Landscape of alcohol-related hepatocellular carcinoma in the last 15 years highlights the need to expand surveillance programs

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Background & Aims: Alcohol abuse and metabolic disorders are leading causes of hepatocellular carcinoma (HCC) world-wide. Alcohol-related aetiology is associated with a worse prognosis compared with viral agents, because of the lower percentage of patients diagnosed with HCC under routine surveillance and a higher burden of comorbidity in alcohol abusers. This study aimed to describe the evolving clinical scenario of alcohol-related HCC over 15 years (2006–2020) in Italy.

Methods: Data from the Italian Liver Cancer (ITA.LI.CA) registry were used: 1,391 patients were allocated to three groups based on the year of HCC diagnosis (2006–2010; 2011–2015; 2016–2020). Patient characteristics, HCC treatment, and overall survival were compared among groups. Survival predictors were also investigated.

Results: Approximately 80% of alcohol-related HCCs were classified as cases of metabolic dysfunction-associated fatty liver disease. Throughout the quinquennia, <50% of HCCs were detected by surveillance programmes. The tumour burden at diagnosis was slightly reduced but not enough to change the distribution of the ITA.LI.CA cancer stages. Intra-arterial and targeted systemic therapies increased across quinquennia. A modest improvement in survival was observed in the last

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quinquennia, particularly after 12 months of patient observation. Cancer stage, HCC treatment, and presence of oesophageal varices were independent predictors of survival.

Conclusions: In the past 15 years, modest improvements have been obtained in outcomes of alcohol-related HCC, attributed mainly to underuse of surveillance programmes and the consequent low amenability to curative treatments. Metabolic dysfunction-associated fatty liver disease is a widespread condition in alcohol abusers, but its presence did not show a pivotal prognostic role once HCC had developed. Instead, the presence of oesophageal varices, an independent poor prognosticator, should be considered in patient management and refining of prognostic systems.

Impact and Implications: Alcohol abuse is a leading and growing cause of hepatocellular carcinoma (HCC) worldwide and is associated with a worse prognosis compared with other aetiologies. We assessed the evolutionary landscape of alcohol-related HCC over 15 years in Italy. A high cumulative prevalence (78%) of metabolic dysfunction-associated fatty liver disease, with signs of metabolic dysfunction, was observed in HCC patients with unhealthy excessive alcohol consumption. The alcohol + metabolic dysfunction-associated fatty liver disease condition tended to progressively increase over time. A modest improvement in survival occurred over the study period, likely because of the persistent underuse of surveillance programmes and, consequently, the lack of improvement in the cancer stage at diagnosis and the patients' eligibility for curative treatments. Alongside the known prognostic factors for HCC (cancer stage and treatment), the presence of oesophageal varices was an independent predictor of poor survival, suggesting that this clinical feature should be carefully considered in patient management and should be included in prognostic systems/scores for HCC to improve their performance.

Introduction

Hepatocellular carcinoma (HCC) is the second leading cause of death from cancer worldwide.[1] Almost 90% of HCCs develop in the setting of chronic liver disease, usually within the context of advanced fibrosis or cirrhosis.[2,3]

The incidence of this tumour varies markedly across geographic regions according to the prevalence of its risk factors.[4] Chronic viral hepatitis and alcohol-related liver disease are the main risk factors; however, in high-income countries, the rising prevalence of metabolic disorders has led to an increasing prevalence of HCCs associated with non-alcoholic fatty liver disease (NAFLD).[5,6]

Approximately 30% of HCC cases worldwide are attributable to alcohol abuse,[7] ranging from 20% in Southern European countries (*e.g.* Italy and Spain) to 63% in Eastern countries.[8] Heavy alcohol consumption is associated with a relative risk of 2.07 for the development of this tumour compared with non-consumers, and the annual incidence of HCC in patients with alcohol-related cirrhosis is approximately 3%.[8,9] It is expected that the relative and absolute causative roles of alcohol will increase in the future, as alcohol consumption is rising in many countries,[10] whereas the frequency of potentially causative HBV and HCV viral infections is declining because of the decreased incidence of new infections and the efficacy of antiviral treatments.[11] This changing aetiological scenario has been recently confirmed by a retrospective analysis of the Italian Liver Cancer (ITA.LI.CA) database, showing that the proportion of non-viral HCCs, and particularly of 'metabolic' or 'metabolic + alcohol-related' tumours, is rapidly growing and is challenging that of HCV-related HCCs, which is still the largest aetiological subgroup in Italy.[12]

The prognosis of patients with alcohol-related HCC is worse than that of non-alcohol-related cases because of more frequent delayed detection rates rather than greater cancer aggressiveness or poorer treatment outcomes.[13,14] Indeed, in alcohol abusers a HCC diagnosis is more often made outside surveillance programmes and in the setting of more advanced cirrhosis.[8,15,16] This combination entails a more advanced cancer stage at the time of diagnosis, with a lower amenability to curative treatments, and hence, worse survival.[13] Moreover, a more conservative therapeutic approach to alcohol-related HCCs may be

motivated by the higher prevalence of extrahepatic comorbidities and poorer social conditions of patients, limiting access to a cure. This assumption is supported by the results of a multicentre prospective study conducted in patients with alcohol-related cirrhosis who were periodically screened for HCC; only 56% of these patients underwent curative treatments, despite 77% of the cases having been diagnosed with a tumour within the Milan criteria.[9] Therefore, the above-mentioned unfavourable characteristics of alcohol abusers could have prevented or limited any prognostic improvement reported in an unselected case series of patients with HCC.[17] Despite the growing importance of alcohol abuse in HCC development and its alarming features, this topic has received less attention than other causes of HCC, with research interest mainly focused on the challenging problem of liver damage associated with metabolic disorders.

Recently, a new taxonomy of liver diseases has been proposed that includes the setting of metabolic syndrome, named metabolic dysfunction-associated fatty liver disease (MAFLD).[18] Unlike NAFLD, which was conceived as a diagnosis of exclusion,[19] this new entity includes patients with metabolic dysfunction and liver disease, regardless of the concurrent presence of other causative factors. In Italy, MAFLD accounts for >50% of patients with HCC, and this condition is expected to be detectable in the vast majority of cases of HCC in the forthcoming years.[20] However, the prevalence of MAFLD and its prognostic impact in patients with alcohol-related HCC remains unclear.

This study aimed to describe the evolving landscape of alcohol-related HCC over 15 years (calendar years: 2006–2020) in Italy, where approximately 15% of HCC have been attributed to alcohol abuse.[12]

Patients and methods

Patients

Data were extracted from the ITA.LI.CA registry which currently includes 9,379 patients with HCC consecutively evaluated from January 1986 to December 2020 in 24 medical institutions in Italy. Data were collected prospectively and updated every 2 years. After a biennial control of data quality by the coordinating centre (Semeiotics Unit, Bologna University), the database was available for use for new studies. The participating ITA.LI.CA

centres collected patient data at the time of HCC diagnosis (baseline) and during follow-up. For those patients initially managed outside the ITA.LI.CA network, baseline and follow-up data until the first access to the ITA.LI.CA network were retrospectively obtained. To avoid selection bias, no patient was excluded from the registry as a result of incomplete data ('all comers' recruitment). The management of the ITA.LI.CA database conforms to the current Italian legislation on privacy. According to Italian law, patient consent is not required for retrospective data analysis. Nonetheless, all patients provided written informed consent to undergo each diagnostic and therapeutic procedure and for having their clinical data recorded anonymously in the ITA.LI.CA database. The database used for scientific research was approved by the Institutional Review Board of the ITA.LI.CA Coordinating Center (approval number 99/2012/O/Oss) and the study was conducted following the ethical guidelines of the 1975 Declaration of Helsinki.

For this study, a total of 1,391 consecutive patients with alcohol-related HCC diagnosed from 1 January 2006 to 31 December 2020 were selected. The patients were allocated to three groups according to the year of cancer diagnosis:

- G1 = 2006–2010: n = 308 (22.1%) patients
- G2 = 2011–2015: n = 558 (40.1%) patients
- G3 = 2016–2020: n = 525 (37.8%) patients.

We analysed the following variables: age, sex, alcohol consumption (expressed as alcohol units [AU] per week), drinking habit at the time of HCC diagnosis (categorised as past [abstainers at the cancer diagnosis] or current drinkers), smoking habit (categorised as never, past [had quit smoking before the HCC diagnosis], or current smokers at the time of HCC detection), presence of MAFLD, type 2 diabetes (diabetes or active glucose-lowering therapy) and cirrhosis, Charlson Comorbidity Index, modality of HCC diagnosis (under surveillance, incidental, symptomatic), surveillance interval (categorised as ≤6 months and others), Child-Pugh (C–P) class, albumin/bilirubin (ALBI) grade, Aspartate aminotransferase–Platelet Ratio Index (APRI), Model for End-stage Liver Disease (MELD) score, ECOG Performance Status (PS, categorised as 0, 1, and ≥2), presence of oesophageal varices, platelet count (threshold ≤100,000/μl, below which the presence of clinically significant portal hypertension can be suspected in liver cirrhosis), tumour gross pathology (monofocal, multifocal, 'spreading mass' infiltrative or massive), number of lesions (categorised as 1, 2–3 and >3), size of the greatest lesion (categorised as ≤2, 2.1–5 and >5 cm), presence of portal or caval macrovascular invasion (MVI) and its site (categorised as segmental, main portal branches and portal trunk/caval vein), presence of metastases, serum alpha-foetoprotein (AFP) levels (categorised as ≤10, 11–200, and >200 ng/ml), ITA.LI.CA[21] tumour stage, HCC main treatment (the administered treatment with highest efficacy), causes of death, and patient survival. All these variables were available for >80% of the cases, except for weekly alcohol consumption and surveillance interval.

Aetiology of liver disease
In all patients, the diagnosed liver disease was classified as 'alcohol-related' if the daily ethanol intake was >20 g for women and >30 g for men, for at least 10 years, and no other causes of liver injury, except for features of metabolic syndrome, were found. Such a choice allowed us to enrol patients with both pure alcohol-related liver disease and alcohol-related/metabolic liver damage.

As in our previous study,[20] MAFLD was defined as the presence of type 2 diabetes and/or previous or current overweight or obesity (defined as BMI >25 kg/m^2), or at least 2 of the following hallmarks of metabolic dysfunction:

- impaired fasting glucose (fasting glucose between 100 and 125 mg/dl) or receiving antidiabetic therapy;
- triglycerides >150 mg/dl or receiving specific therapy;
- HDL cholesterol <50 mg/dl in women or <40 mg/dl in men or specific lipid-lowering therapy;
- current or past hypertension (defined as blood pressure >130/85 mmHg) or current antihypertensive treatment.

A subanalysis of the baseline characteristics of the patients was also performed according to the presence or absence of MAFLD.

The presence of cirrhosis was confirmed by histology in 59 (4.3%) patients and by laparotomy or laparoscopy in nine (0.7%) patients; in the remaining cases, the diagnosis was made according to clinical, laboratory, endoscopic, and imaging findings.

If a recent description of oesophageal varices was lacking at the time of HCC diagnosis, endoscopy was considered mandatory. Moreover, when a previously unreported portal vein thrombosis was detected on imaging, the endoscopic examination was repeated regardless of the date of the previous examination. Varices were graded and managed according to the Baveno guidelines available at the time of HCC diagnosis.

Diagnosis and staging
The diagnosis of HCC was classified as follows:

- under surveillance, if HCC was detected during an ultrasound (US)-based surveillance programme (±AFP determination) started at least 1 year before HCC diagnosis. Patients were subgrouped according to the surveillance interval (≤6 months/others). To minimise the effect of length bias, patients under surveillance were maintained in their original group even if the occurrence of symptoms anticipated the scheduled US.
- incidental, when the diagnosis was made during investigations of other diseases or a general check-up outside of regular surveillance.
- symptomatic, if HCC was detected through investigations motivated by the appearance of cancer-related symptoms in patients outside regular surveillance.

A subanalysis of the main characteristics of the patient according to the type of diagnosis (surveillance or no surveillance) was performed. Moreover, the evolution of the modality of HCC diagnosis through the 3 quinquennia was reported for NAFLD + cryptogenic and viral aetiologies.

The diagnosis of HCC was based on typical features of one or more imaging techniques (dynamic computed tomography [CT], magnetic resonance imaging [MRI], and contrast-enhanced US [CEUS]) and/or histological findings according to the European and American guidelines available at the time of patient recruitment.

Cancer burden was assessed using liver CT and/or MRI, and further investigations were systematically performed aimed at detecting extrahepatic involvement for patients with advanced

HCC or for those eligible for liver transplant (LT). In addition, these explorations were also repeated when clinically indicated.

HCC was staged according to the ITA.LI.CA staging system.[21]

Treatment

If patients were subjected to multiple treatments, they were classified considering the most effective treatment (named 'main'), following this hierarchical order: LT, hepatic resection, radiofrequency ablation (RF), percutaneous ethanol injection ablation (PEI), intra-arterial treatment ([IAT], including transarterial chemoembolisation [TACE], transarterial embolisation [TAE], and transarterial radioembolisation [TARE]), systemic therapy, or other therapies and best supportive care (BSC).[22]

Lead-time estimation

For each period, patients diagnosed with HCC during surveillance or incidentally were compared with those with a symptomatic diagnosis for lead-time estimation.[23] The mean ± standard deviation (SD) of lead times for the surveyed patients or those diagnosed incidentally were as follows:

- 8.6 ± 2.1 months and 4.6 ± 1.1 months in G1
- 8.2 ± 2.7 months and 4.4 ± 1.3 months in G2
- 7.7 ± 2.6 months and 4.3 ± 1.3 months in G3.

Statistical analysis

Continuous variables are expressed as median and 25th–75th percentiles and discrete variables as absolute and relative frequencies. Kruskal–Wallis and Mann–Whitney U tests were used to compare continuous variables among the three periods or between two periods. The χ^2 test or Fisher's exact test was used to compare discrete variables, as appropriate. Data missing from covariates included in the ITA.LI.CA staging system were estimated using the maximum likelihood estimation method[24] to obtain a sample size large enough to be representative of the original patient population and not to limit the number of cases included in the multivariate analysis. The lack of significant data distortion as a result of imputation was confirmed by comparing the results obtained with raw and imputed data (Table S1).

Overall survival (OS) was defined as the time elapsed between HCC diagnosis and the patient's death, the last follow-up evaluation, or data censoring (31 December 2020), whichever occurred first, and was reported as the median and 95% CI. OS was calculated according to the Kaplan–Meier method and was compared using the Log-rank test. If the potential for non-proportionality of hazards was evident, piecewise hazard ratios (HRs) were calculated over distinct periods using time-varying Cox regression analysis.

The 'lead-time adjusted' OS (a-OS) was calculated by subtracting the relevant lead-time from the OS obtained from surveyed or incidentally diagnosed patients. Survival rates at 1, 2, 3, 4, and 5 years were also reported, and the proportions of patients alive at any time in the 3 quinquennia were compared using the χ^2 test.

To provide a more comprehensive picture of the changing HCC scenario in the 3 quinquennia, a subanalysis of the evolution of main treatment, causes of death, and a-OS in patients with NAFLD + cryptogenetic and viral HCC was also performed.

Baseline characteristics (except for alcohol consumption and surveillance interval) were tested using univariate and multivariate Cox analyses to identify their associations with a-OS.

Variables associated with a-OS in the univariate analysis (p <0.10) were entered into the multivariate models. Adjusted HR and 95% CI were reported for each prognostic factor. To avoid collinearity between covariates, the components of the ITA.LI.CA staging system (PS, tumour burden, AFP, and liver function tests) were excluded from the model that included this system. Moreover, we created two additional models to test the prognostic significance of the C–P classes and ALBI grades. The three models tested were as follows:

Model 1 (C–P-based) included age, MAFLD, cirrhosis, modality of HCC diagnosis, **C–P class**, Eastern Cooperative Oncology Group-Performance Status (ECOG PS), platelet count, oesophageal varices, AFP levels, gross tumour pathology, size of the greatest lesion, metastases, MVI, and the main treatment.

Model 2 (ALBI-based) included age, MAFLD, cirrhosis, modality of HCC diagnosis, **ALBI grade**, ECOG PS, platelet count, oesophageal varices, AFP levels, gross tumour pathology, size of the greatest lesion, metastases, MVI, and the main treatment.

Model 3 (ITA.LI.CA-based) included age, MAFLD, cirrhosis, modality of HCC diagnosis, platelet count, oesophageal varices, **ITA.LI.CA cancer stage**, and the main treatment.

A two-tailed p value <0.05 was considered statistically significant. All statistical analyses were performed with SPSS v28.0 (Apache Software Foundation, Chicago, IL, USA).

Details of the deposited data, software, and corresponding methods are reported in the CTAT Table.

Results

Demographic and clinical characteristics

We observed an increase in the median age at HCC diagnosis, from 67 years in G1–G2 to 69 years in G3 (p = 0.028), whereas the large predominance of males (≥92%) did not change over time (Table 1).

The distribution of the weekly median AU did not change over time (p = 0.313), with 56 (40–56), 46 (30–60), and 50 (30–70) in G1, G2, and G3, respectively. However, the proportion of current drinkers was significantly higher in G1 (p <0.001).

Smoking habits varied (p <0.001), showing a reduction in never-smokers (from 56.7% in G1 to 47.7% in G3) and current smokers (from 30.9% to 25.5%), and an increase in the proportion of people who had quit smoking before HCC diagnosis (from 12.4% to 26.8%).

The overall prevalence of patients fulfilling MAFLD criteria was very high (77.8%) (Fig. 1), and tended to increase across quinquennia (76.0%, 79.5%, and 80.0%). The comparison of baseline characteristics between patients with MAFLD and 'non-MAFLD' alcohol-related HCC is reported in Table S2. In patients with MAFLD, the prevalence of type 2 diabetes and comorbidities was significantly higher, whereas the prevalence of cirrhosis and the median MELD score were lower than those observed in the counterpart (Table S2).

Considering the entire population (Table 1), after the first calendar period the proportion of patients with cirrhosis decreased from 96.1% to 92.8% (p = 0.049).

Comorbidity burden, measured using the Charlson Comorbidity Index, maintained a median score of 3 during the study period.

Table 1. Demographic and clinical characteristics of patients with alcohol-related hepatocellular carcinoma in the 3 quinquennia.

Variables	Available N (%)	2006–2010 n (%) 308 (22.1)	2011–2015 n (%) 558 (40.1)	2016–2020 n (%) 525 (37.7)	p value
Demographic and clinical features					
Age, years					
Median (25th–75th)	1,391 (100)	67.5 (60–73)	67 (63–73)	69 (63–75)	0.028
Sex (M/F)	1,391 (100)	284/24 (92.2/7.8)	523/35 (93.7/6.3)	486/39 (92.6/7.4)	0.641
Alcohol consumption (AU/week)	808 (58.1)	178 (57.8)	310 (55.6)	320 (61.0)	0.313
Median (25th–75th)		56 (40–56)	46 (30–60)	50 (30–70)	
Drinking habit	1,391 (100)	308 (22.2)	558 (40.1)	525 (37.7)	<0.001
Past		98 (31.8)	298 (53.4)	240 (45.7)	
Current		210 (68.2)	260 (46.6)	285 (54.3)	
Smoking habit	1,149 (82.6)	233 (74.9)	465 (83.3)	451 (85.9)	<0.001
Never		132 (56.7)	258 (55.5)	215 (47.7)	
Past		29 (12.4)	83 (17.8)	121 (26.8)	
Current		72 (30.9)	124 (26.7)	115 (25.5)	
MAFLD	1,369 (98.4)	308 (100)	550 (98.6)	511 (97.3)	0.301
Yes		234 (76.0)	437 (79.5)	411 (80.0)	
Type 2 diabetes	1,391 (100)	308 (100)	558 (100)	525 (100)	0.208
Yes		116 (37.7)	241 (43.2)	228 (43.4)	
Cirrhosis	1,369 (98.4)	305 (99.0)	550 (98.6)	514 (97.9)	0.049
Yes		293 (96.1)	504 (91.6)	477 (92.8)	
Charlson Comorbidity Index	1,391 (100)	308 (100)	558 (100)	525 (100)	0.204
Median (25th–75th)		3 (2–4)	3 (2–4)	3 (2–4)	
Modality of HCC diagnosis	1,270 (91.3)	282 (91.6)	502 (90.0)	486 (92.6)	0.250
Under surveillance		107 (37.9)	228 (45.4)	221 (45.5)	
Incidental		121 (42.9)	192 (38.2)	190 (39.1)	
Symptomatic		54 (19.1)	82 (16.3)	75 (15.4)	
Surveillance interval	392 (70.5)[a]	65 (60.7)	153 (67.1)	174 (78.7)	0.010
≤6 months		41 (63.1)	119 (77.8)	142 (81.6)	
Others		24 (36.9)	34 (22.2)	32 (18.4)	
Child–Pugh class	1,391 (100.0)	308 (100.0)	558 (100.0)	525 (100.0)	0.567
A		175 (56.8)	298 (53.4)	277 (52.8)	
B		107 (34.7)	218 (39.1)	212 (40.4)	
C		26 (8.4)	42 (7.5)	36 (6.9)	
ALBI grade	1,391 (100.0)	308 (100.0)	558 (100.0)	525 (100.0)	0.270
Grade 1, ≤−2.60		52 (16.9)	105 (18.8)	108 (20.6)	
Grade 2, >−2.60 ≤−1.39		212 (68.8)	397 (71.1)	352 (67.2)	
Grade 3, >−1.39		44 (14.3)	56 (10.0)	64 (12.2)	
APRI	1,155 (83.0)	261 (84.7)	456 (81.7)	438 (83.4)	0.603
First tertile		75 (28.7)	158 (34.6)	146 (33.3)	
Second tertile		94 (36.0)	149 (32.7)	147 (33.6)	
Third tertile		92 (35.2)	149 (32.7)	145 (33.1)	
MELD score	1,391 (100.0)	308 (100.0)	558 (100.0)	525 (100.0)	0.156
Median (25th–75th)		11.0 (8.4–14.0)	10.3 (8.2–14.0)	10.2 (8.3–13.4)	
ECOG PS	1,391 (100.0)	308 (100.0)	558 (100.0)	525 (100.0)	0.113
0		196 (63.6)	370 (66.3)	376 (71.6)	
1		77 (25.0)	132 (23.7)	97 (18.5)	
≥2		35 (11.4)	56 (10.0)	52 (9.9)	
Oesophageal varices	1,391 (100.0)	308 (100.0)	558 (100.0)	525 (100.0)	0.238
Yes		140 (45.5)	255 (45.7)	264 (50.3)	
Platelet count	1,391 (100.0)	308 (100.0)	558 (100.0)	525 (100.0)	0.075
≤100,000/μl		102 (33.1)	195 (34.9)	211 (40.2)	
Tumour burden and stage					
Gross pathology	1,391 (100.0)	308 (100.0)	558 (100.0)	525 (100.0)	0.684
Monofocal		135 (43.8)	279 (50.0)	255 (48.6)	
Multifocal		151 (49.0)	241 (43.2)	229 (43.6)	
Infiltrative		14 (4.2)	20 (3.6)	22 (4.2)	
Massive		9 (2.9)	18 (3.2)	19 (4.2)	
Number of lesions	1,290 (92.7)	286 (92.9)	520 (93.2)	484 (92.2)	0.012
1		135 (47.2)	279 (53.7)	255 (52.7)	
2 or 3		82 (28.7)	162 (31.2)	156 (32.2)	
>3		69 (24.1)	79 (15.2)	73 (15.1)	
Size of the greatest lesion	1,376 (98.9)	307 (99.7)	553 (99.1)	516 (98.3)	0.091
≤2 cm		71 (23.1)	150 (27.1)	156 (30.2)	
2.1–5.0 cm		154 (50.2)	253 (45.8)	248 (48.1)	
>5 cm		82 (26.7)	150 (27.1)	112 (21.7)	
MVI	1,391 (100.0)	308 (100.0)	558 (100.0)	525 (100.0)	0.717

Table 1 (continued)

Variables	Available N (%)	2006–2010 n (%) 308 (22.1)	2011–2015 n (%) 558 (40.1)	2016–2020 n (%) 525 (37.7)	p value
Yes		42 (13.6)	87 (15.6)	81 (15.4)	
MVI site	210 (100.0)	42 (100.0)	87 (100.0)	81 (100.0)	0.004
Segmental		1 (2.4)	6 (6.9)	7 (8.6)	
Main portal branches		6 (14.3)	39 (44.8)	29 (35.8)	
Portal trunk/caval vein		35 (83.3)	42 (48.3)	45 (55.6)	
Metastases	1,391 (100.0)	308 (100.0)	558 (100.0)	525 (100.0)	0.028
Yes		10 (3.2)	33 (5.9)	15 (2.9)	
Alpha-foetoprotein levels	1,391 (100.0)	308 (100.0)	558 (100.0)	525 (100.0)	0.025
≤10 ng/ml		162 (52.6)	305 (54.7)	321 (61.1)	
11–200 ng/ml		101 (32.8)	151 (27.1)	128 (24.4)	
>200 ng/ml		45 (14.6)	102 (18.3)	76 (14.5)	
ITA.LI.CA tumour stage	1,391 (100)	308 (100.0)	558 (100.0)	525 (100.0)	0.136
0		52 (16.9)	115 (20.6)	120 (22.9)	
A		71 (23.1)	129 (23.1)	58 (11.0)	
B1		42 (13.6)	74 (13.3)	93 (17.7)	
B2		44 (14.3)	51 (9.1)	53 (10.1)	
B3		12 (3.9)	39 (7.0)	26 (5.0)	
C		36 (11.7)	69 (12.4)	50 (9.5)	
D		51 (16.6)	81 (14.5)	86 (16.4)	

Levels of significance: <0.05 (Kruskal–Wallis test and χ^2 test).
Among patients under surveillance, the interval was specified in 392 cases, representing the 70.5% of these patients.
ALBI, albumin–bilirubin; APRI, AST to Platelet Ratio Index; ECOG-PS, Eastern Cooperative Oncology Group Performance Status; HCC, hepatocellular carcinoma; ITA.LI.CA, Italian Liver Cancer; MAFLD, metabolic dysfunction associated fatty liver disease; MELD, model for end-stage liver disease; MVI, macrovascular Invasion.

Overall, the severity of liver disease, as assessed by the C–P class distribution, MELD score, and ALBI grade, and the prevalence of clinically significant portal hypertension (highlighted by the presence of oesophageal varices) remained unchanged over time. Similarly, the ECOG PS did not change significantly, despite an increasing trend in the proportion of PS 0 (63.6%, 66.3%, and 71.6%).

Regarding the modality of HCC diagnosis, both symptomatic (19.1%, 16.3%, and 15.4%) and incidental diagnoses (42.9%, 38.2%, and 39.1%) tended to decrease after the first quinquennium, favouring diagnoses made under surveillance (37.9%, 45.4%, and 45.5%); however, these trends did not reach statistical significance ($p = 0.250$). Among the patients surveyed, the predominant surveillance interval was always ≤6 months, and the prevalence of HCC detected under this surveillance programme progressively increased (63.1%, 77.8%, and 81.6%; $p = 0.010$).

Overall, the surveyed patients showed a significantly better distribution of baseline C–P classes, ECOG PS, tumour burden, AFP levels and ITA.LI.CA stages, so that they were more frequently suited for curative treatments (56.1% *vs.* 38.8%), and their median a-OS was longer (34.7 *vs.* 28.4 months) than their counterpart (Table S3).

Table S4 shows the evolution of diagnostic modalities in contemporary patients with non-alcohol-related HCC. In the NAFLD + cryptogenic population (n = 628), the proportion of HCC detected under surveillance was similar to that observed in alcohol-related disease, and did not significantly change across quinquennia (41.5%, 47.9%, and 44.9%). Instead, in viral patients (n = 4,296), the proportion of HCC detected under surveillance was always >60%, showing its nadir (61.2%) in the last quinquennium.

Fig. 1. **Metabolic dysfunction-associated fatty liver disease (MAFLD) prevalence among patients with hepatocellular carcinoma originally considered as merely alcohol-related.**

Tumour burden

The prevalence of patients with monofocal HCC tended to be higher (albeit not significantly) after the first quinquennium (from 43.8% to approximately 50% in G2 and G3) at the expense of multinodular tumours (particularly of those with more than three nodules), whereas the proportion of infiltrative or massive HCC remained very low over time (Table 1).
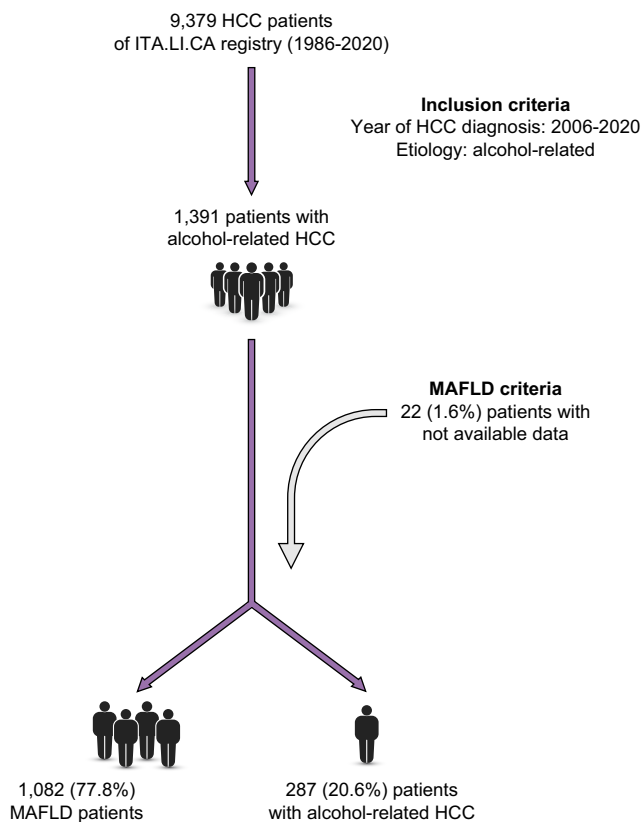
Table 2. Main treatments performed for hepatocellular carcinoma and causes of death.

	Available	2006–2010	2011–2015	2016–2020	
	N (%)	n (%)	n (%)	n (%)	p value
Main treatment	1,385 (99.6)	308 (100.0)	558 (100.0)	519 (98.9)	<0.001
Liver transplant		12 (3.9)	25 (4.5)	21 (4.6)	
Resection		49 (15.9)	83 (14.9)	69 (13.3)	
Ablation		90 (29.2)	162 (29.0)	147 (28.3)	
IAT		69 (22.4)	141 (25.3)	135 (26.0)	
Systemic therapy		13 (4.2)	32 (5.7)	38 (7.3)	
Others		16 (5.2)	1 (0.2)	2 (0.4)	
BSC		52 (16.9)	95 (17.0)	91 (17.5)	
Not known		7 (2.3)	19 (3.4)	16 (3.1)	
Causes of death	771 (100.0)	239 (31.0)	350 (45.4)	182 (23.6)	<0.001
Tumour progression		109 (45.6)	155 (44.3)	72 (39.6)	
Liver failure		39 (16.3)	75 (21.4)	47 (25.8)	
Haemorrhage		5 (2.1)	10 (2.9)	7 (3.8)	
Kidney failure		4 (1.7)	10 (2.9)	1 (0.5)	
Infection		1 (0.4)	10 (2.9)	15 (8.2)	
Embolism		1 (0.4)	0 (0.0)	4 (2.2)	
Other		70 (29.3)	58 (16.6)	22 (12.6)	
Not known		10 (4.2)	32 (9.1)	13 (7.1)	

Levels of significance: <0.05 (χ^2 test).
BSC, best supportive care; IAT, intra-arterial therapy.

Concomitantly, a tendency toward a more favourable distribution of cancer size with a progressive increase in tiny tumours (≤2 cm) was observed (from 23.1% to 27.1% and 30.2% ($p = 0.091$).

The proportion of patients with MVI remained stable at approximately 15% throughout the study. Nevertheless, among patients with MVI, there was a significant ($p = 0.004$) shift in the site of vascular invasion from extrahepatic vessels (portal trunk and caval vein, 83.3%, 48.3%, and 55.6%) to the main portal branches (14.3%, 44.8%, and 35.8%) through the 3 quinquennia.

The prevalence of extrahepatic spread was low and stable, with its nadir in G3 (2.9%).

The distribution of AFP levels favourably changed ($p = 0.025$), as the proportion of patients with a normal value (≤10 ng/ml) progressively increased (52.6%, 54.7%, and 61.1%) at the expense

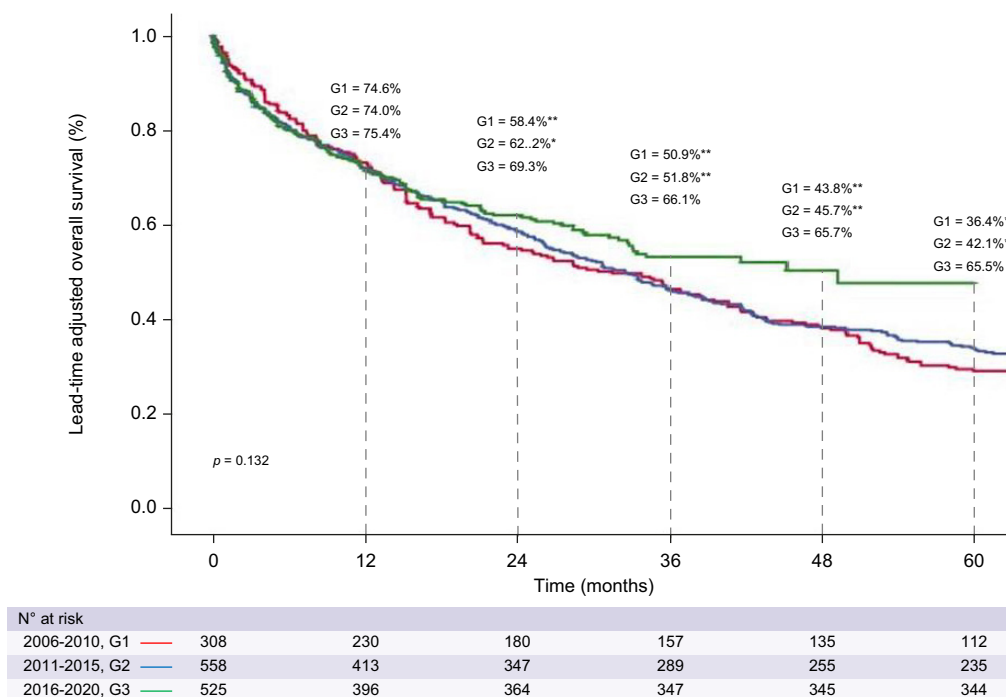| N° at risk						
2006-2010, G1	308	230	180	157	135	112
2011-2015, G2	558	413	347	289	255	235
2016-2020, G3	525	396	364	347	345	344

Fig. 2. Lead-time adjusted overall survival according to quinquennia. Levels of significance: p <0.05 (log-rank test). Asterisks refer to a significantly different proportion of at-risk patients between G1 or G2 vs. G3: *p <0.05, **p <0.001.

Table 3. Univariate Cox proportional hazard regression analysis of factors affecting the lead time-adjusted survival.

		Univariate analysis		
Variables		Exp(B)	95% CI	p value
Age (years)		1.013	1.005–1.022	0.002
Sex				
F	Ref. Cat.	–	–	
M		1.017	0.773–1.339	0.902
Drinking habit				
Past	Ref. Cat.	–	–	
Current		0.946	0.821–1.090	0.444
Smoking habit				
Never	Ref. Cat.	–	–	
Past		1.065	0.867–1.307	0.549
Current		0.958	0.795–1.154	0.651
Modality of HCC diagnosis				
Surveillance	Ref. Cat.	–	–	
Incidental		0.975	0.826–1.150	0.760
Symptomatic		1.780	1.460–2.169	<0.001
Type 2 diabetes		0.975	0.846–1.125	0.731
MAFLD		0.806	0.681–0.954	0.012
Cirrhosis		1.390	1.028–1.878	0.032
Child–Pugh class				
A	Ref. Cat.	–	–	
B		1.705	1.467–1.983	<0.001
C		4.343	3.414–5.523	<0.001
MELD score		1.062	1.048–1.076	<0.001
ALBI grade				
Grade 1, ≤-2.60	Ref. Cat.	–	–	
Grade 2, >-2.60 ≤-1.39		1.580	1.292–1.932	<0.001
Grade 3, >-1.39		3.791	2.941–4.888	<0.001
APRI				
First tertile	Ref. Cat.	–	–	
Second tertile		1.118	0.921–1.358	0.259
Third tertile		1.627	1.346–1.966	<0.001
ECOG PS				
0	Ref. Cat.	–	–	
1		1.933	1.635–2.285	<0.001
≥2		4.566	3.722–5.601	<0.001
Charlson Comorbidity Index		1.058	1.016–1.102	0.006
Oesophageal varices		1.496	1.298–1.724	<0.001
Platelet count				
>100,000/μl	Ref. Cat.	–	–	
≤100,000/μl		1.174	1.015–1.359	0.031
Alpha-foetoprotein levels				
≤10 ng/ml	Ref. Cat.	–	–	
11–200 ng/ml		1.377	1.169–1.620	<0.001
>200 ng/ml		1.973	1.632–2.386	<0.001
Tumour gross pathology				
Single	Ref. Cat.	–	–	
Multifocal		1.636	1.408–1.900	<0.001
Infiltrative		4.818	3.491–6.651	<0.001
Massive		4.016	2.780–5.800	<0.001
Number of lesions				
1	Ref. Cat.	–	–	
2–3 lesions		1.408	1.187–1.671	<0.001
>3 lesions		2.189	1.804–2.657	<0.001
Size of the greatest lesion				
≤2.0 cm	Ref. Cat.	–	–	
2.1–5.0 cm		1.214	1.012–1.457	0.037
>5 cm		2.283	1.873–2.782	<0.001
MVI				
No	Ref. Cat.	–	–	
Segmental		2.186	1.131–4.226	0.020
Main portal branches		2.282	1.714–3.039	<0.001
Portal trunk/caval vein		2.960	2.362–3.709	<0.001
Metastases		3.075	2.286–4.138	<0.001
ITA.LI.CA tumour stage				
0	Ref. Cat.	–	–	
A		1.103	0.865–1.408	0.429

Table 3 (*continued*)

Variables		Exp(B)	95% CI	p value
Univariate analysis				
B1		1.567	1.192–2.062	0.001
B2		1.670	1.264–2.205	<0.001
B3		2.289	1.618–3.239	<0.001
C		3.559	2.719–4.658	<0.001
D		4.426	3.479–5.629	<0.001
Main treatment				
BSC	Ref. Cat.	–	–	
Liver transplant		0.024	0.012–0.048	<0.001
Resection		0.086	0.066–0.113	<0.001
Ablation		0.118	0.095–0.147	<0.001
IAT		0.211	0.172–0.259	<0.001
Systemic therapy		0.457	0.339–0.616	<0.001
Others		0.799	0.479–1.331	0.389

Levels of significance: <0.05 (Cox regression model).
ALBI, albumin–bilirubin; APRI, AST to Platelet Ratio Index; BSC, best supportive care; ECOG-PS, Eastern Cooperative Oncology Group Performance Status; HCC, hepatocellular carcinoma; IAT, intra-arterial therapy; ITA.LI.CA, Italian Liver Cancer; MAFLD, metabolic dysfunction associated fatty liver disease; MELD, model for end-stage liver disease; MVI, macrovascular Invasion; Ref. Cat., reference category.

of those with values ranging from to 11–200 ng/ml (32.8%, 27.1%, and 24.4%).

The distribution of ITA.LI.CA stages did not change significantly over time (*p* = 0.136).

Treatment

The distribution of the main HCC treatments received by the patients changed significantly with time (Table 2). Namely, the proportion of curative treatments (surgery or ablation) and BSC did not change, whereas the proportion of both IAT (from 22.4% to 26.0%) and systemic treatment (from 4.2% to 7.3%) progressively increased (*p* <0.001). Notably, when sorafenib became available in clinical practice, it became the main systemic treatment, with other agents almost completely disappearing. As a result, in the last quinquennium, approximately 18% of patients underwent surgical interventions, 28% percutaneous ablation, 26% IAT, and 7% received systemic therapy with TKI.

The treatment allocation of patients with NAFLD + cryptogenic and viral HCC across the quinquennia is reported in Table S5.

Causes of death and survival

During a median follow-up of 24.3 months (25th–75th, 8.1–47.1), 771 patients died (Table 2). The main causes of death were tumour progression (43.2%) and liver failure (21.2%). No differences in the causes of death were observed between patients with MAFLD and those non-MAFLD (Table S2). Their distribution changed across quinquennia (*p* <0.001), with an increasing death rate attributable to liver failure, bleeding, infections, and embolism; conversely, mortality from tumour progression, kidney failure, and other causes declined (Table 2).

The median a-OS improved in the last quinquennium, being 31.4 months (95% CI 22.6–40.2) in G1, 32.5 months (95% CI 27.6–37.4) in G2, and 49.2 months (n.d.) in G3, although this change did not reach statistical significance (*p* = 0.132) (Fig. 2). The a-OS rates across quinquennia were: 74.6%, 74.0%, and 75.4% at 1 year, 58.4%, 62.2% and 69.3% at 2 years, and 36.4%, 42.1% and 65.5% at 5 years, respectively. The a-OS in the last quinquennium

was compared with the other time periods using a piecewise analysis (using as the starting point 1 year after HCC detection). This analysis showed a significant a-OS improvement (HR, 0.51; 95% CI 0.33–0.78; *p* = 0.002, compared with the first quinquennium, and HR, 0.63; 95% CI 0.43–0.94; *p* = 0.023, compared with the second quinquennium).

Sensitivity analyses performed in the entire population showed that both the ITA.LI.CA staging system and ALBI grades could efficiently stratify patients according to a-OS (Fig. S1).

Fig. S2 describes the changes over time in a-OS observed in patients with HCC originating from NAFLD + cryptogenic or viral liver disease.

Uni- and multivariate analyses

In the univariate analysis, the variables associated with a-OS were age, the mode of diagnosis of HCC, the presence of MAFLD and cirrhosis, C–P class, MELD score, ALBI grade, ECOG PS, Charlson Comorbidity Index, presence of oesophageal varices, platelet count, AFP levels, gross pathology, number of lesions, size of the largest lesion, presence of MVI or metastases, ITA.LI.CA stage, and the main treatment for HCC (Table 3).

The independent prognostic factors identified by the three models of the multivariate analysis summarised in Table 4 (each including at least 88% of the initial cases) were as follows:

Model 1 (*C–P-based*): age, C–P class, ECOG PS ≥2, oesophageal varices, platelet count, AFP levels, gross tumour pathology, size of the greatest lesion, MVI, and main treatment.

Model 2 (*ALBI-based*): ALBI grade, ECOG PS ≥2, oesophageal varices, platelet count, AFP levels, gross tumour pathology, size of the largest lesion, MVI, and main treatment.

Model 3 (*ITA.LI.CA-based*): oesophageal varices, ITA.LI.CA tumour stage, and main treatment.

Notably, oesophageal varices and the main treatment were independent prognostic factors in all models. Variables related to tumour burden and liver function were independent prognosticators in Models 1 and 2 and, as components of the ITA.LI.CA stage, even in Model 3.

Table 4. Multivariate analyses of factors affecting the lead time-adjusted survival, based on three different models.

Variables		Model 1 n = 1,222 (87.9%)			Model 2 n = 1,222 (87.9%)			Model 3 n = 1,235 (88.8%)		
		Exp(B)	95% CI	*p* value	Exp(B)	95% CI	*p* values	Exp(B)	95% CI	*p* value
Age		1.010	1.000–1.020	0.044	1.007	0.998–1.017	0.126	1.006	0.997–1.016	0.187
MAFLD		0.928	0.770–1.119	0.434	0.919	0.764–1.106	0.371	0.910	0.760–1.090	0.307
Cirrhosis		0.960	0.688–1.340	0.811	0.940	0.671–1.317	0.720	1.007	0.723–1.402	0.968
Modality of HCC diagnosis										
Surveillance/Incidental	Ref. Cat.									
Symptomatic		0.980	0.800–1.200	0.841	0.955	0.778–1.173	0.663	1.112	0.912–1.355	0.293
Child–Pugh class					NA	NA	NA	NA	NA	NA
A	Ref. Cat.									
B		1.407	1.179–1.679	<0.001						
C		1.766	1.292–2.414	<0.001						
ALBI grade		NA	NA	NA				NA	NA	NA
Grade 1, ≤-2.60	Ref. Cat.									
Grade 2, >-2.60 ≤-1.39					1.349	1.082–1.682	0.008			
Grade 3, >-1.39					1.820	1.346–2.460	<0.001			
ECOG PS								NA	NA	NA
0	Ref. Cat.									
1		1.102	0.909–1.336	0.325	1.119	0.924–1.356	0.249			
≥2		1.643	1.265–2.133	<0.001	1.712	1.326–2.211	<0.001			
Platelet count										
>100,000/μl	Ref. Cat.									
≤100,000/μl		1.225	1.035–1.450	0.019	1.214	1.025–1.439	0.025	1.177	0.998–1.387	0.053
Oesophageal varices		1.242	1.052–1.465	0.010	1.261	1.070–1.486	0.006	1.254	1.066–1.475	0.006
Alpha–foetoprotein levels								NA	NA	NA
≤10 ng/ml	Ref. Cat.									
11–200 ng/ml		1.054	0.878–1.266	0.574	1.068	0.890–1.281	0.479			
>200 ng/ml		1.325	1.053–1.667	0.016	1.315	1.044–1.656	0.020			
Tumour gross pathology								NA	NA	NA
Single	Ref. Cat.									
Multifocal		1.145	0.965–1.360	0.122	1.150	0.969–1.366	0.109			
Infiltrative		1.971	1.281–2.869	0.002	1.938	1.296–2.896	0.001			
Massive		1.842	1.165–2.912	0.009	1.931	1.218–3.005	0.005			
Size of the greatest lesion								NA	NA	NA
≤2.0 cm	Ref. Cat.									
2.1–5.0 cm		1.031	0.845–1.257	0.764	1.025	0.840–1.250	0.808			
>5 cm		1.439	1.133–1.827	0.003	1.445	1.138–1.835	0.002			
Metastases		0.991	0.698–1.408	0.960	0.888	0.627–1.260	0.506	NA	NA	NA
MVI								NA	NA	NA
No	Ref. Cat.									
Segmental		1.221	0.620–2.405	0.563	1.273	0.648–2.501	0.483			
Main portal branches		0.865	0.613–1.220	0.409	0.888	0.631–1.250	0.496			
Portal trunk/caval		1.327	1.016–1.734	0.038	1.351	1.036–1.762	0.026			
ITA.LI.CA tumour stage		NA	NA	NA	NA	NA	NA			
0	Ref. Cat.									
A								1.146	0.885–1.483	0.303
B1								1.451	1.070–1.969	0.017
B2								1.389	1.025–1.881	0.034
B3								1.452	0.994–2.121	0.054
C								1.988	1.454–2.718	<0.001
D								2.243	1.692–2.973	<0.001
Main treatment										
BSC	Ref. Cat.									
Liver transplant		0.039	0.019–0.077	<0.001	0.038	0.019–0.077	<0.001	0.035	0.017–0.069	<0.001
Resection		0.176	0.126–0.244	<0.001	0.166	0.120–0.230	<0.001	0.144	0.105–0.198	<0.001
Ablation		0.216	0.164–0.284	<0.001	0.204	0.156–0.267	<0.001	0.180	0.139–0.233	<0.001

(continued on next page)

Table 4 (continued)

	Multivariate models								
	Model 1 n = 1,222 (87.9%)			Model 2 n = 1,222 (87.9%)			Model 3 n = 1,235 (88.8%)		
Variables	**Exp(B)**	**95% CI**	***p* value**	**Exp(B)**	**95% CI**	***p* values**	**Exp(B)**	**95% CI**	***p* value**
IAT	0.343	0.267–0.440	<0.001	0.328	0.256–0.420	<0.001	0.286	0.227–0.362	<0.001
Systemic therapy	0.732	0.517–1.036	0.079	0.690	0.489–0.975	0.036	0.577	0.412–0.807	0.001
Others	0.830	0.454–1.517	0.545	0.766	0.422–1.392	0.382	0.886	0.487–1.614	0.693

Model 1 includes: age, MAFLD, cirrhosis, modality of HCC diagnosis, **Child–Pugh class**, ECOG PS, platelet count, oesophageal varices, alpha–foetoprotein levels, tumour gross pathology, size of the greatest lesion, metastasis, MVI and main treatment.
Model 2 includes: age, MAFLD, cirrhosis, modality of HCC diagnosis, **ALBI grade**, ECOG PS, platelet count, oesophageal varices, alpha-foetoprotein levels, tumour gross pathology, size of the greatest lesion, metastasis, MVI and main treatment.
Model 3 includes: age, MAFLD, cirrhosis, modality of HCC diagnosis, platelet count, oesophageal varices, **ITA.LI.CA tumour stage** and main treatment. Levels of significance: *p* <0.05 (Cox regression model).
ALBI, albumin–bilirubin; BSC, best supportive care; HCC, hepatocellular carcinoma; IAT, Intra-arterial therapy; ITA.LI.CA, Italian Liver Cancer; MAFLD, metabolic associated fatty liver disease; MVI, macrovascular invasion; NA, not assessed; Ref. Cat., reference category.

Discussion

This multicentre study, including a large cohort of patients managed in the 'real world' setting of clinical practice, provides a dynamic picture spanning 15 years of the clinical landscape of alcohol-related HCC in Italy. The 'all comers' strategy adopted for the inclusion of patients in the ITA.L.ICA network did not change over time and therefore the observed variations confidently reflect the evolving clinical scenario that occurred in this population rather than changes as a result of patient referral. Instead, these patients, as well as those with other aetiologies of HCC, could benefit from improvements in the management of HCC and cirrhosis during the data collection period.

All patients reported weekly alcohol intake far beyond the amount considered tolerable, although no healthy amount of alcohol intake exists;[10] indeed, the alcohol-related risk for malignancies starts at a daily dose as low as 10 g.[25] Moreover, as alcohol synergises with other liver carcinogens (infectious and metabolic),[26] its negative effects should be considered when defining a 'tolerable' amount of alcohol intake.

Taking these considerations into account, novel information provided by our study suggests that with the advent of the MAFLD definition, most patients with HCC previously classified as having a 'merely' alcohol-related disease (according to their alcohol abuse and the apparent absence of other causes of liver injury) migrated to this new taxonomic group (Fig. 1), and their prevalence tended to increase over time. The 'epidemic' expansion of metabolic traits among patients with HCC is not sparing other aetiologies.[20] Moreover, as mobility restrictions and social stress caused by the COVID-19 pandemic has led to increased alcohol consumption and increased incidence of metabolic disorders in the general population of many countries, a further increase in the prevalence of patients with chronic liver disease characterised by both offending factors can be anticipated. Our study indicates that dysmetabolic traits are present in most patients with dangerously unhealthy alcohol use, and the lower prevalence of cirrhosis in patients with 'MAFLD' compared with merely alcohol-related cases (Table S2) would suggest that these traits boost hepatocarcinogenesis, increasing the risk of HCC

development in pre-cirrhotic stages, as in patients with NAFLD.[19] Unexpectedly, MAFLD (*i.e.* the presence of features of metabolic syndrome) did not independently affect the prognosis of our patients, in whom the fundamental prognosticators remained those usually reported for HCC, such as PS, liver function tests, portal hypertension signs (oesophageal varices and low platelet counts), tumour burden, AFP levels, and HCC treatment. Thus, it can be inferred that once HCC appears in the context of alcohol-related liver disease, the co-presence of features of metabolic disorders does not seem to significantly affect the risk of death. The similar distribution of the causes of death between patients with alcohol-related and alcohol/MAFLD-related HCC supports this hypothesis.

Another meaningful finding of this study is that the proportion of alcohol-related HCC detected by regular surveillance remained below 50% across all 3 quinquennia evaluated. This figure was comparable to that observed in NAFLD + cryptogenic patients during the same study period and was considerably lower than that observed in patients with viral diseases (Table S4). This difference has various well-known causes, including lower awareness of underlying liver disease by patients and/or providers and poorer adherence to surveillance programmes among alcohol abusers.[15] As expected, HCC diagnoses made outside surveillance programmes were associated with worse oncologic profiles, lower amenability to curative treatments, and poorer survival compared with patients diagnosed within surveillance programmes (Table S3). Indeed, the protective role of periodic screening relies on an anticipated cancer diagnosis and increased amenability to curative/effective HCC treatments, as evidenced by the disappearance of the positive prognostic impact of surveillance when challenged by cancer stage in multivariate analysis. The persistent underuse of surveillance led to three sequentially associated key findings of our investigation: (i) modest improvement in cancer burden at the time of diagnosis, (ii) steady use of curative treatments for HCC, and (iii) modest improvement in patient survival. The lack of a significant overall prognostic improvement may rely on the stability of several prognostic determinants over time, such as liver

function, comorbidity burden, and ITA.LI.CA cancer stage, despite some, albeit modest, improvements in relieving tumour burden.

Nevertheless, it should not be overlooked that in the last quinquennium, the a-OS of patients significantly improved when the survival was calculated using as starting point 12 months after HCC diagnosis (Fig. 2). This "delayed" improvement could have several determinants: (a) better management of cirrhosis complications; (b) the observed decrease in tumours with more than three nodules, MVI of extrahepatic veins, and abnormal AFP levels; (c) the increased use of IAT (and its improved outcome);[27] and (d) the abandonment of systemic therapies with unproven efficacy in favour of sorafenib, and the improved results obtained with this therapy over time.[28]

In our study, all HCC treatments produced a benefit compared with BSC, with a clear hierarchical classification, confirming the utility of detecting HCCs in stages that allow to obtain the most effective responses to treatments. Moreover, HCC therapy was an independent prognostic factor in all multivariate models, even when challenged by the cancer stage. Such a finding lends support to the management of patients with HCC according to the 'therapeutic hierarchy' approach, that is treating every patient with the most effective treatment usable according to liver function, PS, tumour burden, and comorbidities, rather than according to a 'stage-dictated' strategy.[22,29]

Our study also showed that the ITA.LI.CA staging system and ALBI grade, both derived from a population of patients with HCC with different aetiologies, provide reliable prognostic information even for the subset of patients with alcohol-related HCC, and hence, can be confidently used in this setting.

Finally, as previously reported,[30] the presence of oesophageal varices is another independent prognostic factor. This is not surprising as varices, which reveal the presence of clinically significant portal hypertension, indicate a more advanced stage of liver disease and a lower amenability to HCC treatments compared with patients without varices. The prognostic significance of oesophageal varices emphasises two important aspects: first, their presence cannot be disregarded in the management of patients with HCC, as pointed out by a recent expert opinion article;[31] second, this variable should be included in prognostic scores for HCC to improve their performance.

Our study has several limitations. First, owing to its retrospective design, it was vulnerable to the effects of unintended biases and, therefore, its results should be scrutinised in this light. Second, an unavoidable drawback of multicentre databases established in clinical practice is the presence of missing data, which can be managed using data imputation methods. However, these methods need to be carefully applied to avoid potential distortion of results, a risk which increases with the increasing percentage of missing data. Thus, we only applied imputation methods to covariates with <25% of missing data. Consequently, the BMI was excluded from this manipulation, making it impossible to determine its independent prognostic value. Third, analyses of *clinical* databases provide results that are vulnerable to selection bias, which does not disturb the reviews of population-based registries. Therefore, despite our investigation relying on a large, multicentre, and broadly distributed HCC population managed in both academic and non-academic hospitals, the results cannot be generalised to the entire HCC population. Indeed, the Italian population registry currently estimates a 5-year survival rate of approximately 20% for patients with primary liver cancer,[32] a figure much lower than that we observed in the last quinquennium. Fourth, some transient differences between the periods, although statistically significant, may not be clinically meaningful. Conversely, for variables showing a unidirectional trend that eventually reached statistical significance, it can be expected that this behaviour is predictive of forthcoming changes in outcomes of alcohol-related HCC. Fifth, data on alcohol intake after HCC diagnosis were not available and, although only one-fourth of patients were active consumers of alcohol at the time of cancer detection, this drawback prohibited the possibility of testing another potentially important predictor of outcome. Lastly, since the survival of patients with HCC is generally the composite result of a sequence of treatments, particularly in patients diagnosed at early or intermediate stages, the result achieved by any 'main' treatment should be interpreted in this light.

In conclusion, in patients with alcohol-related HCC, any improvement in cancer burden at diagnosis was limited by persistent underuse of surveillance programmes. Consequently, the amenability to curative treatments did not increase, and survival showed only modest improvement. Therefore, achieving marked prognostic improvement relies on the implementation of health policies that can expand the prescription of surveillance strategies and increase patient adherence to these programmes. Moreover, as the presence of oesophageal varices represents an independent negative prognostic factor, this clinical aspect should be carefully considered in the prognosis and management of patients with HCC. Lastly, the clinical features of metabolic disorders are extremely common in patients with alcohol-related liver disease; however, once HCC appears, these may not significantly affect the prognosis of these patients.

Abbreviations

AFP, alpha-foetoprotein; ALBI, albumin/bilirubin; a-OS, adjusted overall survival; APRI, aspartate aminotransferase–Platelet Ratio Index; BCLC, Barcelona Clinic Liver Cancer; BSC, best supportive care; CCA, cholangiocarcinoma; CEUS, contrast-enhanced ultrasound; C–P, Child–Pugh; ECOG PS, Eastern Cooperative Oncology Group-Performance Status; CT, computed tomography; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HR, hazard ratio; IAT, intra-arterial treatment; LT, liver transplant; MAFLD, metabolic dysfunction associated fatty liver disease; MELD, model for end-stage liver disease; MRI, magnetic resonance imaging; MVI, macrovascular invasion; NAFLD, non-alcoholic fatty liver disease; OS, overall survival; PEI, percutaneous ethanol injection; RF, radiofrequency ablation; TACE, transarterial chemoembolisation; TAE, transarterial embolisation; TARE, transarterial radioembolisation; TKI, tyrosine-kinase inhibitor; US, ultrasound.

Conflicts of interest
CC (speaker fees, advisory board): Eisai, Ipsen and MSD; EGG (advisory board, consulting fees): Astra Zeneca, Eisai, MSD, and Roche; FGF (advisory board, consulting fees): AbbVie, Bayer, Eisai, Gilead, MSD, and Intercept; FP (consulting or lecture fees): Astra Zeneca, Bayer, Bracco, EISAI, ESAOTE, Exact Sciences, IPSEN, MSD, Roche, Samsung, and Tiziana Life Sciences; GR (lectures, advisory board, consulting fees): Gilead, Alfa Wasserman, Intercept, and Eisai; FT (research grant, advisory board, consulting fees): Astra Zeneca, AbbVie, Bayer, Eisai, Gilead, MSD, and Roche.

Please refer to the accompanying ICMJE disclosure forms for further details.

Authors' contributions
Concept of the study: FT, LB, NR, VS. Statistical analysis: LB. Drafting of the manuscript: FT, LB, NR, VS. Data collection, revision for important intellectual content and approval of the final manuscript: all authors. Guarantors of the article: NR, FT.

Data availability statement
The data of this study were supplied by the ITA.LI.CA Consortium and confidential patient level data are available from this Consortium upon motivated request to the guarantor(s) (FT).

Supplementary data
Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhepr.2023.100784.

Appendix
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Author names in bold designate shared co-first authorship

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Supplemental information

Landscape of alcohol-related hepatocellular carcinoma in the last 15 years highlights the need to expand surveillance programs

Nicola Reggidori, Laura Bucci, Valentina Santi, Benedetta Stefanini, Lorenzo Lani, Davide Rampoldi, Giorgia Ghittoni, Fabio Farinati, Alberto Masotto, Bernardo Stefanini, Andrea Mega, Elisabetta Biasini, Francesco Giuseppe Foschi, Gianluca Svegliati-Baroni, Angelo Sangiovanni, Claudia Campani, Giovanni Raimondo, Gianpaolo Vidili, Antonio Gasbarrini, Ciro Celsa, Mariella Di Marco, Edoardo G. Giannini, Rodolfo Sacco, Maurizia Rossana Brunetto, Francesco Azzaroli, Donatella Magalotti, Filomena Morisco, Gian Ludovico Rapaccini, Gerardo Nardone, Alessandro Vitale, Franco Trevisani, and for the Italian Liver Cancer (ITA.LI.CA) group

Supplementary Materials

Landscape of alcohol-related hepatocellular carcinoma in the last 15 years highlights the need to expand surveillance programs

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Fig. S1. Lead-time adjusted overall survival according to the ITA.LI.CA staging system (A) and ALBI grade (B) in the whole study population. Levels of significance: <0.05 (Log-rank test).
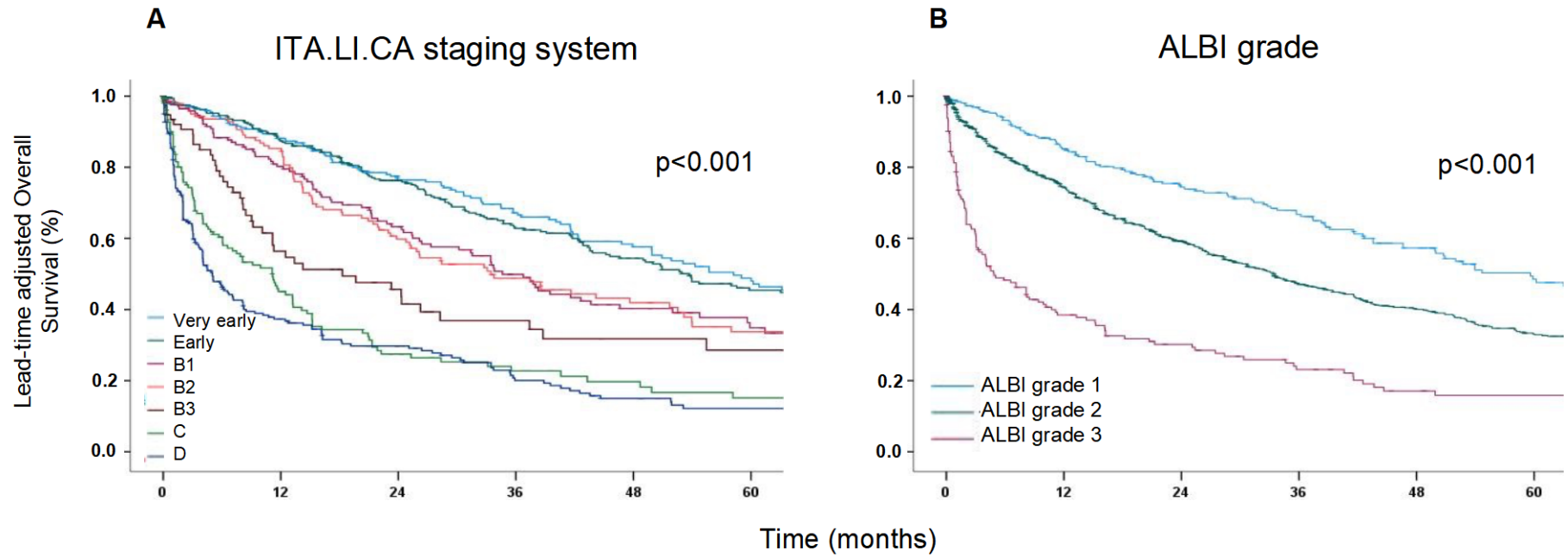
Fig. S2. Lead-time adjusted overall survival in patients with a non-alcohol related aetiology diagnosed with HCC in the three quinquennia. (A) viral patients. (B) NAFLD + cryptogenic patients. Levels of significance: <0.05 (Log-rank test).
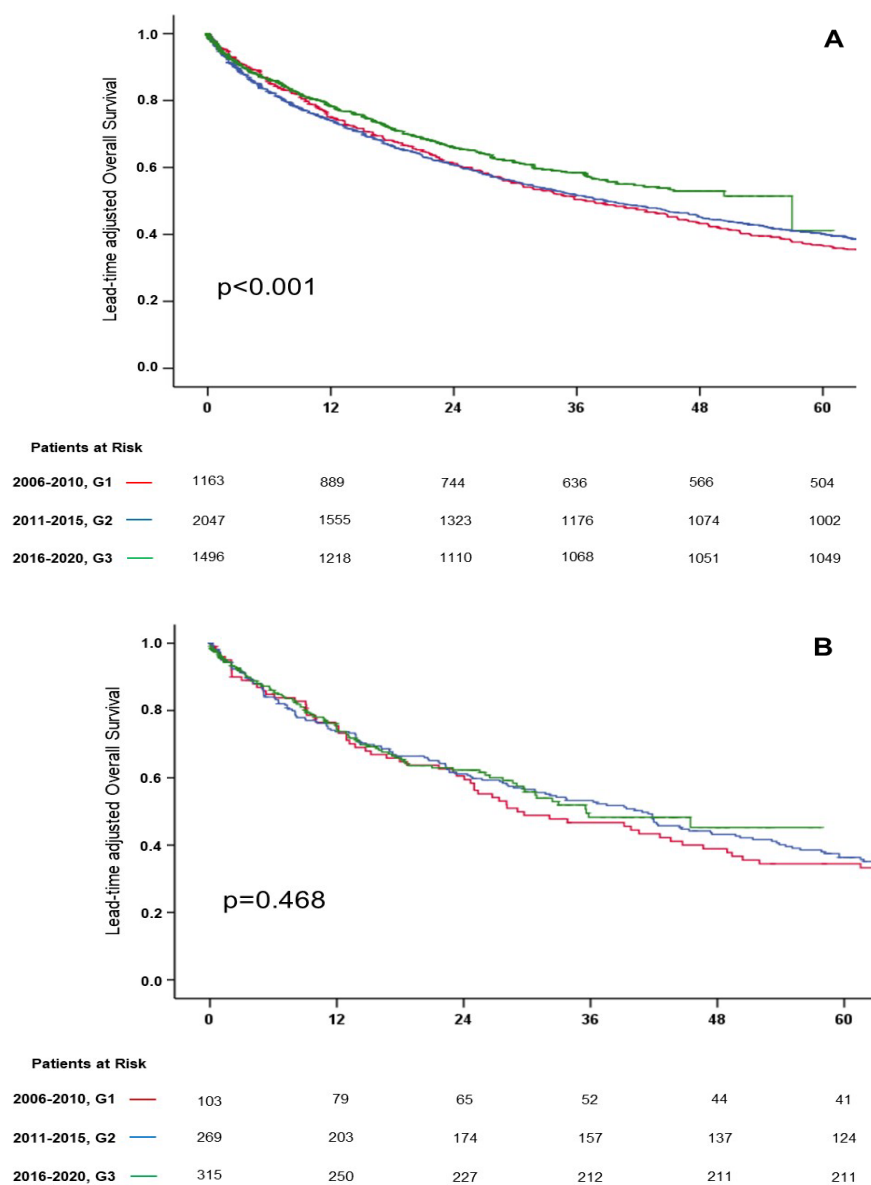
Legend Fig. S2 - To calculate the lead-time for each period, patients diagnosed with HCC during surveillance or incidentally were challenged against those with a symptomatic diagnosis [1]. The mean ± standard deviation (SD) of lead-time for surveyed and incidentally diagnosed patients were:
*- **viral patients**, 8.8±2.0 and 4.3±1.1 months in G1, 8.5±2.3 and 4.1±1.2 months in G2, and 8.1±2.4 and 4.1±1.2 months in G3;*
*- **NAFLD + cryptogenic patients**, 6.1±1.4 and 4.0±0.8 months in G1, 6.2±1.2 and 3.9±0.9 months in G2. and 5.7±1.6, and 3.8±0.9 months in G3.*
The lead-time adjusted overall survival did not change in NAFLD + cryptogenic patients across the quinquennia, whereas it significantly improved in viral patients in the last quinquennium. Considering that in viral patients the rate of curative treatments (surgery + ablation) did not change during the entire study period (56.3%, 58.2% and 55.3%) and the IAT use tendentially decrease (Supplementary table 5), their prognostic improvement could be mainly attributable to the

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increasing use of sorafenib and to a reduction of competing cirrhosis-related mortality, attributable to the expanding proportion of HCCs arising in a setting of controlled HBV infection or cured HCV infection by antiviral drugs. The latter assumption would be supported by the decreased rate (from 20% to 15%) of mortality due to liver failure only observed in viral patients.

Table S1. Distribution of non-imputed variables across the three quinquennia.
Levels of significance: <0.05 (χ2 test).

	Available	2006-2010	2011-2015	2016-2020	p-values
	n. (%)	n. (%)	n. (%)	n. (%)	
		308 (100)	558 (100)	525 (100)	
Alpha-fetoprotein levels	1150 (82.7)	264 (85.7)	438 (78.5)	448 (85.3)	0.018
≤10 ng/ml		145 (54.9)	245 (55.9)	285 (63.6)	
11-200 ng/ml		84 (31.8)	116 (26.5)	111 (24.8)	
>200 ng/ml		35 (13.3)	77 (17.6)	52 (14.2)	
ECOG PS	1331 (95.7)	294 (95.5)	531 (95.2)	506 (96.4)	0.118
0		188 (63.9)	358 (67.4)	366 (72.3)	
1		71 (24.1)	117 (22.0)	88 (17.4)	
≥2		35 (11.9)	56 (10.5)	52 (10.3)	
Tumour gross pathology	1329 (95.5)	296 (96.1)	537 (92.3)	496 (94.5)	0.607
Monofocal		128 (43.2)	268 (49.9)	241 (48.6)	
Multifocal		147 (49.7)	232 (43.2)	215 (43.3)	
Infiltrative		12 (4.1)	20 (3.7)	22 (4.4)	
Massive		9 (3.0)	17 (3.2)	18 (3.6)	
Number of lesions	1087 (78.1)	216 (70.1)	445 (79.7)	426 (81.1)	0.007
1		128 (59.3)	268 (60.2)	241 (56.6)	
2 or 3		46 (21.3)	121 (27.2)	137 (32.2)	
>3		42 (19.4)	56 (12.6)	48 (11.3)	
Size of the greatest lesion	1275 (91.7)	283 (91.9)	508 (91.0)	484 (92.2)	0.080
≤2 cm		66 (23.3)	144 (28.3)	151 (31.2)	
2.1-5.0 cm		144 (50.9)	235 (46.3)	235 (48.6)	
>5 cm		73 (25.8)	129 (25.4)	98 (20.2)	

Legend Table S1 - The comparison of the distribution of imputed (reported in Table 1) and raw data did not show significant data distortions caused by the imputation method.

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Table S2. Demographic and clinical characteristics of patients with merely alcohol-related and alcohol/MAFLD-related hepatocellular carcinoma.
Levels of significance: <0.05 (Mann-Whitney U test and χ2 test).

Variables	n. (%)	Pure alcohol-related HCCs "non-MAFLD" n. (%) 287 (21.0)	Alcohol-MAFLD-related HCCs "MAFLD" n. (%) 1082 (79.0)	p-values
Demographic and clinical features				
Age, years	1369 (100)	66.0 (61-73)	68 (63-74)	**0.024**
Median (25th-75th)				
Sex (M/F)	1369 (100)	265/22 (92.3/7.7)	1006/76 (93.0/7.0)	0.708
Alcohol consumption (AU/week)	808 (59.0)	163 (56.8)	635 (58.7)	0.597
Median (25th-75th)		50 (35-60)	50 (30-60)	
Drinking habit	1369 (100)	287 (100)	1082 (100)	0.305
Past		125 (43.6)	508 (47.0)	
Current		162 (56.4)	574 (53.0)	
Smoking habit	1128 (81.1)	236 (82.2)	892 (82.4)	**0.011**
Never		125 (53.0)	466 (52.2)	
Past		34 (14.4)	198 (22.2)	
Current		77 (32.6)	228 (25.6)	
Type 2 diabetes	1369 (100)	287 (100)	1082 (100)	**<0.001**
Yes		47 (16.4)	535 (49.4)	
Cirrhosis	1347 (96.9)	283 (98.6)	1065 (98.4)	**0.038**
Yes		271 (95.8)	982 (92.2)	
Charlson Comorbidity Index	1391 (100)	287 (100)	1082 (100)	**<0.001**
Median (25th-75th)		3 (2 - 4)	3 (3 - 5)	
Modality of HCC diagnosis	1253 (90.1)	259 (90.2)	994 (91.9)	0.680
Under surveillance		109 (42.1)	436 (43.9)	
Incidental		102 (39.4)	396 (39.8)	
Symptomatic		48 (18.5)	162 (16.3)	
Surveillance interval	388 (71.2)*	70 (64.2)	318 (72.9)	0.101
≤6 months		59 (84.3)	239 (75.2)	
Others		11 (15.7)	79 (24.8)	
Child-Pugh class	1369 (100)	287 (100)	1082 (100)	0.246
A		152 (53.0)	589 (54.4)	
B		107 (37.3)	419 (38.7)	
C		29 (9.8)	74 (6.8)	
ALBI grade	1369 (100)	287 (100)	1082 (100)	0.191
Grade 1, ≤ -2.60		45 (15.7)	219 (20.2)	
Grade 2, > -2.60 ≤ -1.39		204 (71.1)	739 (78.3)	
Grade 3, > -1.39		38 (13.2)	124 (11.5)	
APRI	1139 (83.2)	228 (79.4)	911 (84.2)	0.317
First tertile		66 (28.9)	309 (33.9)	

Second tertile		84 (36.8)	299 (32.8)	
Third tertile		78 (34.2)	303 (33.3)	
MELD score	1391 (100)	287 (100)	1082 (100)	**0.014**
Median (25th-75th)		11.0 (8.8-14.0)	10.3 (8.0-13.6)	
ECOG PS	1369 (100)	287 (100)	1082 (100)	0.746
0		192 (66.9)	732 (67.7)	
1		62 (21.6)	242 (22.4)	
≥2		33 (11.5)	108 (10.0)	
Oesophageal varices	1369 (100)	287 (100)	1082 (100)	0.096
Yes		149 (51.9)	503 (46.4)	
Platelet count	1369 (100)	287 (100)	1082 (100)	0.224
≤100,000/mmc		113 (39.4)	384 (35.5)	

Tumour burden and stage

Gross pathology	1369 (100)	287 (100)	1082 (100)	0.900
Monofocal		138 (48.1)	522 (48.2)	
Multifocal		127 (44.3)	485 (44.8)	
Infiltrating		11 (3.8)	43 (4.0)	
Massive		11 (3.8)	43 (4.0)	
Number of lesions	1272 (92.9)	265 (92.3)	1007 (93.1)	0.846
1		138 (52.1)	522 (51.8)	
2 or 3		79 (29.8)	315 (31.3)	
>3		48 (18.1)	170 (16.9)	
Size of the greatest lesion	1355 (99.0)	281 (97.9)	1074 (99.3)	0.334
≤2cm		87 (31.0)	287 (26.7)	
2.1-5.0 cm		130 (46.3)	514 (47.9)	
>5 cm		64 (22.8)	263 (25.4)	
MVI	1369 (100)	287 (100)	1082 (100)	0.479
Yes		47 (16.4)	159 (14.7)	
Site of MVI	206 (100)	47 (100)	159 (100)	0.732
Segmental		4 (8.5)	10 (6.3)	
Main portal branches		18 (38.3)	55 (34.6)	
Portal trunk/caval vein		25 (53.2)	94 (59.1)	
Metastasis	1369 (100)	287 (100)	1082 (100)	0.311
Yes		15 (5.2)	42 (3.9)	
Alpha-fetoprotein levels	1369 (100)	287 (100)	1082 (100)	0.513
≤10 ng/ml		154 (53.7)	621 (57.4)	
11-200 ng/ml		85 (29.6)	290 (26.8)	
>200 ng/ml		48 (16.7)	171 (15.8)	
ITA.LI.CA tumour stage	1369 (100)	287 (100)	1082 (100)	0.429
0		65 (22.6)	220 (20.3)	
A		55 (19.2)	271 (25.0)	
B1		35 12.2)	134 (12.4)	
B2		37 (12.9)	109 (10.1)	
B3		18 (6.3)	58 (5.4)	
C		31 (10.8)	120 (11.1)	
D		46 (16.0)	170 (15.7)	
Causes of death	762 (100)	176 (100)	586 (100)	0.442
Tumour progression		77 (43.8)	255 (43.5)	

Liver failure	32 (18.2)	128 (21.8)
Hemorrhage	4 (2.3)	18 (3.1)
Kidney failure	3 (1.7)	12 (2.0)
Infection	4 (2.3)	22 (3.8)
Embolism	2 (1.1)	3 (0.5)
Other	36 (20.5)	114 (19.5)
Not known	18 (10.2)	34 (5.8)

*: among patients under surveillance, the interval was specified in 388 cases.

Abbreviations: ALBI, Albumin-Bilirubin; APRI, AST to Platelet Ratio Index; BSC, Best Supportive Care; ECOG-PS, Eastern Cooperative Oncology Group Performance Status; HCC, Hepatocellular Carcinoma; IAT, Intra-Arterial Therapy; ITA.LI.CA, Italian Liver Cancer; MAFLD, Metabolic dysfunction Associated Fatty Liver Disease; MELD, Model of End-stage Liver Disease; MVI, Macrovascular Invasion.

Table S3. Characteristics and outcomes of surveyed and non-surveyed patients.
Levels of significance: <0.05 (Mann-Whitney U test and χ2 test).

Variables	Available	Surveyed patients	Non-surveyed patients	P-values
	n. (%)	n. (%)	n. (%)	
		556 (43.8)	**714 (56.2)**	
Demographic and clinical features				
Age, years Median (25th-75th)	1270 (100)	67.0 (62-73)	68.5 (63-75)	**0.003**
Sex (M/F)	1270 (100)	510/46 (91.7(8.3)	670/44 (93.8/6.2)	0.146
Child-Pugh class	1270 (100)	556 (100)	714 (100)	**0.012**
A		315 (56.7)	377 (52.8)	
B		212 (38.1)	268 (37.5)	
C		29 (5.2)	69 (9.7)	
ECOG PS	1270 (100)	556 (100)	714 (100)	**<0.001**
0		415 (74.6)	436 (61.1)	
1		102 (18.3)	177 (24.8)	
≥2		39 (7.0)	101 (14.1)	
Tumour burden and stage				
Gross pathology	1270 (100)	556 (100)	714 (100)	**<0.001**
Monofocal		317 (57.0)	290 (40.6)	
Multifocal		219 (39.4)	351 (49.2)	
Infiltrating		17 (3.1)	37 (5.2)	
Massive		3 (0.5)	36 (5.0)	
Number of lesions	1177 (84.6)	536 (96.4)	641 (89.8)	**<0.001**
1		317 (59.1)	290 (45.2)	
2 or 3		155 (28.9)	214 (33.4)	
>3		64 (11.9)	137 (21.4)	
Size of the greatest lesion	1256 (90.3)	553 (99.5)	703 (98.4)	**<0.001**
≤2 cm		210 (38.0)	142 (20.2)	
2.1-5.0 cm		273 (49.4)	324 (46.1)	
>5 cm		70 (12.7)	237 (33.7)	
MVI	1270 (100)	556 (100)	714 (100)	**<0.001**
Yes		60 (10.8)	142 (19.9)	
MVI site	202 (100)	60 (100)	142 (100)	0.188
Segmental		6 (10.0)	8 (5.6)	
Main portal branches		16 (26.7)	55 (38.7)	
Portal trunk/caval vein		38 (63.3)	79 (55.6)	
Metastases	1270 (100)	556 (100)	714 (100)	**<0.001**
Yes		9 (1.6)	45 (6.3)	
Alpha-fetoprotein levels	1270 (100)	556 (100)	714 (100)	**0.002**
≤10 ng/ml		343 (61.7)	376 (52.7)	
11-200 ng/ml		145 (26.1)	209 (29.3)	
>200 ng/ml		68 (12.2)	129 (18.1)	

ITA.LI.CA tumour stage	1270 (100)	556 (100)	714 (100)	**<0.001**
0		165 (29.7)	102 (14.3)	
A		159 (28.6)	145 (20.3)	
B1		52 (9.4)	85 (13.3)	
B2		50 (9.0)	84 (11.8)	
B3		21 (3.8)	50 (7.0)	
C		41 (7.4)	102 (14.3)	
D		68 (12.2)	136 (19.0)	
Main treatment	1264 (90.9)	552 (99.3)	712 (99.7)	**<0.001**
Liver transplant		33 (6.0)	20 (2.8)	
Resection		66 (12.0)	114 (16.0)	
Ablation		211 (38.2)	142 (19.9)	
IAT		137 (24.8)	184 (25.8)	
Systemic therapy		16 (2.9)	56 (7.9)	
Others		5 (0.9)	11 (1.5)	
BSC		68 (12.3)	162 (22.8)	
Not known		16 (2.9)	23 (3.2)	
a-OS, months	1270 (100)	556 (100)	714 (100)	**0.049**
Median (95% CI)		34.7 (29.5-40.0)	28.4 (23.1-33.7)	

Abbreviations: a-OS, Lead-time adjusted Overall Survival; BSC, Best Supportive Care; ECOG-PS, Eastern Cooperative Oncology Group Performance Status; IAT, Intra-Arterial Therapy; ITA.LI.CA, Italian Liver Cancer; MVI, Macrovascular Invasion.

Table S4. Modalities of HCC diagnosis in NAFLD + cryptogenic and viral patients.
Levels of significance: <0.05 (χ2 test).

	Available	2006-2010	2011-2015	2016-2020	p-values
	n. (%)	n. (%)	n. (%)	n. (%)	
NAFLD + cryptogenic patients, n (%)	687 (100)	103 (100)	269 (100)	315 (100)	0.660
Modality of HCC diagnosis	628 (91.4)	94 (91.3)	240 (89.2)	294 (93.3)	
Under surveillance		39 (41.5)	115 (47.9)	132 (44.9)	
Incidental		36 (38.3)	87 (36.3)	118 (40.0)	
Symptomatic		19 (20.2)	38 (15.8)	44 (15.0)	
Viral patients, n (%)	4706 (100)	1163 (100)	2047 (100)	1496 (100)	**<0.001**
Modality of HCC diagnosis	4296 (91.3)	1058 (91.0)	1846 (90.2)	1392 (93.0)	
Under surveillance		683 (64.6)	1304 (70.6)	852 (61.2)	
Incidental		249 (23.5)	356 (19.3)	390 (28.0)	
Symptomatic		126 (11.9)	186 (10.1)	150 (10.8)	

Abbreviations: HCC, Hepatocellular Carcinoma; NAFLD, Non-alcoholic Fatty Liver Disease.

Legend Table S4 - To highlight the causes of the decreased use of surveillance in viral patients during the last quinquennium, we made a year-by-year analysis (data not reported in detail) which showed an abrupt fall (51.4%) of diagnoses made under surveillance in 2020, when a rigid lockdown to control the COVID-19 pandemic was in place, limiting the possibility to attend regular check-ups. Conversely, this fall was not observed in both alcohol-related and metabolic liver diseases. We do not have an explanation for such a discrepancy.

Table S5. Main treatment and causes of death in NAFLD + cryptogenic and viral patients diagnosed with HCC.
Levels of significance: <0.05 (Mann-Whitney U test and χ2 test).

	Available n. (%)	2006-2010 n. (%)	2011-2015 n. (%)	2016-2020 n. (%)	p-values
NAFLD + cryptogenic patients, n (%)	687 (100)	103 (100)	269 (100)	315 (100)	
Main treatment					0.285
Liver transplant		4 (3.9)	14 (5.2)	20 (6.3)	
Resection		28 (27.2)	61 (22.7)	58 (18.4)	
Ablation		28 (16.3)	60 (22.3)	84 (26.7)	
IAT		13 (12.6)	65 (24.2)	65 (20.6)	
Systemic therapy		9 (8.7)	14 (5.2)	25 (7.9)	
Others		1 (1.0)	3 (1.1)	5 (1.6)	
BSC		19 (18.4)	45 (16.7)	45 (14.3)	
Not known		1 (1.0)	7 (2.6)	13 (4.1)	
Causes of death	332 (100)	75 (100)	153 (100)	104 (100)	**0.040**
Tumour progression		34 (45.3)	61 (39.9)	52 (50.0)	
Liver failure		13 (17.3)	48 (31.4)	21 (20.2)	
Hemorrhage		2 (2.7)	2 (1.3)	1 (1.0)	
Kidney failure		1 (1.3)	4 (2.6)	5 (4.8)	
Infection		1 (1.3)	4 (2.6)	4 (3.8)	
Embolism		1 (1.3)	1 (0.7)	1 (1.0)	
Other		21 (28.0)	20 (13.1)	10 (9.6)	
Not known		2 (2.7)	13 (8.5)	10 (9.6)	
Viral HCC patients, n (%)	4706 (100)	1163 (100)	2047 (100)	1496 (100)	
Main treatment					**<0.001**
Liver transplant		76 (6.5)	141 (6.9)	92 (6.1)	
Resection		187 (16.1)	363 (17.7)	276 (18.4)	
Ablation		392 (33.7)	688 (33.6)	461 (30.8)	
IAT		254 (21.8)	399 (19.5)	285 (19.1)	
Systemic therapy		53 (4.6)	148 (7.2)	140 (9.4)	
Others		34 (2.9)	10 (0.5)	12 (0.8)	
BSC		135 (11.6)	362 (12.8)	183 (12.2)	
Not known		32 (2.8)	36 (1.8)	47 (3.1)	
					<0.001
Causes of death	2391 (100)	817 (100)	1127 (100)	447 (100)	
Tumour progression		403 (49.6)	532 (47.2)	227 (50.8)	
Liver failure		160 (19.7)	231 (20.5)	69 (15.4)	
Haemorrhage		20 (2.5)	46 (4.1)	28 (6.3)	
Kidney failure		10 (1.2)	13 (1.2)	8 (1.8)	

Infection	10 (1.2)	29 (2.6)	14 (3.1)
Embolism	3 (0.4)	1 (0.1)	4 (0.9)
Other	179 (22.0)	162 (14.4)	33 (7.4)
Not known	32 (3.9)	113 (10.0)	64 (14.3)

BSC, Best Supportive Care; HCC, Hepatocellular Carcinoma; IAT, intra-arterial therapy; NAFLD, Non-alcoholic Fatty Liver Disease.

Legend Table S5 - *The rate of curative treatments (surgery and ablation) did not change over the study period in both subgroups (viral patients: 56.3%, 58.2% and 55.3%; NAFLD + cryptogenic patients: 47.4%, 50.2% and 51.4%). In the viral group, the proportion of patients undergoing systemic therapy (sorafenib) doubled compared with the first quinquennium.*
Regarding the causes of death, among viral patients a 5% reduction of mortality rate from liver failure occurred in the last quinquennium, likely attributable to the expanding proportion of HCCs arising in a setting of controlled HBV infection or cured HCV infection by the antiviral treatments. Both aetiological groups showed a triplication of deaths due to infections.

Reference

[1] Cucchetti A, Trevisani F, Pecorelli A, Erroi V, Farinati F, Ciccarese F, et al. Estimation of lead-time bias and its impact on the outcome of surveillance for the early diagnosis of hepatocellular carcinoma. J Hepatol 2014;61:333–41. https://doi.org/10.1016/j.jhep.2014.03.037.