such as obesity, diabetes and hyperlipidaemia, associated with fatty liver.[3] Indeed, non-alcoholic fatty liver disease (NAFLD) has grown over the past two decades from a relatively unknown disease (and underestimated in terms of clinical consequences) to the recognised most common cause of chronic liver disease in the world, considering that NAFLD is estimated to affect 25% of the general population.[4] Non-alcoholic steatohepatitis (NASH), the subtype of NAFLD that can progress to cirrhosis, HCC and liver-related death,[5] is the most rapidly increasing indication for liver transplantation in the USA.[6]

Conversely, vaccination and therapy for HBV infection, prevention campaigns for sexual and iatrogenic transmission of HBV and HCV and the availability of potent antiviral agents for HCV are reducing the burden of chronic viral liver diseases.[7] Data on the prevalence of NAFLD-associated HCC are not recent and controversial, ranging from 14.1% in the USA to 35% in Northern England, with a greater than 10-fold increase in 10 years.[8 9] The geographical distribution in Europe shows that Italy has a relatively high incidence of primary liver cancer[1] but the prevalence of NAFLD-HCC is controversial and largely unknown.[3 10–12]

An international panel of experts has recently proposed a panel of clear and simple criteria for the diagnosis of *metabolic (dysfunction) associated fatty liver disease* (MAFLD), which transforms the diagnosis of NAFLD from an exclusion to an inclusion process.[13 14] The diagnosis relies on the recognition of underlying metabolic abnormalities, given that NAFLD may frequently coexist with other conditions. The term MAFLD thus represents an umbrella definition including several subphenotypes, with overlapping contributors in individual patients, such as inappropriate alcohol consumption and viral hepatitis. Combined aetiology is expected to make the natural history of disease worse than that of pure MAFLD. Although dissenting opinions were expressed,[15] the new MAFLD definition definitely focuses on metabolic disorders as primary factors or cofactors in the development of fatty liver.

To our knowledge, studies evaluating the prevalence of MAFLD (based on the new definition and diagnostic criteria) in patients with HCC are lacking. The primary aim of the present study was thus to assess the epidemiological trajectories, in recent and future years, of MAFLD-HCC in the Italian Cancer Liver (ITA.LI.CA) database that represents the largest and most comprehensive HCC data collection of the last 20 years in a Western country. Secondary aims were the analyses of overall survival, staging and treatment allocation of patients with MAFLD-HCC, compared with non-MAFLD HCC.

METHODS

Patients

We analysed the ITA.LI.CA registry, currently including 7816 patients consecutively diagnosed with HCC and followed-up by 23 centres (9 acting as primary and 14 as tertiary referral centres) from January 1987 to December 2019. The inclusion criterion was the presence of HCC diagnosed according to Italian or international guidelines available at the time of cancer detection. Data were collected prospectively and updated every 2 years; entries are regularly checked for consistency by the group coordinator and, whenever clarification or additional information are deemed necessary, relevant cases are returned to the recruiting centre before final inclusion. The ITA.LI.CA database management conforms to the past and the current Italian legislation regarding privacy, and the present study conforms to the ethical guidelines of the Declaration of Helsinki. Due to the design of the database and of the study it was not possible to involve patients and the public in any way in this research.

For the purpose of this study, we analysed 6882 consecutive patients diagnosed with HCC and enrolled in the ITA.LI.CA database from 2002 to 2019 (first semester) in order to rely on a follow-up of at least 2 years. Data before 2002 were excluded because too many data were missing for descriptive statistics. To describe epidemiological trends the study period was divided in nine consecutive fractions (from 2002–2003 to 2018–2019).

Aetiology and diagnosis of liver disease

The aetiology of chronic liver disease and HCC was defined by clinicians participating in the ITA.LI.CA. programme at time of record upload, according to generally agreed criteria[12 16 17]:

- HBV, for carriers of HBV surface antigen (±hepatitis delta virus);
- HCV, for patients positive for serum anti-HCV antibody;
- Alcohol, in the presence of daily ethanol intake exceeding 20 g for women and 30 g for men, for more than 10 years, in the absence of any other cause of liver injury.

Other aetiologies, including haemochromatosis, Wilson disease, α-1 antitrypsin deficiency, primary biliary cirrhosis and sclerosing cholangitis, were defined according to clinical records. Aetiologies and comorbidities were taken from the initial records of individual cases in the ITA.LI.CA database, that are locked immediately after inclusion.

The presence of cirrhosis (YES/NO) was defined at time of enrolment on the basis of clinical/laboratory data, eventually supported by liver biopsy, but biopsy was not mandatory and there was not a specific field describing how the diagnosis was made (ie, merely clinical or histological).[12 16 17] In the population defined without cirrhosis (n=480 patients), the degree of hepatic fibrosis was based on the fibrosis-4 (FIB-4) index, as follows:

- Absence of fibrosis (<1.30);
- Fibrosis F1–F2 (>1.3 and <3.25, or >1.3 and <2 for patients older than 65);
- Fibrosis F3 (>3.25, or >2 for patients older than 65).[18]

In a sensitivity analysis, the upper FIB-4 limit for patients aged below 65 was also set at 2.67.[19]

At time of enrolment, the presence of steatosis was not systematically defined by imaging or histology and no retrospective data

were available. Accordingly, MAFLD cases were defined only by the presence of at least one of the following characteristics: (a) overweight/obesity (body mass index (BMI) >25 kg/m^2); (b) type 2 diabetes; (c) evidence of metabolic dysregulation,[13] defined by the presence of at least two of the following criteria:

1. Fasting glucose levels 100–125 mg/dL or antidiabetic treatment;
2. Triglycerides >1.7 mmol/L (150 mg/dL) or specific drug treatment;
3. High-density lipoprotein cholesterol <1.0 mmol/L (40 mg/dL) in men or <1.3 mmol/L (50 mg/dL) in women or specific drug treatment;
4. Blood pressure >130/85 mm Hg or specific drug treatment.

Three additional proposed criteria for metabolic dysregulation (waist circumference, high sensitivity C reactive proteins and Homeostasis Model Assessment index) were not available in the ITA.LI.CA database.

We then stratified HCC cases into three groups[13]:

- S-MAFLD (single aetiology MAFLD): including patients with HCC with a diagnosis of either MAFLD or MAFLD-cirrhosis, in the absence of any additional aetiology;
- M-MAFLD (mixed aetiology MAFLD): including patients with HCC with a diagnosis of either MAFLD or MAFLD-cirrhosis and with additional aetiological factor(s) (ie, HCV, HBV, at risk alcohol intake);
- Non-MAFLD: including patients with HCC not associated with metabolic disorders.

True cryptogenic HCC cases, defined by the absence of any defined risk factor, were included in the non-MAFLD cohort.

Staging and treatment of HCC

Cancer burden was assessed by liver CT and/or MRI, while further investigations aimed at detecting extrahepatic tumour spread were generally carried out when clinically indicated or routinely in patients with advanced HCC or candidates for liver transplantation (LT). HCC was staged according to Barcelona Clinic Liver Cancer (BCLC) and ITA.LI.CA staging systems.[20–25]

When patients underwent multiple treatments, they were classified according to the most effective one using the following hierarchy: LT, liver resection (LR), percutaneous ablation (ABL), transarterial chemoembolisation/embolisation or radioembolisation (IAT, intra-arterial therapies), sorafenib (SOR) and other therapies or best supportive care (OTHER/BSC).[25–27]

Study design and statistical analysis

The objective of this study was to compare the epidemiology, the clinical characteristics, the management and outcome of MAFLD and non-MAFLD HCC described in a large, nationally representative cohort.

We performed two main analyses. First, we compared the epidemiological trends of MAFLD and non-MAFLD groups by their frequency across biennials. Epidemiological trends were graphically shown and the statistical significance of differences was evaluated using a linear regression model and analysis of variance. Linear regression models were also used to explore future trajectories of MAFLD and non-MAFLD HCC.

Second, we compared S-MAFLD, M-MAFLD and non-MAFLD HCC in terms of patients' baseline characteristics, staging, treatment allocation and overall survival. In order to perform this comparison, continuous variables were summarised by median (25%–75% CI) and groups were compared by Mann-Whitney U test. Categorical variables were summarised with frequencies and percentages, and groups compared by χ^2 test. Following McCaffrey *et al* indications, absolute standardised mean difference and the Kolmogorov-Smirnov statistic were used to assess aetiology-related imbalances on baseline variables (ie, each subgroup was compared with the rest of the population).[28]

Propensity score values and inverse probability weights (IPW) were then calculated using generalised boosted models as described by McCaffrey *et al*.[28] This is a *machine learning technique* using a flexible estimation method that can adjust for a large number of covariates. In the presence of multiple treatments, the authors proposed to use this methodology in the following fashion to obtain weights: first, create dummy indicators for each of the aetiological group (aetiology group vs rest of the population), then fit separate models to each dummy aetiological indicator and obtain the estimated propensity score for the given aetiological group.

All potential confounders were included in boosted models: age and sex, surveillance for HCC, performance status (PS), Child-Pugh-Turcotte class, model for end stage liver disease score (MELD), clinically relevant portal hypertension, tumour-related variables (size and number of lesions, macrovascular invasion, metastases, α-fetoprotein (AFP) values) and main treatment. Variables related to MAFLD definition (ie, BMI, diabetes, hypertension and dyslipidaemia) were excluded from the models. In order to reduce the type I error rate (because of the inflated sample size in the pseudo data), we used stabilised weights (SW) as:

SW=p/PS for the study group, and SW=(1-p)/(1-PS) for the control group where p is the probability of aetiology without considering covariates and PS is the propensity score. The overall survival was calculated from the date of HCC diagnosis to the date of death, last follow-up evaluation or censoring date (31 December 2019). Unweighted and weighted survival curves were calculated using the Kaplan-Meier method and compared using the log-rank test. A weighted multivariable Cox survival model was also calculated.

The proportional-hazards assumption was tested on the basis of Schoenfeld residuals.

Since recent literature indicates that the prognosis of patient with HCC is influenced not only by cancer-related death, but also by liver failure and extrahepatic causes of death, weighted competing-risk analyses were performed using the methodology provided by Fine and Gray.[29–31]

Survival analyses were performed both before and after correction for the lead-time bias in patients with HCC diagnosed under surveillance, as previously reported.[32] Missing data of study covariates always involved less than 10% of patients, and were estimated using the maximum likelihood estimation method.[33]

The prognostic performance of ITA.LI.CA staging[34] and BCLC classification[21] was calculated using the Harrel Concordance Index, and the Akaike Information Criterion (AIC) derived by a Cox regression model. The AIC is particularly useful to compare ordinary prognostic systems with a different number of stages/points. A low AIC value testifies a high homogeneity and monotonicity of gradients, while high values of concordance-index indicate high discriminatory ability and monotonicity of gradients.[34]

All analyses were performed in JMP Pro V.15.2.0 (2019 SAS Institute), Stata V.13.0 (Copyright 1985–2013 StataCorp LP) and R application V.4.0.0 GUI 1.71 (S. Urbanek & H.-J. Bibiko, R Foundation for Statistical Computing, 2016). A two-tailed p value<0.05 was considered statistically significant.

Table 1 Metabolic characteristics of S-MAFLD, M-MAFLD and non-MAFLD patients with hepatocellular carcinoma

Variables	S-MAFLD (N=1181) Number (%)	M-MAFLD (N=3524) Number (%)	Non-MAFLD (N=2177) Number (%)
Body weight			
Normal	381 (32.26)*	1861 (52.81)*	2177 (100.00)*
Overweight	435 (36.83)*	1241 (35.22)*	0*
Obesity	365 (30.90)*	422 (11.98)*	0*
Type 2 diabetes	803 (68.00)*	1597 (45.32)*	0*
Pre-diabetes	188 (15.92)*	1199 (34.02)*	651 (29.90)*
Hypertension	615 (52.08)*	1631 (46.28)*	281 (12.91)*
Hypertriglyceridaemia	586 (49.62)*	461 (13.08)*	20 (0.92)*
Low HDL cholesterol	197 (49.62)*	1676 (47.56)*	361 (16.58)*

*P value<0.05 in the comparison of each group versus all remaining cases.
HDL, high density lipoprotein; MAFLD, metabolic associated fatty liver disease; M-MAFLD, mixed aetiology MAFLD; S-MAFLD, single aetiology MAFLD.

RESULTS

Baseline characteristics, staging and main treatment

Patient's metabolic baseline characteristics are described in table 1. Globally, 1181 cases were classified as S-MAFLD (17.1%), 3524 (51.2%) as M-MAFLD and 2177 (31.6%) as non-MAFLD. By definition, metabolic alterations were rare in the non-MAFLD cohort. Type 2 diabetes, obesity and hypertriglyceridaemia were significantly more common in S-MAFLD than in M-MAFLD. Notably, 381 cases without other aetiological factors (30.1% of S-MAFLD) and 1861 with viral or alcohol comorbidities (52.8% of M-MAFLD) were included in the respective cohorts because of the presence of diabetes or two metabolic factors, in the absence of overweight/obesity ('lean MAFLD').[13 14]

Demographic data and tumour characteristics are shown in table 2. Cirrhosis was present in 85.6% of patients with S-MAFLD HCC, in contrast to the near totality of other groups (95.1% in M-MAFLD and 94.3% in non-MAFLD, p value vs S-MAFLD: <0.05 for both). Notably, 113/1181 patients with S-MAFLD were classified as fibrosis F0–F2 according to FIB-4 score (9.6%) versus 72/3524 of M-MAFLD (2.0%) and 53/2177 of non-MAFLD (2.4%) (p<0.001 for both comparisons). These figures did not change considerably when the FIB-4 cut-off of advanced fibrosis was set at 2.67 for patients aged <65 (7.79%, 1.53% and 1.93% in S-MAFLD, M-MAFLD and non-MAFLD, respectively) (data not reported in detail, p<0.001). In S-MAFLD, the presence of HCC was diagnosed less frequently during surveillance compared with other groups (p<0.05). Moreover, S-MAFLD HCCs were significantly larger and more frequently associated with metastases, but with lower AFP levels compared with HCC of other aetiology (p<0.05). S-MAFLD HCCs were less frequently in ITA.LI.CA stage 0 and treated with LT and ABL, and were more frequently treated with LR, SOR, OTHER/BSC therapies than other groups (table 2, p<0.05).

Patients with non-MAFLD were younger, had more frequently clinically relevant portal hypertension and MELD >10 than MAFLD; they had less frequent extrahepatic spread, but more frequent macrovascular invasion and high AFP levels than non-MAFLD (p<0.05). As a consequence, they were less frequently in ITA.LI.CA stage A and more commonly in stages B2 and C and treated with IAT than MAFLD (table 2, p<0.05).

In the M-MAFLD cohort (online supplemental table 1), the presence of HCV was the most common cofactor (67%).

Table 2 Demographic data and liver-related and tumor-related characteristics in S-MAFLD, M-MAFLD and non-MAFLD patients with hepatocellular carcinoma

Variables	S-MAFLD (N=1181) Number (%) or median (Q1–Q3)	M-MAFLD (N=3524) Number (%) or median (Q1–Q3)	Non-MAFLD (N=2177) Number (%) or median (Q1–Q3)
Female sex	219 (18.54)*	1009 (28.63)*	353 (16.24)*
Age (years)	69 (63–75)*	69 (61–76)*	67 (58–74)*
Age >70 years	508 (43.01)	1607 (45.60)*	821 (37.71)*
Surveillance	533 (45.13)*	2177 (61.78)*	1329 (61.05)*
FIB-4 grade in patients diagnosed without cirrhosis			
F0	22 (1.86)*	11 (0.31)*	10 (0.46)*
F1–2	91 (7.71)*	61 (1.73)*	43 (1.98)*
F3	69 (5.84)*	102 (2.89)*	71 (3.26)*
Diagnosis of cirrhosis	999 (84.59)*	3350 (95.06)*	2053 (94.30)*
CRPH	887 (75.11)*	2818 (79.97)	1796 (82.50)*
MELD	10 (8–12)	10 (8–12)*	10 (8–12)*
MELD >10	422 (35.73)*	1220 (34.62)*	1072 (49.24)*
Child B and C	360 (30.48)	1091 (30.96)	689 (31.65)
ECOG PS>0	346 (29.30)	1040 (29.51)*	563 (25.86)*
Number of nodules	1 (1–3)	1 (1–3)	1 (1–3)
Multinodular	563 (47.67)	1650 (46.82)	1041 (47.82)
Largest diameter (mm)	35 (22–56)*	30 (20–47)*	30 (20–50)
Largest diameter >50 mm	319 (27.01)*	701 (19.89)*	472 (21.68)
Macrovascular invasion	161 (13.63)	454 (12.88)*	357 (16.40)*
Metastases	84 (7.11)*	151 (4.29)	79 (3.62)*
AFP (ng/ml)	7 (5–162)	17 (7–239)*	34 (7–756)*
AFP >1000 ng/mL	182 (15.41)*	560 (15.89)*	468 (21.50)*
Radical therapy	581 (49.20)	1830 (51.93)*	1091 (50.11)
ITA.LI.CA stage			
0	158 (13.38)*	612 (17.37)*	376 (17.27)
A	294 (24.89)	883 (25.06)*	481 (22.10)*
B1	285 (24.13)	836 (23.72)	504 (23.15)
B2	94 (7.96)	261 (7.41)	184 (8.45)*
B3	91 (7.71)	230 (6.53)	151 (6.94)
C	113 (9.57)	243 (6.90)*	219 (10.06)*
D	146 (12.36)	459 (13.03)	262 (12.04)
BCLC stage			
0	42 (3.56)*	193 (5.48)	114 (5.24)
A	527 (44.62)*	1665 (47.25)*	970 (44.56)*
B	209 (17.70)	499 (14.16)*	352 (16.17)
C	340 (28.79)*	914 (25.94)	590 (27.10)
D	63 (5.33)	253 (7.18)	151 (6.94)
Main therapy			
LT	33 (2.79)*	163 (4.63)	104 (4.78)
LR	225 (19.05)*	491 (13.93)*	322 (14.79)
ABL	298 (25.23)*	1132 (32.12)*	639 (29.35)*
IAT	267 (22.61)	762 (21.62)*	520 (23.89)*
SOR	83 (7.03)*	193 (5.48)*	126 (5.79)
OTHER/BSC	275 (24.3)*	702 (19.90)	466 (21.40)

*P value<0.05 in the comparison of each group versus other groups all remaining cases.
ABL, percutaneous ablation or alcohol injection; AFP, α-fetoprotein; BCLC, Barcelona Clinic Liver Cancer; CRPH, clinically relevant portal hypertension; FIB-4, fibrosis-4 index; IAT, intra-arterial therapy; ITA.LI.CA, Italian Liver Cancer; LR, liver resection; LT, liver transplantation; MAFLD, metabolic associated fatty liver disease; MELD, model for end stage liver disease; M-MAFLD, mixed aetiology MAFLD; OTHER/BSC, other therapies or best supportive care; ECOG PS, Eastern Cooperative Oncology Group performance status; Q1, first quartile; Q3, third quartile; S-MAFLD, single aetiology MAFLD; SOR, sorafenib.

Patients with HBV and who are alcoholic were younger, less frequently women and less frequently diagnosed under surveillance than patients with HCV. Moreover, HBV and alcohol had more advanced tumours and more decompensated cirrhosis than patients with HCV.

Epidemiological trends and trajectories of MAFLD and non-MAFLD HCC

The proportion of S-MAFLD significantly increased over the study period (figure 1A), from 3.6% in 2002–2003 to 28.9% in 2018–2019 (p<0.001). Conversely, the proportion of patients with HCV significantly decreased (from 64.4% to 45.8%, p<0.001), as well as that of HBV (from 15.7% to 10.6%, p<0.001), leading to a sharp fall of the overall viral aetiology (p<0.001). The proportion of alcohol-related HCC also decreased (from 14.5% to 12.4%, p<0.001).

Differently from S-MAFLD, the proportion of M-MAFLD remained almost stable over time (figure 1B), from 46.8% in the first biennium to 48.4% in the last period (p=0.445). Furthermore, the relative proportion of patients with non-MAFLD significantly and continuously decreased over time, from 49.6% to 22.7% (p<0.001). Globally (figure 1C), the majority of Italian patients with HCC (68.4%) were defined as MAFLD (sum of S-MAFLD and M-MAFLD) and the proportion significantly increased over time (from 50.4% to 77.3%, p<0.001).

Using linear regression models, we extended to future years the epidemiological trends of MAFLD and non-MAFLD HCC (figure 1 panels A–C). We calculated that S-MAFLD HCC should overcome HCV HCC (figure 1A), as well as M-MAFLD HCC (figure 1B) in about 4 and 6 years, respectively. MAFLD HCC will become the only form of HCC in Italy in about 10–12 years (figure 1C).

Outcomes

Using stabilised IPW we obtained three pseudo-populations with sample sizes similar to that of original populations, but very well balanced for all baseline non-metabolic characteristics (table 3). Risk of death curves and multivariable analyses before (online supplemental figure 1 and online supplemental table 2) and after correction for lead-time bias in patients with HCC diagnosed under surveillance (figure 2, table 4, and online supplemental table 3) largely overlapped; for this reason, only the analyses after correction are presented.

After a median follow-up for survivors of 70.8 months (95% CI: 67.1 to 73.7), median overall survival was significantly lower (p=0.000) in non-MAFLD (23.8 months) than in S-MAFLD (28.1 months) and M-MAFLD (27.1 months) (figure 2A). Data were confirmed also after weighting, with a significantly lower overall risk of death in MAFLD compared with patients with non-MAFLD HCC (figure 2B). These results were confirmed also when the same curves were not adjusted for lead time bias (online supplemental figure 1).

Online supplemental figure 2 and 3 showed that the outcome of patients with M-MAFLD was not significantly influenced by the presence of different aetiological factors. Other subgroup analyses in patients with S-MAFLD and M-MAFLD suggested that metabolic factors similarly influenced the risks of death in the two cohorts (online supplemental table 4); in particular, in both cohorts the presence of diabetes was significantly associated with an increased risk of death from non-HCC-related causes, whereas BMI >25 kg/m^2 was associated with a reduced all-cause risk of death (online supplemental table 4).

The ITA.LI.CA staging provided a more granular stratification of patients (tables 2 and 3) and a better prognostic performance (online supplemental figure 4) than BCLC classification.

At multivariable weighted Cox analysis (table 4), ITA.LI.CA stage and the main treatment showed a strong impact on death risk; both S-MAFLD and M-MAFLD groups showed a significant lower risk of death compared with patients with non-MAFLD (p=0.003 and p=0.001, respectively). As to the weighted competing risk of death specifically due to HCC progression, both S-MAFLD and M-MAFLD, had a significantly lower risk of death compared with non-MAFLD (p=0.000) (table 4, figure 2C). Interestingly, S-MAFLD had a significantly higher weighted competing risk of death due to non-HCC-related causes compared with non-MAFLD (p=0.012, table 4, figure 2D). These results were confirmed also when the same analyses were not adjusted for lead time bias (online supplemental table 3) and when patients with non-cirrhosis (n=406) were removed from the analysis (online supplemental table 3).

DISCUSSION

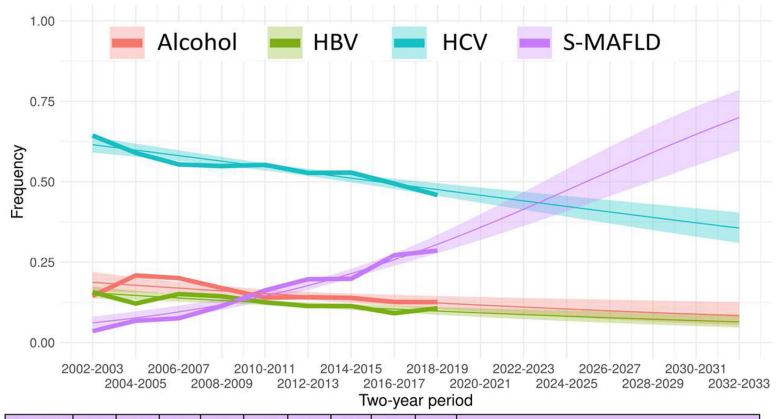
Our analysis of the ITA.LI.CA. database shows that the majority of HCC cases in Italy may be classified as MAFLD-related according to a recent proposal,[13] and that in about 6 years MAFLD of pure metabolic origin (S-MAFLD) will be the primary cause of incident HCC. While it is already known that MAFLD is associated with an higher cardiovascular mortality,[35] this is the first time that the prevalence of metabolic comorbidities in HCC has been so clearly defined. Either overweight/obesity or diabetes or two independent metabolic factors, potentially involved in HCC development, were present in two-thirds of the Italian patients with HCC recruited in the last 18 years, a proportion increasing to 77.3% in the last period (2018–2019).

The present classification of MAFLD might be improved for the identification of relative weight of the different parameters defining aetiology.[15] Although there were no possibilities to differentiate the association of the different metabolic risk factor in both MAFLD-HCC groups, our evidence opens a totally new scenario for treatment of the most common form of liver cancer, prompting for careful assessment and treatment of diabetes and excess body weight not only for their well-known association with severe cardiovascular involvement. On this regard, data shown in online supplemental table 1 and online supplemental figure 2 and 3 support one important finding of this study, that is, the metabolic factors, when superimposed to other aetiological agents, tend to normalise time-to-outcome among the different aetiological factors, but have a specific role when occur isolated determining a moderately different outcome (online supplemental table 4).

Only few and controversial data of HCC associated to hepatic steatosis have been generated in real-life clinical practice. Concurrent to the rapid advances in the treatment of both HBV and HCV and their declining role as prevalent oncogenic risk factors, the proportion of NAFLD-related HCC was reported to be dramatically increased in the USA in a few studies, not in others.[36–39] Three studies in Europe showed that NAFLD/NASH accounted for a very small proportion of liver-related deaths and LT.[3 40 41] However, it is unlikely that European diagnostic codes reliably pick up the occurrence of NAFLD or NASH, since codes do not recognise NASH-related cirrhosis and very low NAFLD awareness still exists among healthcare professionals and institutions all over Europe, including Italy.[42]

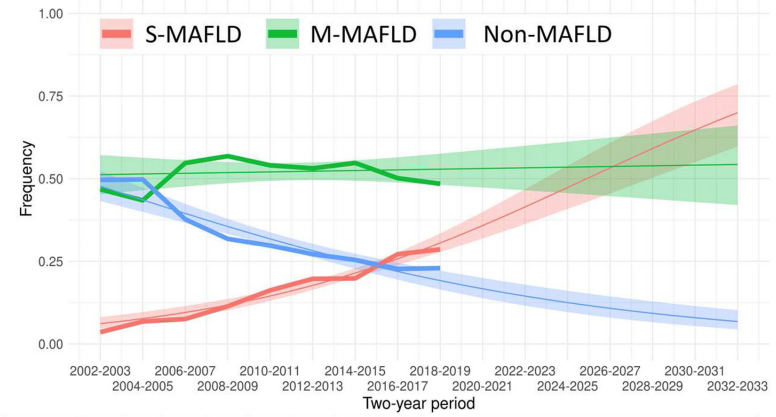
In order to have insight on the relative contribution of aetiological agents and to evaluate the epidemiological trends and trajectories of HCC associated to metabolic diseases in both recent and future years, we thus applied the new definition of MAFLD to the large ITA.LI.CA cohort. Compared with declining rates of HCV-related, HBV-related and alcohol-related HCC, the epidemiological trend of 'pure' MAFLD HCC (S-MAFLD) showed an impressive eightfold increase, accounting for 28.9% of all HCC diagnosed in the last study period, whereas the proportion

A



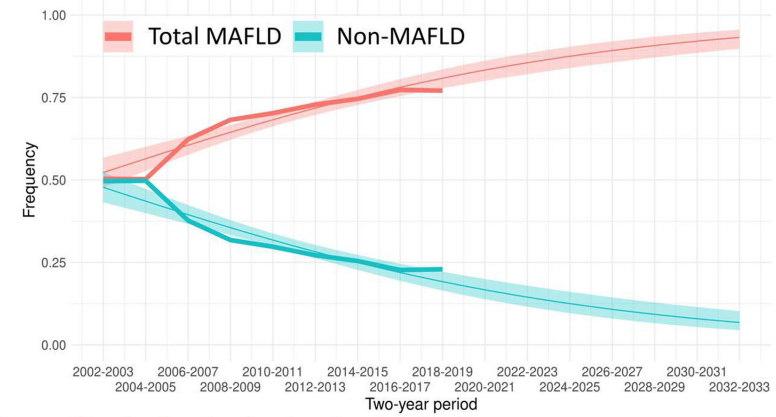
S-MAFLD	28	28	35	76	146	208	230	261	169	---
Alcohol	102	86	93	113	125	150	159	124	73	---
HBV	104	50	70	96	113	120	130	86	62	---
HCV	450	243	257	366	496	557	608	469	268	---

B



S-MAFLD	28	28	35	76	146	208	230	261	169	---
M-MAFLD	274	179	254	379	484	562	628	481	283	---
Non-MAFLD	390	205	175	212	268	287	293	214	133	---

C



Total MAFLD	302	207	289	455	630	770	858	742	452	---
Non-MAFLD	390	205	175	212	268	287	293	214	133	---

Figure 1 Epidemiological trends and future trajectories of S-MAFLD-HCC and HCC of other aetiologies in Italian Cancer Liver database, period 2002–2019 (A). Epidemiological trends and future trajectories of S-MAFLD, M-MAFLD and non-MAFLD cases (B). Epidemiological trends and future trajectories of MAFLD and non-MAFLD cases (C). HBV, hepatitis B virus; HCC, hepatitis C virus; HCC, hepatocellular carcinoma; MAFLD, metabolic associated fatty liver disease; M-MAFLD, mixed aetiology MAFLD; S-MAFLD, single aetiology MAFLD.

Table 3 Demographic data and liver-related and tumor-related characteristics of S-MAFLD, M-MAFLD and non-MAFLD pseudo-populations with hepatocellular carcinoma obtained using stabilised inverse probability weights

Variables	S-MAFLD (N=1121) Number (%) or median (Q1–Q3)	M-MAFLD (N=3457) Number (%) or median (Q1–Q3)	NON-MAFLD (N=2155) number (%) or median (Q1–Q3)
Female sex	258 (23.03)	799 (23.11)	495 (22.96)
Age (years)	69 (63–75)	69 (61–76)	67 (58–74)
Age >70 years	475 (42.29)	1482 (42.88)	928 (43.08)
Surveillance	655 (58.43)	2042 (59.06)	1270 (58.53)
FIB-4 grades in patients diagnosed without cirrhosis			
F0	5 (0.47)	17 (0.44)	7 (0.32)
F1–2	31 (2.73)	90 (2.60)	57 (2.62)
F3	33 (2.98)	119 (3.43)	72 (3.34)
Diagnosis of cirrhosis	1052 (93.81)	3232 (93.49)	2019 (93.72)
CRPH	902 (80.46)	2773 (80.22)	1730 (80.31)
MELD	10 (8–12)	10 (8–12)	10 (8–12)
MELD >10	433 (38.62)	1350 (39.22)	856 (39.72)
Child B and C	350 (31.23)	1082 (31.30)	680 (31.56)
ECOG PS>0	313 (27.94)	985 (28.49)	611 (28.38)
Number of nodules	1 (1–3)	1 (1–3)	1 (1–3)
Multinodular	534 (47.67)	1625 (47.00)	1022 (47.23)
Largest diameter (mm)	35 (22–56)	30 (20–47)	30 (20–50)
Largest diameter >50 mm	238 (21.20)	746 (21.57)	462 (21.42)
Macrovascular invasion	152 (13.54)	477 (13.80)	302 (14.03)
Metastases	57 (5.08)	148 (4.28)	81 (3.74)
AFP (ng/mL)	7 (5–162)	17 (7–239)	34 (7–756)
AFP >1000 ng/mL	187 (16.67)	583 (16.87)	365 (16.96)
Radical therapy	568 (50.66)	1765 (51.05)	1092 (50.69)
ITA.LI.CA stage			
0	167 (14.92)	579 (16.74)	391 (18.14)
A	281 (25.04)	842 (24.35)	488 (22.64)
B1	268 (23.93)	825 (23.87)	502 (23.30)
B2	84 (7.45)	268 (7.76)	186 (8.63)
B3	71 (6.33)	244 (7.07)	140 (6.49)
C	105 (9.39)	256 (7.39)	180 (8.34)
D	145 (12.94)	443 (12.81)	268 (12.45)
BCLC stage			
0	41 (3.62)	176 (5.09)	130 (6.01)
A	526 (46.92)	1608 (46.53)	935 (43.38)
B	176 (15.68)	528 (15.26)	350 (16.26)
C	312 (27.82)	900 (26.05)	591 (27.42)
D	67 (5.96)	244 (7.07)	149 (6.93)
Main therapy			
LT	33 (2.93)	171 (4.94)	96 (4.46)
LR	178 (15.91)	484 (14.01)	315 (14.63)
ABL	332 (29.63)	1062 (30.72)	658 (30.52)
IAT	251 (22.42)	773 (22.37)	503 (23.34)
SOR	67 (6.00)	195 (5.64)	123 (5.72)
OTHER/BSC	259 (23.10)	771 (22.30)	460 (21.34)

No differences between groups were demonstrated.
ABL, percutaneous ablation or alcohol injection; AFP, α-fetoprotein; BCLC, Barcelona Clinic Liver Cancer; CRPH, clinically relevant portal hypertension; FIB-4, fibrosis-4 index; IAT, intra-arterial therapy; ITA.LI.CA, Italian Liver Cancer; LR, liver resection; LT, liver transplantation; MAFLD, metabolic associated fatty liver disease; MELD, model for end stage liver disease; M-MAFLD, mixed aetiology MAFLD; OTHER/BSC, other therapies or best supportive care; ECOG PS, Eastern Cooperative Oncology Group performance status; Q1, first quartile; Q3, third quartile; S-MAFLD, single aetiology MAFLD; SOR, sorafenib.

of M-MAFLD HCC remained almost stable over time (around 50%). For the future, it is reasonable to hypothesise that rates will progressively decline in this cohort, due to the role of direct-acting antiviral (DAA) treatment in the eradication of HCV.[43–45] By using linear regression models, we prolonged the epidemiological trajectories seen for MAFLD and non-MAFLD HCC into the next few years, showing that MAFLD HCC might become the only form of HCC in about 10–12 years (figure 1C). This analysis, obtained from a real-world, prospectively-collected HCC database with accurate check of metabolic factors present in all included patients, can overcome the problem generated by the lack of a specific diagnostic code for NAFLD and should be considered in designing health policies aimed at treating patients with HCC.

One potential bias could derive by the lack of viral levels and the effect of antiviral therapies in the ITA.LI.CA. database. For these reasons, and in agreement with previous analyses,[12 16 17] HBV-HCC or HCV-HCC were defined according to the definition of clinicians at time of record upload. Patients with HCV/HBV with a suppressed virus might have a different outcome within the M-MAFLD or non-MAFLD cohorts, although several data from the literature suggest that previous HCV could still be an important aetiological factor at time of HCC occurrence.[46–48] The principal aim of our study that was to describe the epidemiological and prognostic features of the S-MAFLD HCC population in Italy, with the M-MAFLD and non-MAFLD populations as control groups. To reach this goal, it was important to have a completely pure S-MAFLD cohort, by excluding all patients with a previous viral history, although suppressed/cured at time of HCC diagnosis. According to this strategy, our study indicates that changes in the epidemiology of liver disease (higher pressure of metabolic factors, lower pressure of viral factors) are also modifying the features of patients with HCC, since patients with S-MAFLD were older, more frequently men and less frequently cirrhotic with clinically relevant portal hypertension and a surveillance-related diagnosis, with larger tumours and extrahepatic metastases. These characteristics will limit treatment strategies, influencing the prognosis, the risk of cancer-related and non-cancer-related death.

In both non-MAFLD and M-MAFLD groups most patients had an underlying cirrhosis (94.3% and 95.0%, respectively) and about 60% of HCC was detected under surveillance. Numbers are different in the S-MAFLD group, with 15% of patients without cirrhosis and HCC detected under surveillance in less than half of cases. However, more than 5% of S-MAFLD were diagnosed with F3 fibrosis by the FIB-4 index, thus making the sum of cases with advanced fibrosis (F3) or cirrhosis above 90% (table 1). These values are in contrast with other settings, where an increased risk of HCC was reported in the precirrhotic stage of NAFLD and less than 50% of the previously called NAFLD-associated HCC was described to occur in a cirrhotic background.[30 49–52] The presence of referral bias, derived from studies in NASH cohorts, and the low sample size, lack of homogeneity and poor diagnostic accuracy of previous studies, compared with the accurate scrutiny of all cases enrolled in the prospective Italian database, might explain the difference. Conversely, as shown in table 1, our data underline the importance of overweight/obesity (present in 67% of patients with S-MAFLD), pre-existing hyperglycaemic or overt diabetes (83.9% of S-MAFLD) as factors associated with HCC, in the absence of other comorbid conditions responsible for chronic liver diseases.[53–56] Moreover, the striking difference in surveillance might explain why S-MAFLD HCC were larger, more frequently multinodular, metastatic and with higher AFP levels compared with HCC of any other aetiology (table 1).

To analyse the net impact of MAFLD on overall and competing risks of death, we reduced the effect of baseline differences among subgroups with stabilised IPW method (table 2). Expectedly, the three pseudo-populations, very well balanced for

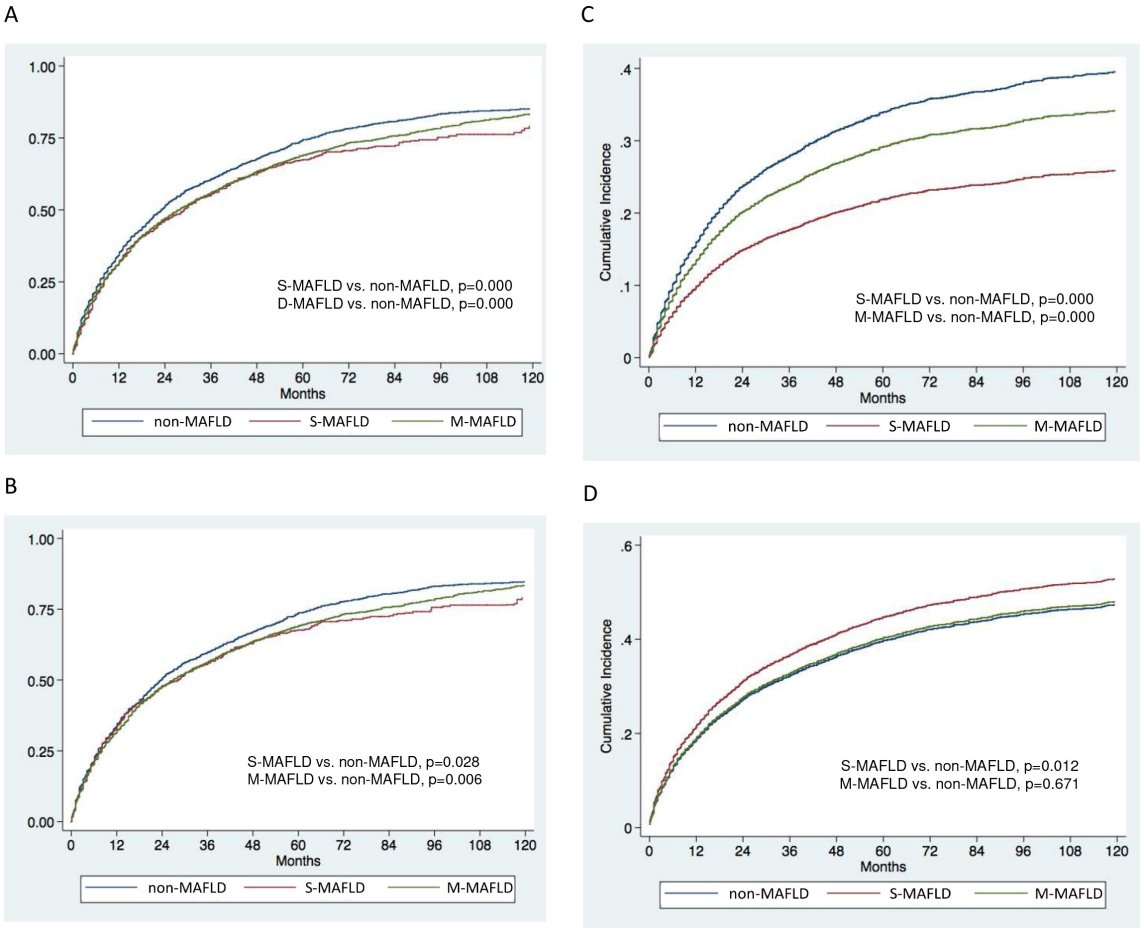


Figure 2 Kaplan-Meier overall failure curves comparing S-MAFLD, M-MAFLD and non-MAFLD groups before (A) and after weighting (B). Weighted competing risk curves comparing S-MAFLD, M-MAFLD and non-MAFLD groups for different failure competing events: death due to hepatocellular carcinoma progression (C), death due to other causes (D). MAFLD, metabolic associated fatty liver disease; M-MAFLD, mixed aetiology MAFLD; S-MAFLD, single aetiology MAFLD.

Table 4 Overall and competing risks multivariable Cox models using stabilised inverse probability weights

	All causes of death		HCC-related death		Other causes of death	
Variables	**HR (95% CI)**	**P value**	**HR (95% CI)**	**P value**	**HR (95% CI)**	**P value**
Non-MAFLD (ref)	–	–	–	–	–	–
S-MAFLD	0.86 (0.77 to 0.95)	0.003	0.57 (0.48 to 0.66)	0.000	1.17 (1.04 to 1.33)	0.012
M-MAFLD	0.89 (0.83 to 0.96)	0.001	0.83 (0.75 to 0.92)	0.000	1.03 (0.94 to 1.12)	0.595
ITA.LI.CA stage	–	–	–	–	–	–
0 (ref)	1.16 (1.05 to 1.29)	0.004	1.25 (1.03 to 1.50)	0.023	1.10 (0.97 to 1.24)	0.131
A	1.55 (1.39 to 1.72)	0.000	2.03 (1.70 to 2.44)	0.000	1.08 (0.95 to 1.23)	0.256
B1	1.82 (1.60 to 2.07)	0.000	2.74 (2.21 to 3.39)	0.000	0.98 (0.82 to 1.17)	0.836
B2	2.07 (1.79 to 2.39)	0.000	3.53 (2.83 to 4.41)	0.000	0.75 (0.60 to 0.93)	0.008
B3	2.05 (1.76 to 2.40)	0.000	3.33 (2.67 to 4.14)	0.000	0.80 (0.65 to 0.98)	0.032
C	2.56 (2.25 to 2.93)	0.000	2.37 (1.93 to 2.92)	0.000	1.33 (1.13 to 1.56)	0.001
D						
Main treatment	0.14 (0.11 to 0.18)	0.000	0.19 (0.12 to 0.29)	0.000	0.36 (0.28 to 0.46)	0.000
LT	0.35 (0.31 to 0.39)	0.000	0.57 (0.48 to 0.68)	0.000	0.56 (0.48 to 0.65)	0.000
LR	0.46 (0.42 to 0.51)	0.000	0.68 (0.59 to 0.78)	0.000	0.71 (0.63 to 0.81)	0.000
ABL	0.69 (0.62 to 0.76)	0.000	0.80 (0.70 to 0.93)	0.002	0.91 (0.80 to 1.03)	0.147
IAT	1.09 (0.94 to 1.26)	0.274	1.36 (1.13 to 1.65)	0.002	0.71 (0.57 to 0.90)	0.004
SOR	–	–	–	–	–	–
OTHER/BSC (ref)						

ABL, percutaneous ablation or alcohol injection; HCC, hepatocellular carcinoma; IAT, intra-arterial therapy; ITA.LI.CA, Italian Liver Cancer; LR, liver resection; LT, liver transplantation; MAFLD, metabolic associated fatty liver disease; M-MAFLD, mixed aetiology MAFLD; OTHER/BSC, other therapies or best supportive care; S-MAFLD, single aetiology MAFLD; SOR, sorafenib.

baseline characteristics, maintained significant differences for metabolic variables (ie, body weight, diabetes, hypertension and dyslipidaemia) strictly related to MAFLD definition. By the use of the ITA.LI.CA staging system, preferred to the BCLC classification in multivariable survival analysis for its better ability to stratify patients (tables 2 and 3) and survival (online supplemental figure 4),[17 23–25 34 57] we found a significantly lower risk of death in patients with MAFLD both before (figure 2A) and after the application of SW (figure 2B). Controversial data exist on this issue.[30 58–62] In our setting, more than 60% of patients were classified as stage 0 to B1 by the ITA.LI.CA system, and in the three groups (S-MAFLD, M-MAFLD and non-MAFLD) the proportion of patients receiving curative treatments was similar. IPW transformation shows that the protective effect of MAFLD on liver-related survival is independent of HCC stage and type of treatment (figure 2); at multivariable (IPW adjusted) analysis, MAFLD remained an independent risk factor for all-cause death, together with ITA.LI.CA staging and main treatment (table 4).

Despite their larger tumour size, patients with MAFLD showed a significantly lower weighted competing risk of death related to HCC progression than non-MAFLD (HR 0.57 and HR 0.83 in S-MAFLD and M-MAFLD, respectively)(figure 2C and table 4), in keeping with a less aggressive phenotype. However, it cannot be excluded that a higher competing mortality (by other causes) concurred to this result. In our setting, the expected prognostic advantage provided by lower HCC-related mortality on the overall risk of death was partially counterbalanced by a significantly higher risk of death by other causes in S-MAFLD (figure 2B–D, and table 4). In this competitive scenario, metabolic comorbidities might increase the risk of death associated with cardiovascular events, or even exacerbate the mortality caused by the complications of cirrhosis, such as infections and variceal bleeding, independently of liver cell failure. Lastly, patients with viral infection(s) as cause or cofactor of liver disease can now take advantage from antiviral therapies blocking—or even reversing—the progression of cirrhosis, dampening the risk of liver-related death in the future (table 4).

There are no pathogenetical data to explain the reduced aggressiveness of MAFLD HCC. While HCV uses its RNA genome and viral associated structural and non-structural proteins to alter cellular pathways to influence all 10 hallmarks of cancer,[63] the pathogenesis of NAFLD-associated HCC is not well understood.[5] Differently from other solid tumours, HCC develops on a milieu of chronic inflammation that drives the oncogenic pathways[64]; it can postulated that the higher severity of HCV-related liver injury, compared with NAFLD, is responsible for the higher aggressiveness of HCV-HCC.[65] This was confirmed by Sanyal *et al* in a prospective study where patients with NAFLD had a lower risk of progression to patients with HCC versus HCV.[66]

Several limitations and strengths should be discussed. A major limitation is represented by the retrospective nature of the study that makes it vulnerable by unintended biases. Moreover, the application of new diagnostic criteria to reclassify patients may suffer from a certain degree of imprecision. However, the database has been in use for a long time by well-trained physicians of ITA.LI.CA centres, and this reduces the risk of insufficient data and of misinterpretation of metabolic features. Three metabolic parameters considered in the original MAFLD definition (waist circumference, insulin resistance and C reactive protein)[13] were not available, and this definitely reduced the number of lean patients classified as MAFLD. Accordingly, the prevalence of MAFLD, is potentially underestimated, but underestimation should be limited, considering that subjects with waist circumference and insulin resistance exceeding the proposed cut-off should be largely included among patients with MAFLD with overweight/obesity and diabetes. On the other hand, our definition of M-MAFLD for patients with HCC based only on metabolic factors without clear evidence of present or past hepatic steatosis probably overestimates the prevalence of M-MAFLD cases. According to our M-MAFLD definition probably most European countries would already have only MAFLD HCCs. Certainly, steatosis was very likely to have occurred in patients with alcohol abuse and with HCV infection representing 87% of the total M-MAFLD population (online supplemental table 1).

Nonetheless, a few interesting results of the MAFLD category should be underlined: (a) it provides a defined picture of the S-MAFLD, representing the real focus of this study; and (b) the definition allows for a deeper analysis of the prognostic impact of individual metabolic factors in the M-MAFLD population (online supplemental table 4).

A further limitation is that the ITA.LI.CA database covers subjects diagnosed with HCC and does not include the very large cohort of MAFLD cases, without liver cancer, where outcome is dictated by end-stage liver failure or cardiovascular disease. In the presence of HCC, the outcome is largely driven by liver disease, although a few cardiovascular events are possible. Given the uncertainty of the exact role played by liver disease progression and/or additional cardiovascular disease we only considered all-cause mortality in the final analysis. Additionally, we were only able to distinguish between HCC and non-HCC-related death to perform the competing risk survival analysis.

The main strength of the study resides in the analysis of a very large database of patients with HCC in a Western country, uniformly managed over the past 20 years and including multiple, prospectively-collected risk factors that are the basis for MAFLD criteria assignment, as well as solid data on tumour characteristics, treatment and outcomes.

In conclusion, our study showed a significant increase in S-MAFLD HCC cases from 2002 to 2019, expected to exceed the incidence of HCV-HCC (figure 1A) and HCC of mixed aetiology (presumed M-MAFLD) (figure 1B) in about 4 and 6 years, respectively. Again, taking advantage from the new MAFLD definition, our study emphasises the close association between metabolic factors and HCC as shown by the constant prevalence of M-MAFLD during the entire study period. Although associated with a lower risk of HCC-associated death, the new scenario does not appear to be less gloomy in a community perspective. The progressive decline of HCV-associated HCC has already been replaced by metabolic-related HCC, with/without associated viral and non-viral aetiological factors. The possibility to use potentially curative treatments represents a prognostic mainstay, independent from cancer stage, further supporting the proposed 'therapeutic hierarchy' approach to patients with HCC.[24] The apparently less aggressive phenotype is counterbalanced by higher competing risks, late diagnosis and screening difficulties. At present, there are no approved drugs for MAFLD, and the surveillance of the immense population with diabetes and obesity is not feasible. In the future, only the integration of healthcare personnel of different specialties into a network model of care, as well as healthcare policies to reduce the burden of metabolic diseases, might smoothen the sky-rocketing incidence of the new HCC phenotype.

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