Liver Cancer

Research Article

Liver Cancer
DOI: 10.1159/000553063

Received: November 11, 2025
Accepted: June 4, 2026
Published online: July 2, 2026

Alcohol Plays a Detrimental Role in the Prognosis of Hepatocellular Carcinoma Related to Steatotic Liver Disease

Stefano Gitto[a] Alessandro Vitale[b] Gianluca Svegliati-Baroni[c] Giulio Marchesini[d] Francesco Paolo Russo[e] Luca Miele[f] Claudia Campani[a] Valentina Adotti[a] Martina Rosi[a] Francesco Vizzutti[a] Mariarosaria Marseglia[d, g] Andrea Martini[h] Angelo Sangiovanni[i] Giuseppe Cabibbo[j] Giacomo Zaccherini[k] Giorgia Ghittoni[l] Maria Di Marco[m] Francesco Giuseppe Foschi[n] Filomena Morisco[o] Sara Grasselli[p] Carlo Saitta[q] Francesca Romana Ponziani[r] Maurizia Rossana Brunetto[s] Donatella Magalotti[t] Francesco Azzaroli[u] Andrea Mega[v] Rodolfo Sacco[w] Gerardo Nardone[x] David Sacerdoti[y] Sara Boninsegna[z] Gianpaolo Vidili[A] Franco Trevisani[B] Edoardo G. Giannini[C] Fabio Marra[a]
on behalf of the Italian Liver Cancer (ITA.LI.CA) group

[a]Department of Experimental and Clinical Medicine, University of Florence, Florence, Italy; [b]Department of Surgery, Oncology, and Gastroenterology, University of Padova, Padua, Italy; [c]Liver Injury and Transplant Unit, Polytechnic University of Marche, Ancona, Italy; [d]IRCCS Azienda Ospedaliero-Universitaria Policlinico di Sant'Orsola-Malpighi, Bologna, Italy; [e]Gastroenterology and Multivisceral Transplant Unit, Azienda Ospedale-Università Padova, Padua, Italy; [f]Department of Translational Medicine and Surgery, Università Cattolica del Sacro Cuore, Rome, Italy; [g]Division of Internal Medicine, Hepatobiliary Diseases and Immunoallergology, University of Bologna, Bologna, Italy; [h]UOC Clinica Medica 5 Azienda Ospedale Università Padova, Padua, Italy; [i]Division of Gastroenterology and Hepatology, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy; [j]Gastroenterology and Hepatology Unit, Department of Health Promotion, Mother and Child Care, Internal Medicine and Medical Specialties, PROMISE, University of Palermo, Palermo, Italy; [k]Department of Medical and Surgical Sciences, University of Bologna, Bologna, Italy; [l]Gastroenterology Unit, Belcolle Hospital, Viterbo, Italy;

Stefano Gitto, Alessandro Vitale, Gianluca Svegliati-Baroni, Giulio Marchesini, Francesco Paolo Russo, and Luca Miele equally contributed to this work and share first authorship.
Franco Trevisani, Edoardo G. Giannini, and Fabio Marra share senior authorship.
Present address: Stefano Gitto's current additional affiliation: SOD Alcologia, Azienda Ospedaliero Universitaria Careggi and Centro Alcologico Regionale Toscano, Florence, Italy.

karger@karger.com
www.karger.com/lic

Correspondence to:
Fabio Marra, fabio.marra@unifi.it
Alessandro Vitale, alessandro.vitale@unipd.it

[m]Medicine Unit, Bolognini Hospital, Seriate, Italy; [n]Department of Internal Medicine, Ospedale per gli Infermi di Faenza, Faenza, Italy; [o]Department of Clinical Medicine and Surgery, Diseases of the Liver and Biliary System Unit, University of Naples "Federico II", Naples, Italy; [p]Department of Medicine and Surgery, Infectious Diseases and Hepatology Unit, University of Parma and Azienda Ospedaliero-Universitaria of Parma, Parma, Italy; [q]Department of Clinical and Experimental Medicine, Unit of Medicine and Hepatology, University of Messina, Messina, Italy; [r]Liver Unit, CEMAD-Centro Malattie dell'Apparato Digerente, Medicina Interna e Gastroenterologia, Università Cattolica del Sacro Cuore, Fondazione Policlinico Universitario Gemelli IRCCS, Rome, Italy; [s]Department of Clinical and Experimental Medicine, Hepatology and Liver Physiopathology Laboratory, University Hospital of Pisa, Pisa, Italy; [t]Radiology Unit Fanti, IRCCS Azienda Ospedaliero-Universitaria di Bologna, Bologna, Italy; [u]Gastroenterology Unit, IRCCS Azienda Ospedaliero-Universitaria di Bologna, Bologna, Italy; [v]Gastroenterology Unit, Bolzano Regional Hospital, Bolzano, Italy; [w]Gastroenterology and Digestive Endoscopy Unit, Foggia University Hospital, Foggia, Italy; [x]Department of Clinical Medicine and Surgery, Hepato-Gastroenterology Unit, University of Naples "Federico II", Naples, Italy; [y]Liver Unit, Department of Medicine, University of Verona, Azienda Ospedaliera Universitaria Integrata of Verona, Verona, Italy; [z]Gastroenterology Unit, Ospedale Sacro Cuore Don Calabria, Negrar, Italy; [A]Department of Medical, Surgical and Experimental Sciences, Clinica Medica Unit, University of Sassari, Azienda Ospedaliero-Universitaria di Sassari, Sassari, Italy; [B]Italian Liver Cancer Association, Bologna, Italy; [C]Gastroenterology Unit, Department of Internal Medicine, University of Genoa, Genoa, Italy

Keywords
Alcohol · Steatosis · Hepatocellular carcinoma

Abstract
Introduction: The recently adopted nomenclature of steatotic liver disease (SLD) introduces new diagnostic categories, including metabolic dysfunction-associated steatotic liver disease (MASLD), the intermediate metabolic dysfunction and alcohol-related liver disease (MetALD), and alcohol-associated liver disease (ALD). However, their specific impact on the outcomes of hepatocellular carcinoma (HCC) remains unclear. This study aimed to evaluate how alcohol consumption influences prognosis in patients with SLD-related HCC. ***Methods:*** We analyzed data from 2,864 HCC patients enrolled in the nationwide ITA.LI.CA database (2008–2022), stratifying those with SLD based on alcohol intake into MASLD, MetALD, and ALD. A comparator group with hepatitis B virus (HBV)-related HCC was also included. Multivariable Cox regression and competing risk analyses were employed to assess survival and cause-specific mortality. ***Results:*** Among SLD-related HCC, MASLD accounted for 47.1%, ALD 18.7%, and MetALD 7.2%. Patients with ALD showed the poorest liver function, more advanced tumor stage, and the highest mortality risk. Alcohol use progressively worsened prognosis from MASLD to ALD. MetALD and ALD were both associated with increased liver failure- and extrahepatic-related deaths compared to MASLD. In multivariable models, tumor burden, liver decompensation, and alcohol intake were significant predictors of mortality. Notably, metabolic comorbidities impacted prognosis predominantly in MetALD and ALD, suggesting an interaction between alcohol and systemic metabolic dysfunction. ***Conclusion:*** Alcohol consumption exerts a dose-dependent detrimental effect on clinical outcomes in SLD-related HCC. These findings support a distinct prognostic stratification for HCC patients with MetALD and ALD, reinforcing the need for alcohol abstinence in individuals with metabolic liver disease.

Introduction

Hepatocellular carcinoma (HCC) accounts for approximately 80% of primary liver cancers and represents a major cause of mortality among patients with cirrhosis [1, 2]. Accumulating evidence indicates that hepatic steatosis, now referred to as steatotic liver disease (SLD) according to the recently updated nomenclature, contributes to the rising incidence of HCC observed over the last 2 decades [3]. A pivotal aspect of the new nomenclature is the ability to categorize a spectrum of conditions of steatosis associated with varying levels of alcohol consumption within a unified diagnostic framework [4]. Specifically, patients with SLD and at least one cardiometabolic risk factor are diagnosed with metabolic dysfunction-associated steatotic liver disease (MASLD) in the presence of none or low alcohol intake (<20 g/day in women and <30 g/day in

men). Individuals with intermediate alcohol intake (20–50 g/day in women and 30–60 g/day in men, respectively) are classified as metabolic dysfunction and alcohol-related liver disease (MetALD), whereas individuals with high alcohol intake (>50 or >60 g/day in women and men, respectively) are defined as having alcohol-associated liver disease (ALD), based on the rationale that such levels of consumption override the possible contribution of metabolic derangements [4].

The identification of different groups of SLD has a strong impact on the clinical course and outcomes of patients. The probability of survival is shorter in ALD than in MASLD, with intermediate values in patients with MetALD. To what extent these differences identified by the new classification affect the clinical history of patients with HCC is currently unknown. The present study was undertaken to compare epidemiology, clinical characteristics, management, and outcome of specific subgroups of patients with HCC based on the underlying presence of MASLD, MetALD or ALD [4]. We also included in the analysis a group of patients with HCC associated with chronic hepatitis B infection, in the absence of other concurrent etiologies.

Methods

Study Groups and Variables

Patients with a diagnosis of HCC included in the ITA.LI.CA database between January 1, 2008, and December 31, 2022, were enrolled. All patients had at least one cardiometabolic risk factor and were stratified according to their reported alcohol consumption in MASLD (<20 g or 30 g/day in women and men, respectively), MetALD (between 20 g and 50 g/day or 30 g and 60 g for women and men), and ALD (alcohol consumption higher than 50 g or 60 g in women and men). For homogeneity, patients with ALD in the absence of cardiometabolic risk factors were not included. Cirrhosis was defined at enrollment based on clinical and laboratory data and/or liver biopsy. Cardiometabolic criteria were defined according to the recent consensus paper [4] as the presence of at least one of the following characteristics: (a) body mass index (BMI) ≥25 kg/m^2; (b) diagnosis of prediabetes or type 2 diabetes, or treatment for type 2 diabetes; (c) blood pressure ≥130/85 mm Hg or specific antihypertensive drug treatment; (d) plasma triglycerides ≥150 mg/dL or lipid-lowering treatment; (e) plasma high-density lipoprotein (HDL)-cholesterol ≤40 mg/dL (males) or ≤50 mg/dL (females) or lipid-lowering treatment.

Etiologies and comorbidities were obtained from the initial individual records in the ITA.LI.CA database, which are locked immediately after inclusion. We did not include patients with ongoing or previous hepatitis C or hepatitis D. Patients with other relevant causes of liver disease (i.e., autoimmune or cholestatic) were also excluded. Conversely, patients with HBV-related liver disease and alcohol consumption or with the presence of cardiometabolic criteria were maintained.

The following clinical and treatment-related variables were recorded: age, sex, comorbidities (expressed as Charlson Comorbidity Index [CCI]), the Eastern Cooperative Oncology Group performance status scale (ECOG-PSS), surveillance, specific cardiometabolic criteria, liver disease etiology, presence of cirrhosis, severity of liver disease (Model for End-stage Liver Disease [MELD] and Child-Pugh-Turcotte [CPT] class, platelet count, presence of gastroesophageal varices [endoscopic diagnosis], ascites, hepatic encephalopathy) and tumor characteristics: number and size of nodules, intra or extra-hepatic vascular invasion, metastases, alpha-fetoprotein (AFP) levels, ITA.LI.CA tumor stage [5]. The diagnosis of HCC and evaluation of the response to treatment were based on the European Association for the Study of the Liver (EASL) guidelines [6].

The ITA.LI.CA database complies with both past and current Italian privacy legislation and adheres to the ethical standards outlined in the 1964 Declaration of Helsinki and its subsequent amendments [7]. The Institutional Review Board of the participating centers approved the observational studies based on these registries. Data are collected prospectively and updated every 2 years. The group coordinator regularly checks entries for consistency, and if clarification or additional information is needed, relevant cases are returned to the recruiting center before final inclusion.

Staging and Treatment of HCC

Surveillance for HCC in the enrolled patients was carried out with ultrasound at 6-month intervals [6].

Cancer burden was assessed by CT and/or MRI scans. Furthermore, additional investigations to detect extrahepatic tumor spread were conducted when clinically indicated or routinely for those patients with advanced HCC or undergoing evaluation for liver transplantation. HCC was staged according to the Barcelona Clinic Liver Cancer (BCLC) and the ITA.LI.CA staging systems [5–8]. When patients underwent multiple treatments, they were classified according to the most effective one, following this hierarchy: liver transplantation (LT), liver resection (LR), percutaneous ablation (ABL), transarterial chemoembolization/embolization or radioembolization (collectively indicated as IAT, intra-arterial therapies), systemic therapy or other therapies (SOT), and best supportive care (BSC) [9].

Statistical Analysis

Baseline characteristics, staging, treatment allocation, and overall survival were analyzed comparing patients with MASLD, MetALD, ALD, and HBV. Continuous variables were reported as median (25%–75% confidence interval), and the Mann-Whitney U test was utilized to compare groups. Categorical variables were presented as frequencies and percentages, and the chi-squared test was applied for comparisons. Absolute standardized mean differences assessed etiology-related imbalances in baseline variables (i.e., each subgroup was compared to the MASLD group, which served as the reference).

Overall survival (OS) was calculated from the date of HCC diagnosis to the date of death, last follow-up evaluation, or censoring (December 31, 2022). Survival curves were calculated using the Kaplan-Meier method and compared using the Log-Rank test. Five multivariable Cox survival models were calculated: one for all patients and one for each etiology subgroup (MASLD, MetALD, ALD, and HBV). Variables included in each model were selected using the LASSO Cox method. The proportional-hazards assumption was tested based on Schoenfeld residuals.

Since recent literature indicates that the prognosis of HCC patients is influenced not only by cancer-related death but also by liver failure and extra-hepatic causes of death, competing-risk analyses were performed using the methodology provided by Fine & Gray [10, 11]. Specifically, we analyzed HCC-related, liver failure-related and extra-hepatic disease-related causes of death. HCC-related death was defined as death attributable to tumor progression or HCC-induced liver decompensation. Liver failure–related death referred to hepatic decompensation not directly attributable to tumor progression. Extra-hepatic causes included cardiovascular events, infections, other malignancies, and unknown causes.

Patients lost at follow-up were censored as patients dead for extra-hepatic disorders. Following recent recommendations on the analysis of competing-risk data [12], the Fine-Gray sub-distribution model was pre-specified as the primary analysis for our prognostic aim, while cause-specific Cox proportional-hazards models, in which subjects experiencing a competing event were censored at the time of the competing event, were performed as a pre-specified sensitivity analysis to support etiologic interpretation of each cause of death.

Missing data of study covariates always involved less than 10% of patients and were estimated using the multiple imputation method [13]. All analyses were performed using STATA Stata/SE 18.0 (1985–2023). A 2-tailed p value <0.05 was considered statistically significant.

Results

Baseline Characteristics, Cancer Diagnosis, Staging, and Main Treatment

The selection process of the study cohort is illustrated in Figure 1. The process selected 2089 SLD cases, with a large predominance of MASLD (64.5%) followed by ALD (25.6%) and MetALD (9.9%); 775 patients (27.1% of the whole cohort investigated in this study) were categorized as HBV. All HBV patients were on taking antiviral therapy (entecavir or tenofovir). The patients' baseline characteristics are presented in Table 1. Subjects with MASLD-related HCC were older than all other groups, with more than half of the patients over 70 years old ($p < 0.001$). All patients with SLD had at least one metabolic component and presented with overweight, hypertension, type 2 diabetes, or dyslipidemia more frequently than the HBV subgroup. All three SLD subgroups were more frequently classified as stage C in the ITALICA staging system than HBV patients ($p = 0.003$). HBV-related HCCs were more often treated with liver transplantation ($p < 0.001$). Only one third of patients with SLD were diagnosed with HCC while under surveillance, compared to more than half of the HCCs discovered in HBV patients ($p < 0.001$). Patients with ALD, in comparison with those with MASLD, were more frequently males and cirrhotics. They tended to show more often esophageal varices and, by a functional point of view, to be more frequently in CTP B/C class. Regarding HCC patterns, patients with ALD showed a higher incidence of vascular invasion than MASLD-related HCC.

Cox Multivariable Survival Analysis

Data from the Cox survival analysis are presented in Table 2. Considering the whole patient cohort, the risk of death was associated with more severe liver disease, such as being in CTP classes B or C, and with sodium levels. Accordingly, indicators of portal hypertension (varices and ascites) and the ECOG-PSS significantly correlated with the risk of death. Considering tumor characteristics, the risk of death was associated with extra-hepatic vascular invasion (VP4 - liver cancer study group of Japan [14]), AFP levels, and ITA.LI.CA stages B1, B2, B3, and C.

When the MASLD subgroup was selectively analyzed, ascites and CTP class B/C, tumor size and extra-hepatic vascular invasion were all associated with the risk of death. Interestingly, in the MetALD subgroup, parameters of metabolic dysfunction, such as hypertension, and comorbidities were significant predictors of mortality. In this group, a MELD score >10 (rather than the CTP class) was also associated with mortality. Among tumor

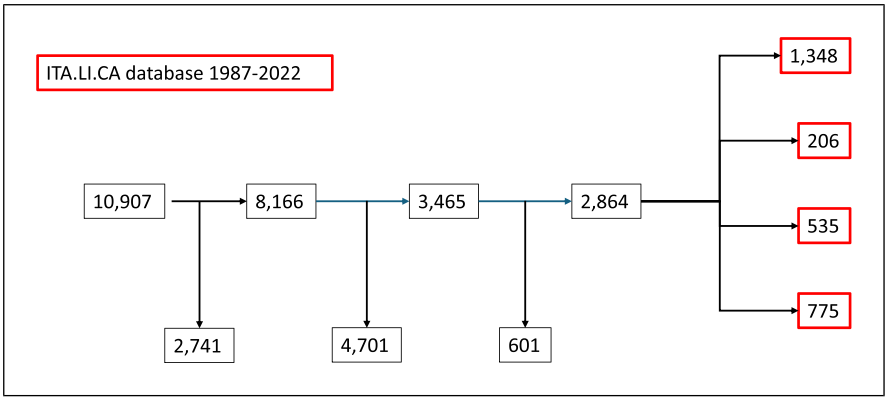


Fig. 1. Flowchart of patient selection. Flow diagram illustrating the selection of patients included between January 1, 2008, and December 31, 2022, in the ITA.LI.CA database and enrolled in the present analysis. Patients with hepatocellular carcinoma (HCC) and at least one cardiometabolic risk factor were stratified according to alcohol intake, based on the recently proposed nomenclature, into metabolic dysfunction–associated steatotic liver disease (MASLD), metabolic dysfunction and alcohol-related liver disease (MetALD), and alcohol-related liver disease (ALD). Starting from the patients in the entire database (n = 10,907), 2,741 patients were excluded because their HCC diagnosis was before 2008. Patients with hepatitis C virus infection, autoimmune liver diseases, cholestatic liver diseases, or hepatitis D virus infection were excluded (n = 4,701). Finally, 601 patients were excluded because they had an unknown weekly alcohol consumption. The final number of enrolled patients was 2,864, including the study etiological target populations (MASLD, MetALD, and ALD) and a comparator group with hepatitis B virus (HBV)-related HCC without other concomitant etiologies. ITA.LI.CA, Italian Liver Cancer; HCC, hepatocellular carcinoma; MASLD, metabolic dysfunction associated steatotic liver disease; MetALD, metabolic dysfunction and alcohol-associated liver disease; ALD, alcohol-associated liver disease; HBV, hepatitis B virus.

patterns, only extrahepatic vascular invasion appeared to be an independent predictor.

For patients with ALD, the presence of overweight at diagnosis was an independent predictor of mortality. Additionally, varices, CTP class B and C, sodium levels, and the ECOG-PSS >1 were significantly associated with the risk of death, as well as tumor size. In HBV patients, ascites and CTP classes B/C, along with AFP classes 1 and 2 significantly correlated with the mortality risk, whereas tumor patterns showed no associations.

Systemic therapy was associated with the highest mortality risk across the entire cohort, as well as in MASLD, ALD, and HBV. In the MetALD subgroup, treatment with intra-arterial therapy was the most significant predictor of mortality among the therapeutic options, showing the highest hazard ratio (HR) of 25.260 (p = 0.002).

As shown in Figure 2, again considering MASLD subgroup as reference, ALD exhibited the worst survival (p = 0.06) while the better was observed in patients with HBV-related HCC (p = 0.003).

Competing Risk Multivariate Analysis

The multivariable competing risk analysis for HCC-related, liver failure-related, and other cause-related death is reported in Table 3. Moreover, Figure 3 graphically represents the cumulative incidence of death curves according to liver disease etiologies obtained from the multivariate analyses in Table 3 (i.e., adjusted curves). ALD and HBV, as etiology of underlying liver disease, showed a relevant impact on HCC-related death risk (p = 0.018), together with age >70 years, and ITA.LI.CA tumor stage. Concerning the risk of liver failure-related death, the presence of ascites, CTP class, and ECOG-PSS >1 were significant predictors. Analysis of the risk of death related to extra-hepatic causes identified MetALD, age >70 years, ECOG-PSS >1, and ITA.LI.CA tumor stage C as significant predictors. Treatment choice was associated with the HCC risk of death (p = 0.000) and liver failure-related risk of death ($p \leq 0.001$). All therapies except liver resection showed a significant correlation with the risk of death from other causes, although with lower SHR compared to HCC and liver failure analysis. The distribution of extra-hepatic causes of death is reported in online supplementary Table 1 (for all online suppl. material, see https://doi.org/10.1159/000553063).

The absolute number of events observed in each etiologic group, broken down by HCC-related, liver failure-related, and extra-hepatic causes of death, is detailed in online supplementary Table 2. To complement the

Table 1. Baseline patient characteristics

Parameters	MASLD, 1,348 (47.1%)	MetALD, 206 (7.2%)	sd	ALD, 535 (18.7%)	sd	HBV, 775 (27.1%)	sd	*p* value
period	*N* (%)	*N* (%)		*N* (%)		*N* (%)		
2008–2012	275 (20.4)	37 (18.0)	0.007	134 (25.0)	−0.135	277 (35.7)	**−0.349**	<0.001
2013–2017	477 (35.4)	75 (36.4)		212 (39.6)		254 (32.8)		
2018–2022	596 (44.2)	94 (45.6)		189 (35.3)		244 (31.5)		
HCC diagnosed under surveillance	472 (35.0)	72 (35.0)	0.065	197 (36.8)	0.071	404 (52.1)	−0.218	<0.001
Age >70	797 (59.1)	102 (49.5)	−0.275	236 (44.1)	−0.251	244 (31.5)	**−0.566**	<0.001
Males	1,081 (80.2)	193 (93.7)	**0.362**	515 (96.3)	**0.494**	648 (83.6)	0.094	<0.001
Charlson CI >6	534 (39.6)	76 (36.9)	−0.128	228 (42.6)	0.051	155 (20.0)	**−0.492**	<0.001
ECOG PST >1	142 (10.5)	26 (12.6)	0.080	64 (12.0)	0.048	81 (10.5)	−0.040	0.662
Lenght alcohol ≥10 years	155 (11.5)	134 (65)	**1.392**	394 (73.6)	**1.676**	125 (16.1)	0.138	<0.001
Overweight	1,109 (82.3)	176 (85.4)	0.052	426 (79.6)	−0.064	375 (48.4)	**−0.753**	<0.001
Hypertension	1,023 (75.9)	150 (72.8)	−0.049	360 (67.3)	−0.163	366 (47.2)	**−0.589**	<0.001
Diabetes	847 (62.8)	121 (58.7)	−0.204	305 (57.0)	−0.177	202 (26.1)	**−0.909**	<0.001
Dyslipidemia	443 (32.9)	65 (31.6)	−0.020	144 (26.9)	−0.130	99 (12.8)	**−0.528**	<0.001
Metabolic charge								
0	0 (0.0)	0 (0.0)	−0.109	0 (0.0)	−0.241	211 (27.2)	**−1.172**	<0.001
1	240 (17.8)	34 (16.5)		134 (25.0)		242 (31.2)		
2	402 (29.8)	75 (36.4)		179 (33.5)		199 (25.7)		
3	446 (33.1)	60 (29.1)		145 (27.1)		90 (11.6)		
4	260 (19.3)	37 (18.0)		77 (14.4)		33 (4.3)		
Cirrhosis	900 (66.8)	170 (82.5)	**0.301**	490 (91.6)	**0.563**	650 (83.9)	**0.336**	<0.001
Varices	490 (49.1)	77 (47.2)	−0.037	268 (57.1)	0.162	308 (48.2)	−0.018	0.011
Platelet count <100	357 (26.5)	58 (28.2)	0.036	160 (29.9)	0.016	231 (29.8)	0.027	0.293
Ascites	273 (20.3)	55 (26.7)	0.146	132 (24.7)	0.064	148 (19.1)	−0.077	0.016
HE	88 (6.5)	18 (8.7)	0.103	34 (6.4)	−0.037	34 (4.4)	−0.144	0.072
MELD >10	481 (35.7)	87 (42.2)	0.184	228 (42.6)	0.087	274 (35.4)	−0.028	0.010
Child Pugh Class								
A	961 (71.3)	137 (66.5)	0.120	337 (63.0)	0.161	559 (72.1)	−0.051	0.002
B	331 (24.6)	55 (26.7)		159 (29.7)		184 (23.7)		
C	56 (4.2)	14 (6.8)		39 (7.3)		32 (4.1)		
Diameter (cm), mean (SD)	4.858 (3.950)	4.363 (3.124)	−0.165	4.321 (3.314)	−0.113	4.463 (3.537)	−0.117	0.009
Number, mean (SD)	2.550 (2.435)	2.388 (2.742)	−0.028	2.598 (2.288)	0.043	2.445 (2.149)	−0.043	0.527
Metastases	96 (7.1)	11 (5.3)	−0.114	37 (6.9)	0.021	45 (5.8)	−0.039	0.572
Intra-hepatic VI	78 (5.9)	12 (5.8)	0.031	44 (8.2)	0.107	68 (8.8)	0.136	0.049
Extra-hepatic VI	89 (6.7)	17 (8.3)	0.061	34 (6.4)	−0.027	50 (6.5)	−0.031	0.809
AFP, ng/mL								
<100	858 (63.6)	155 (75.2)	−0.231	378 (70.7)	−0.085	487 (62.8)	0.063	0.003
100–1,000	228 (16.9)	26 (12.6)		75 (14.0)		137 (17.7)		
>1,000	262 (19.4)	25 (12.1)		82 (15.3)		151 (19.5)		

Table 1 (continued)

Parameters	MASLD, 1,348 (47.1%)	MetALD, 206 (7.2%)	sd	ALD, 535 (18.7%)	sd	HBV, 775 (27.1%)	sd	*p* value
period	*N* (%)	*N* (%)		*N* (%)		*N* (%)		
ITA.LI.CA tumor stage								
0	175 (13.2)	28 (13.6)	−0.052	83 (15.5)	0.007	143 (18.5)	−0.033	0.003
A	454 (34.2)	84 (40.8)		185 (34.6)		258 (33.3)		
B1	268 (20.2)	31 (15.0)		79 (14.8)		114 (14.7)		
B2	135 (10.2)	19 (9.2)		66 (12.4)		74 (9.5)		
B3	135 (10.2)	16 (7.8)		57 (10.7)		102 (13.2)		
C	161 (12.1)	28 (13.6)		64 (12.0)		84 (10.8)		
Main therapy								
Liver transplantation	65 (4.8)	13 (6.3)	−0.072	33 (6.2)	0.114	95 (12.3)	−0.153	<0.001
Liver resection	291 (21.6)	36 (17.5)		70 (13.1)		154 (19.9)		
Ablation	287 (21.3)	60 (29.1)		130 (24.3)		181 (23.4)		
Intra-arterial therapies	275 (20.4)	51 (24.8)		130 (24.3)		134 (17.3)		
Systemic-other	149 (11.1)	13 (6.3)		54 (10.1)		90 (11.6)		
BSC	281 (20.8)	33 (16.0)		118 (22.1)		121 (15.6)		

SD, standardized difference vs. the MASLD group. Values higher than 0.3 (in bold) indicate moderate or substantial differences. *p* value refers to the comparison between all groups. MASLD, Metabolic Associated Steatotic Liver Disease; MetALD, Metabolic and Alcohol-Related Liver Disease; ALD, Alcohol-Associated Liver Disease; HBV, Hepatitis B Virus; HCC, hepatocellular carcinoma; ECOG PST, Eastern Cooperative Oncology Group Performance Status; HE, hepatic hencephalopathy; MELD, Model for End-stage Liver Disease; AFP, alphafetoprotein; ITA.LI.CA., Italian Liver Cancer; BSC, Best Supportive Care.

primary Fine–Gray analysis and to distinguish between cumulative-incidence and cause-specific (etiologic) interpretations of the hazard ratios, multivariable cause-specific Cox models were fitted as a sensitivity analysis using the same covariates. The resulting cause-specific hazard ratios (csHRs) are reported alongside the subdistribution hazard ratios (sHRs) in Table 3. The two estimands yielded convergent results for the principal biological finding of the study — namely, that ALD etiology was associated with an excess hazard of HCC-related death compared with MASLD (sHR 1.27, 95% CI: 1.04–1.58, $p = 0.018$; csHR 1.24, 95% CI: 1.02–1.51, $p = 0.030$). By contrast, the higher sHR for HCC-related death observed in the HBV group was substantially attenuated in the cause-specific framework (sHR 1.25, 95% CI: 1.04–1.50, $p = 0.018$ vs. csHR 1.06, 95% CI: 0.89–1.27, $p = 0.510$), suggesting that the association in the Fine–Gray model was driven partly by lower competing extra-hepatic and liver-failure mortality among HBV patients rather than by a stronger etiologic association with HCC-related death. Conversely, the lower rate of extra-hepatic death observed in MetALD compared with MASLD was preserved in the cause-specific analysis (csHR 0.69, 95% CI: 0.51–0.94, $p = 0.017$).

Discussion

The new nomenclature of SLD [4] has introduced novel categories, such as MetALD, the impact of which on the characteristics and outcomes of HCC remains largely unexplored. In this study describing the epidemiological, clinical, and prognostic data from a nationwide large cohort of patients with SLD-related HCC, we observed a progressive increase in SLD-related HCC cases from 2008 to 2022, consistent with trends reported in other studies [15, 16]. Notably, in the same period, a decrease in HBV-related cancer was observed. In a recent systematic review and meta-analysis involving 4.5 million adults with SLD from nine countries, the overall pooled prevalence of MetALD was 10%, and that of ALD only 6%, considerably lower than that of MASLD (78%) [17]. In our study in patients with HCC, the prevalence of MetALD was like the one reported in the study by Tampaki et al. [17] in the non-cancer population while ALD was more frequently represented, accounting for 25.6% of all cases. This finding underscores the pro-carcinogenic role of alcohol [18], and supports the new classification of SLD, emphasizing the relevance of alcohol intake in the progression and severity of liver disease. The pro-carcinogenic role of alcohol has been

Table 2. Cox multivariable survival analysis (all patients, MASLD, MetALD, ALD, HBV)

VARIABLES	All patients		MASLD		MetALD		ALD		HBV	
	HR (95% CI)	*p* value	HR (95% CI)	*p* value	HR (95% CI)	*p* value	HR (95% CI)	*p* value	HR (95% CI)	*p* value
Etiology										
MASLD (ref.)	–	–	–	–	–	–	–	–	–	–
MetALD	0.85 (0.67–1.08)	0.205	–	–	–	–	–	–	–	–
ALD	1.00 (0.86–1.17)	0.966	–	–	–	–	–	–	–	–
HBV	0.90 (0.77–1.05)	0.193	–	–	–	–	–	–	–	–
Cirrhosis	–	–	–	–	1.36 (0.67–2.76)	0.386	–	–	–	–
Overweight	–	–	–	–	–	–	0.69 (0.51–0.92)	0.014	–	–
Hypertension	–	–	–	–	0.56 (0.35–0.88)	0.012	–	–	–	–
CCI >6	–	–	–	–	1.51 (1.00–2.28)	0.046	–	–	–	–
Varices	1.20 (1.04–1.37)	0.008	–	–	–	–	1.36 (1.03–1.79)	0.027	–	–
Ascites	1.38 (1.15–1.65)	0.000	1.72 (1.37–2.17)	0.000	1.50 (0.85–2.66)	0.159	–	–	1.53 (1.10–2.12)	0.010
MELD>10	–	–	–	–	1.87 (1.16–3.01)	0.009	–	–	–	–
CTP class										
A (ref.)	–	–	–	–	–	–	–	–	–	–
B	1.29 (1.09–1.52)	0.002	1.64 (1.34–2.02)	0.000	0.93 (0.49–1.78)	0.844	1.40 (1.05–1.88)	0.022	1.47 (1.10–1.98)	0.009
C	1.75 (1.32–2.32)	0.000	1.80 (1.22–2.65)	0.003	2.19 (0.78–6.11)	0.132	2.77 (1.63–4.71)	0.000	2.29 (1.35–3.87)	0.002
Sodium	0.97 (0.96–0.99)	0.014	–	–	–	–	0.95 (0.91–0.98)	0.004	–	–
ECOG PST >1	1.46 (1.21–1.76)	0.000	–	–	–	–	2.22 (1.51–3.27)	0.000	1.22 (0.86–1.74)	0.244
Size of largest nodule	1.00 (0.98–1.02)	0.364	1.03 (1.01–1.06)	0.001	–	–	1.06 (1.01–1.12)	0.015	–	–
Number of nodules	1.02 (0.99–1.05)	0.100	1.02 (0.98–1.05)	0.241	–	–	1.05 (0.98–1.12)	0.110	–	–
Extra-hepatic vascular invasion	1.38 (1.01–1.88)	0.038	1.57 (1.08–2.27)	0.016	2.25 (1.11–4.57)	0.024	–	–	–	–
AFP classes										
1	1.07 (0.89–1.28)	0.424	–	–	–	–	–	–	1.36 (1.04–1.78)	0.023
2	1.35 (1.12–1.61)	0.001	–	–	–	–	–	–	1.48 (1.12–1.96)	0.005
3 (ref.)	–	–	–	–	–	–	–	–	–	–

Table 2 (continued)

VARIABLES	All patients		MASLD		MetALD		ALD		HBV	
	HR (95% CI)	*p* value	HR (95% CI)	*p* value	HR (95% CI)	*p* value	HR (95% CI)	*p* value	HR (95% CI)	*p* value
ITA.LI.CA stage										
0 (ref.)	–	–	–	–	–	–	–	–	–	–
A	1.18 (0.96–1.45)	0.109	1.23 (0.93–1.62)	0.135	–	–	0.76	0.219	1.23 (0.86–1.74)	0.241
B1	1.31 (1.01–1.70)	0.035	1.10 (0.81–1.50)	0.510	–	–	0.96	0.909	1.40 (0.93–2.11)	0.106
B2	1.38 (1.04–1.82)	0.024	1.58 (1.10–2.27)	0.012	–	–	0.68	0.189	1.24 (0.78–1.99)	0.349
B3	2.24 (1.65–3.06)	0.000	1.77 (1.19–2.62)	0.004	–	–	1.30	0.438	1.76 (1.08–2.87)	0.022
C	2.18 (1.55–3.07)	0.000	2.76 (1.84–4.11)	0.000	–	–	1.78	0.062	1.53 (0.92–2.53)	0.097
Main therapy										
Transplant (ref.)	–	–	–	–	–	–	–	–	–	–
Resection	4.77 (3.00–7.59)	0.000	5.05 (2.451–10.40)	0.000	7.78 (0.95–63.36)	0.055	3.72 (1.45–9.51)	0.006	6.01 (3.11–11.63)	0.000
Ablation	6.65 (4.26–10.36)	0.000	7.17 (3.50–14.69)	0.000	9.81 (1.31–73.14)	0.026	6.00 (2.50–14.36)	0.000	6.89 (3.63–13.09)	0.000
Intra-arterial	11.99 (7.69–18.71)	0.000	11.90 (5.81–24.34)	0.000	25.26 (3.34–190.91)	0.002	10.77 (4.49–25.84)	0.000	13.52 (7.07–25.86)	0.000
Systemic or other	14.44 (9.08–22.96)	0.000	14.43 (6.94–30.00)	0.000	18.37 (2.18–154.16)	0.007	16.95 (6.77–42.46)	0.000	19.65 (9.76–39.54)	0.000
BSC	21.54 (13.71–33.84)	0.000	21.76 (10.62–44.60)	0.000	56.84 (7.04–458.37)	0.000	22.17 (9.20–53.41)	0.000	20.92 (10.60–41.27)	0.000

Variables selected using Lasso Cox. MASLD, Metabolic Dysfunction-Associated Steatotic Liver Disease; MetALD, Metabolic and Alcohol-Related Liver Disease; ALD, Alcohol-Associated Liver Disease; HBV, Hepatitis B Virus; CCI, Charlson Comorbidity Index; MELD, Model for End-stage Liver Disease; CPT, Child-Pugh-Turcotte; ECOG PST, Eastern Cooperative Oncology Group Performance Status; AFP, alphafetoprotein; ITA.LI.CA., Italian Liver Cancer; BSC, Best Supportive Care.

recently confirmed in a Korean nationwide study [19] reporting that patients with SLD show a higher incidence of HCC in comparison to other etiologies of chronic liver disease. The annual incidence of HCC was progressively higher in MASLD (0.08%/year), MetALD (0.1%/year), and ALD (0.15%/year) than in patients without SLD (0.03%/year).

In our study, the HBV population was selected as a comparator, given that, unlike HCV infection [20], HBV does not appear to significantly affect metabolic parameters. According to the ITA.LI.CA staging system, all three SLD subgroups presented with more advanced HCC than the HBV group. This finding aligns with the significantly higher proportion of HCCs diagnosed under surveillance in HBV patients. The lower likelihood of HCC diagnosed during surveillance among SLD patients has been reported in several studies [21, 22], including one specifically investigating ALD [23] along with the more severe disease at presentation [23]. Consequently, patients with HBV were more frequently managed with hierarchically superior treatments, such as liver transplantation, with access to transplant being twice as frequent as in ALD and MetALD, and three times higher than in MASLD. Conversely, older age and a higher burden of comorbidities likely represented contraindications to liver transplantation in most SLD patients.

Among the SLD subgroups, patients with ALD exhibited the highest prevalence of cirrhosis, more severe portal hypertension, and the poorest liver function, as indicated by CTP class. Considering the risk of hepatic decompensation in the whole population of patients, the

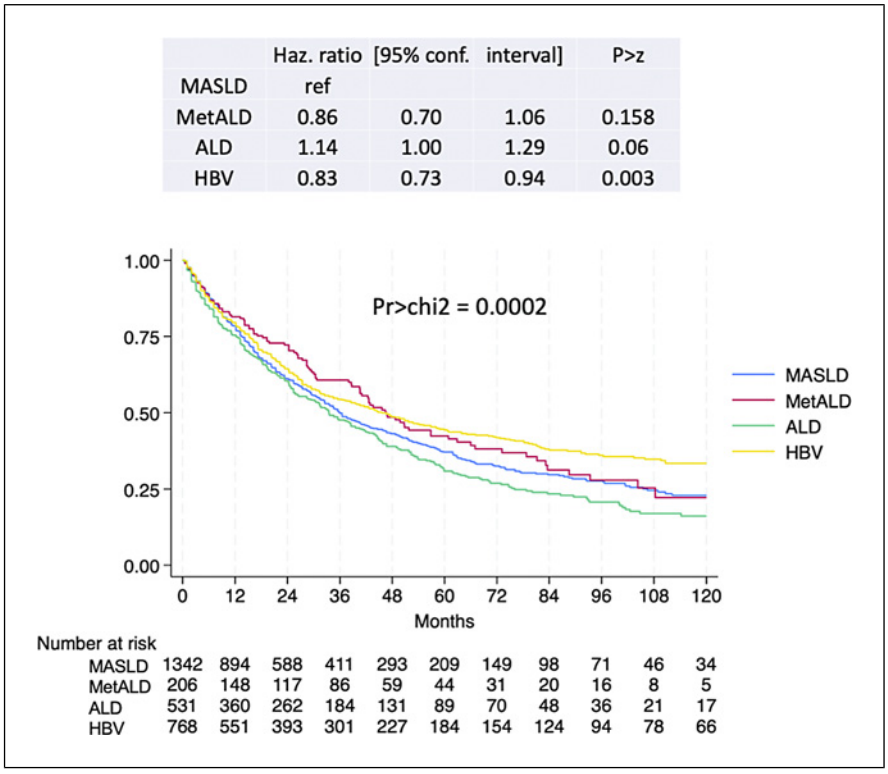


Fig. 2. Survival curves in the different groups of patients with steatotic liver disease and in patients with chronic hepatitis B. Kaplan-Meier curves showing overall survival (OS) in patients with HCC were stratified according to the etiology of the underlying liver disease (MASLD, MetALD, ALD, and HBV). Overall survival was calculated from the date of HCC diagnosis to death from any cause or the last follow-up (censoring date: December 31, 2022). Survival distributions were compared using the log-rank test. MASLD was used as the reference group in comparative analyses. HCC, hepatocellular carcinoma; MASLD, Metabolic dysfunction-associated steatotic liver disease; MetALD, Metabolic and alcohol-associated liver disease; ALD, Alcohol-related Liver Disease; HBV, Hepatitis B Virus.

SLD subclasses exhibit a stepwise increase from MASLD to MetALD to ALD, with hazard ratios escalating from 5 to 8 and then to 10, compared to patients without SLD [24]. These clinical patterns are probably accountable for the poorest survival rates of patients with ALD-related HCC, compared to other SLD subgroups and HBV. Moreover, ALD acted as an independent predictor of HCC-related mortality when considering the competing risks. Similarly, in a retrospective nationwide cohort study of over 1.2 million patients, Oh et al. [25] recently confirmed that MASLD, MetALD, ALD showed higher liver-, cancer-, and HCC-related mortality than the control group and that all-cause specific mortality increased from MASLD to MetALD to ALD.

Our study, in the HCC context, indicates that SLD represents a spectrum of disease influenced by alcohol consumption, transitioning from MASLD to MetALD and ultimately to ALD, with a definite role on HCC-related mortality. Indeed, in our series, under similar metabolic conditions, alcohol significantly affected the prognosis of HCC patients. Recently, in a non-cancer setting [26] the 10-year cumulative incidence of death from liver disorder was reported to be 9.2% (95% CI: 8.0–10.5) for MASLD, 17.7% (95% CI: 15.6–20.1) for MetALD, and 22.1% (95% CI: 18.4–26.3) for ALD, strongly indicating the detrimental role of alcohol. Similarly, patients with MetALD and ALD with metabolic dysfunction had a poorer prognosis than MASLD, underscoring the need for dedicated attention to the impact of alcohol consumption within the context of MASLD [27]. Finally, a growing risk of HCC incidence from MASLD and MetALD to ALD compared with non-SLD subjects was recently reported, indicating the central role of alcohol intake in conditioning the prognosis of SLD [28]. Taken together, these data unarguably demonstrate a detrimental effect of alcohol on several aspects of disease, from clinical presentation to disease severity, and on the response to treatment in patients with HCC.

Interestingly, in the SLD subgroups with intermediate or high alcohol consumption (MetALD or ALD) but not in the group with low or no alcohol consumption (MASLD), metabolic comorbidities seem to influence the prognosis (Table 2), suggesting that alcohol might amplify the systemic effects of metabolic dysregulation [29]. On the other hand, it is interesting to notice that all the subgroups analyzed showed similar predictors of mortality. Consolidated scores of survival such as CTP or MELD, ascites and varices as surrogates of portal hypertension and, finally, HCC characteristics such as size

Table 3. Multivariable competing-risk regression for HCC-related, liver failure-related, and extra-hepatic mortality: Fine-Gray subdistribution hazard ratios (sHR; primary analysis) and cause-specific hazard ratios (csHR; sensitivity analysis)

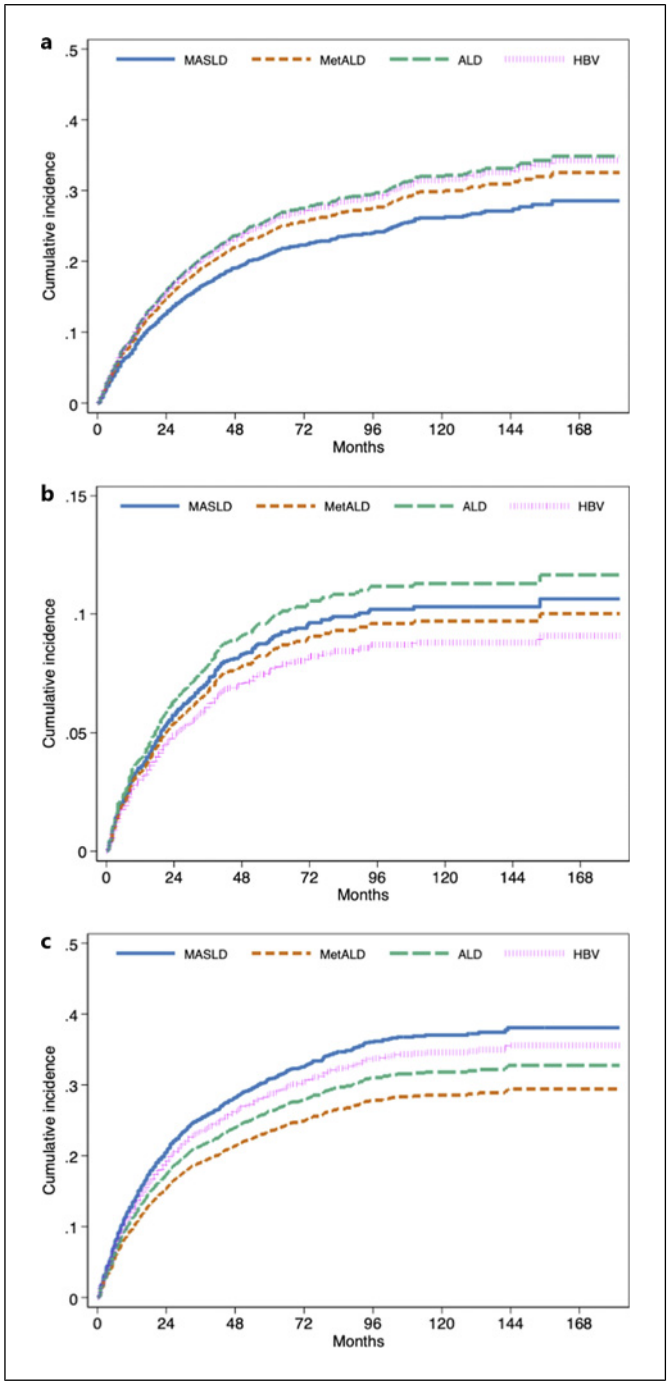
variable	HCC-related death				Liver failure-related death				Extra-hepatic death			
	fine-gray sHR		cause-specific HR		fine-gray sHR		cause-specific HR		fine-gray sHR		cause-specific HR	
	HR (95% CI)	*p* value	HR (95% CI)	*p* value	HR (95% CI)	*p* value	HR (95% CI)	*p* value	HR (95% CI)	*p* value	HR (95% CI)	*p* value
Etiology												
MASLD	*Ref*	*ref*	*ref*	*ref*	*ref*	*ref*						
MetALD	1.17 (0.86–1.59)	0.309	0.92 (0.68–1.23)	0.560	0.94 (0.60–1.47)	0.780	0.76 (0.49–1.18)	0.222	**0.73 (0.54–0.99)**	**0.040**	**0.69 (0.51–0.94)**	**0.017**
ALD	**1.27 (1.04–1.58)**	**0.018**	**1.24 (1.02–1.51)**	**0.030**	1.10 (0.82–1.48)	0.517	1.05 (0.79–1.40)	0.739	0.83 (0.68–1.01)	0.061	0.90 (0.74–1.09)	0.270
HBV	**1.25 (1.04–1.50)**	**0.018**	1.06 (0.89–1.27)	0.510	0.85 (0.62–1.15)	0.283	0.77 (0.58–1.03)	0.081	0.92 (0.77–1.09)	0.321	0.94 (0.79–1.11)	0.436
Age > 70 years	**0.85 (0.73–0.99)**	**0.039**	0.88 (0.75–1.02)	0.081	1.04 (0.81–1.33)	0.775	1.02 (0.81–1.30)	0.844	**1.19 (1.03–1.38)**	**0.021**	**1.17 (1.01–1.35)**	**0.034**
Males	0.87 (0.70–1.08)	0.212	0.98 (0.79–1.21)	0.820	1.10 (0.80–1.52)	0.544	1.17 (0.85–1.60)	0.341	1.09 (0.89–1.33)	0.420	1.11 (0.91–1.35)	0.297
Ascites	0.92 (0.72–1.19)	0.537	1.21 (0.96–1.53)	0.113	**1.83 (1.32–2.53)**	**<0.001**	**2.13 (1.55–2.93)**	**<0.001**	0.90 (0.70–1.15)	0.400	1.16 (0.92–1.45)	0.214
Child-Pugh class												
A	*ref*	*ref*	*ref*	*ref*	*ref*	*ref*						
B	1.07 (0.87–1.32)	0.514	**1.41 (1.15–1.72)**	**0.001**	**2.17 (1.57–2.99)**	**<0.001**	**2.68 (1.97–3.65)**	**<0.001**	1.09 (0.89–1.33)	0.406	**1.38 (1.13–1.67)**	**0.001**
C	0.69 (0.42–1.11)	0.128	1.36 (0.90–2.04)	0.141	**4.04 (2.55–6.42)**	**<0.001**	**6.35 (4.07–9.90)**	**<0.001**	1.02 (0.66–1.57)	0.959	**1.87 (1.28–2.72)**	**0.001**
ECOG-PS >1	1.27 (0.97–1.66)	0.077	**1.56 (1.24–1.96)**	**<0.001**	**1.58 (1.15–2.17)**	**0.005**	**1.82 (1.33–2.47)**	**<0.001**	**0.71 (0.53–0.96)**	**0.024**	0.98 (0.76–1.26)	0.864
AFP, ng/mL												
<100	*ref*	*ref*	*ref*	*ref*	*ref*	*ref*						
100–1,000	1.02 (0.83–1.25)	0.876	1.08 (0.89–1.32)	0.438	**1.40 (1.02–1.89)**	**0.032**	**1.38 (1.02–1.86)**	**0.036**	1.01 (0.83–1.24)	0.911	1.08 (0.88–1.31)	0.467
>1,000	0.94 (0.77–1.16)	0.563	1.05 (0.87–1.26)	0.628	1.19 (0.85–1.67)	0.303	1.30 (0.94–1.81)	0.112	1.21 (0.97–1.52)	0.085	1.19 (0.98–1.46)	0.083
ITA.LI.CA tumor stage												
0	*ref*	*ref*	*ref*	*ref*	*ref*	*ref*						
A	**1.47 (1.10–1.97)**	**0.010**	**1.41 (1.04–1.91)**	**0.026**	1.02 (0.72–1.45)	0.897	0.99 (0.70–1.40)	0.976	0.86 (0.70–1.05)	0.146	0.87 (0.70–1.07)	0.185
B1	**2.23 (1.63–3.06)**	**<0.001**	**2.14 (1.55–2.96)**	**<0.001**	**0.61 (0.39–0.97)**	**0.039**	0.64 (0.41–1.01)	0.057	0.87 (0.68–1.11)	0.270	0.95 (0.74–1.22)	0.694
B2	**2.32 (1.65–3.28)**	**<0.001**	**2.41 (1.70–3.42)**	**<0.001**	0.70 (0.44–1.12)	0.137	0.81 (0.51–1.29)	0.375	0.92 (0.68–1.23)	0.571	1.09 (0.82–1.45)	0.551
B3	**3.00 (2.13–4.23)**	**<0.001**	**4.55 (3.24–6.40)**	**<0.001**	0.68 (0.42–1.11)	0.126	1.34 (0.83–2.15)	0.232	0.86 (0.63–1.17)	0.342	**1.48 (1.11–1.99)**	**0.008**
C	**3.91 (2.76–5.54)**	**<0.001**	**6.28 (4.45–8.86)**	**<0.001**	**0.61 (0.38–1.00)**	**0.049**	1.47 (0.92–2.37)	0.108	**0.62 (0.44–0.88)**	**0.008**	1.36 (0.99–1.87)	0.055

Liver Cancer
DOI: 10.1159/000553063

Table 3 (continued)

variable	HCC-related death				Liver failure-related death				Extra-hepatic death			
	fine-gray sHR		cause-specific HR		fine-gray sHR		cause-specific HR		fine-gray sHR		cause-specific HR	
	HR (95% CI)	*p* value	HR (95% CI)	*p* value	HR (95% CI)	*p* value	HR (95% CI)	*p* value	HR (95% CI)	*p* value	HR (95% CI)	*p* value
Main therapy												
Liver transplantation	*Ref*	*ref*	*ref*	*ref*	*ref*	*ref*						
Liver resection	**7.99 (3.51–18.16)**	**<0.001**	**10.94 (4.78–25.05)**	**<0.001**	**5.61 (1.95–16.10)**	**0.001**	**8.24 (2.88–23.59)**	**<0.001**	1.22 (0.85–1.76)	0.280	**1.71 (1.18–2.48)**	**0.005**
Ablation	**7.99 (3.54–18.04)**	**<0.001**	**12.52 (5.49–28.58)**	**<0.001**	**8.34 (3.03–22.98)**	**<0.001**	**14.18 (5.12–39.23)**	**<0.001**	**1.69 (1.19–2.39)**	**0.003**	**2.51 (1.76–3.57)**	**<0.001**
Intra-arterial therapies	**12.83 (5.70–28.90)**	**<0.001**	**25.69 (11.28–58.48)**	**<0.001**	**9.60 (3.46–26.67)**	**<0.001**	**20.45 (7.32–57.11)**	**<0.001**	**1.81 (1.26–2.59)**	**0.001**	**3.32 (2.31–4.77)**	**<0.001**
Systemic/other	**17.93 (7.82–41.15)**	**<0.001**	**36.08 (15.68–83.02)**	**<0.001**	**6.60 (2.25–19.37)**	**0.001**	**17.30 (5.87–51.00)**	**<0.001**	**1.57 (1.03–2.40)**	**0.037**	**3.26 (2.14–4.96)**	**0.037**
Best supportive care	**13.15 (5.77–29.96)**	**<0.001**	**40.67 (17.76–93.16)**	**<0.001**	**7.94 (2.84–22.20)**	**<0.001**	**27.03 (9.68–75.45)**	**<0.001**	**2.73 (1.85–4.03)**	**<0.001**	**6.24 (4.29–9.06)**	**<0.001**

Subdistribution hazard ratios (sHR) are derived from the Fine–Gray model, in which competing events are not censored; sHR therefore quantify the association between each covariate and the cumulative incidence of the cause of interest. Cause-specific hazard ratios (csHR) are derived from Cox proportional-hazards models in which subjects experiencing a competing event are censored at the time of the competing event; csHR quantify the instantaneous rate of the cause of interest among subjects still at risk and are interpreted as a measure of the etiologic effect of each covariate on that specific cause of death. *Bold values indicate p < 0.05.* Models adjusted for age >70 years, sex, ascites, Child-Pugh class, ECOG performance status, AFP, ITA.LI.CA tumor stage, and main therapy. Variables included after LASSO selection were identical for the two analytic strategies. Patients lost to follow-up (n = 350) were classified as extra-hepatic events under the competing-risk model. AFP, alpha-fetoprotein; ALD, alcohol-associated liver disease; CI, confidence interval; csHR, cause-specific hazard ratio; ECOG, Eastern Cooperative Oncology Group; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HR, hazard ratio; ITA.LI.CA, Italian Liver Cancer; MASLD, metabolic dysfunction-associated steatotic liver disease; MetALD, metabolic dysfunction and alcohol-related liver disease; sHR, subdistribution hazard ratio.



or vascular invasion independently conditioned the prognosis into each subgroup. These considerations underscore the need to thoroughly assess patients with HCC regardless of the underlying etiology of liver disease, carefully evaluating liver function, portal hypertension and HCC staging [6].

Alcohol intake can foster a pro-inflammatory microenvironment, enhance genomic instability, and impair immune surveillance, all factors contributing to the severity of the clinical presentation in the context of HCC [30]. Conversely, our findings on HCC-related-mortality suggest a less aggressive tumor biology in MASLD patients compared to those with a predominantly viral or alcoholic background, as previously observed in the ITA.LI.CA cohort [31] and in surgical series [32]. It should, however, be acknowledged that the higher subdistribution hazard for HCC-related death in HBV patients was no longer evident when a cause-specific Cox model was applied, indicating that this finding is largely driven by the lower competing extra-hepatic and liver-failure mortality of HBV patients

Fig. 3. Adjusted cumulative incidence of cause-specific mortality according to liver disease etiology. Cumulative incidence functions derived from multivariable competing-risk regression models (Fine and Gray subdistribution hazard model) showing the adjusted risk of (**a**) HCC-related death, (**b**) liver failure–related death, and (**c**) extra-hepatic cause–related death according to underlying etiology of liver disease (MASLD, MetALD, ALD, and HBV). Models were adjusted for age, sex, ascites, Child-Pugh class, ECOG performance status, AFP levels, ITA.LI.CA tumor stage, and main treatment. Deaths from other causes were treated as competing events. Subdistribution hazard ratios (SHR) with 95% confidence intervals are reported in Table 3. HCC-related death was defined as death attributable to tumor progression or HCC-induced liver decompensation; liver failure–related death referred to hepatic decompensation not directly attributable to tumor progression; extra-hepatic causes included cardiovascular events, infections, other malignancies, and unknown causes. HCC, hepatocellular carcinoma; MASLD, Metabolic dysfunction-associated steatotic liver disease; MetALD, Metabolic and alcohol-associated liver disease; ALD, Alcohol-related Liver Disease; HBV, Hepatitis B Virus; ECOG, Eastern Cooperative Oncology Group; AFP, alpha-fetoprotein; ITA.-LI.CA, Italian liver cancer.

rather than by a more aggressive tumor biology of viral HCC. Statements regarding the biological aggressiveness of HCC across etiologies should, therefore, be interpreted with the caution prompted by the comparison of the two estimands.

Another intriguing finding of the present study is that MetALD, but not MASLD, represents a strong predictor of death due to extra-hepatic causes as a possible effect of alcohol's systemic impact. The prognostic influence of MetALD on all-cause mortality is in line with the data reported in patients without HCC [17], where patients with MetALD, compared to those without SLD, were at increased risk of all-cause and cancer-related mortality, showing an excess incidence of cardiovascular disease and liver decompensation events. This signal is consistent in both the Fine-Gray and the cause-specific framework (sHR 0.73, 95% CI: 0.54–0.99 and csHR 0.69, 95% CI: 0.51–0.94 for MetALD vs. MASLD, respectively, with MASLD as reference), supporting the interpretation that the lower rate of extra-hepatic death in MetALD compared with MASLD is not solely an artefact of differential timing of competing liver-related events. Nevertheless, given that the cohort is, by design, restricted to patients who have already developed HCC, residual collider bias (i.e., conditioning on the occurrence of HCC) cannot be excluded, and the inference should be regarded as an association rather than a causal claim.

Some limitations of the present study should be acknowledged, including its intrinsic retrospective nature and the fact that steatosis was not systematically assessed by imaging or histology at enrollment. On the other hand, the large number of cases is likely to reduce this possible bias. Notably, as this study is restricted to patients who have already developed HCC, it is prone to selection bias. However, as we already reported [31] analysis of data from a very large HCC cohort can be useful to achieve relevant clinical results and acceptable by a selection point of view. Moreover, the numerical heterogeneity between the analyzed subgroups appears significant in the end. An additional important limitation is that the alcohol intake reported in our database is based on a self-recording system and no follow-up data on alcohol consumption after enrollment are available. Therefore, our data demonstrate an association between alcohol and some outcomes rather than a true dose-response relationship. Future studies should be dedicated to specifically investigate the role of changes in alcohol consumption over time on the prognosis of these subgroups of patients. Finally, differences in cause-specific mortality between etiologic groups may be influenced by baseline differences such as age, surveillance rate, and access to curative treatment, particularly between the HBV and SLD subgroups. Furthermore, although the analysis was well powered for HCC-related (758 events) and extra-hepatic (823 events) events, the smaller number of liver-failure-related deaths (316 in total, of which only 24 in the MetALD subgroup) implies wider confidence intervals around the corresponding hazard ratios and limits the precision of subgroup-level inferences for this specific cause of death.

Multivariate treatment outcomes should imply that certain therapies have a negative prognostic effect. However, in a retrospective observational study, multivariate analysis does not allow causal inference [33]. As an example, systemic therapy and intra-arterial therapy are apparently associated with worse survival but since treatment allocation is strongly determined by disease severity, these findings likely reflect indication bias rather than treatment effect.

In conclusion, this comparative analysis of SLD-related HCC in a large population of patients underscores the importance of steatosis as a health concern in the general population, given the high prevalence of the disease and the still limited therapeutic approaches. Among patients with SLD, those with ALD-related HCC show the worst underlying liver disease and the highest HCC-related death risk in comparison with both MASLD and MetALD. The role of alcohol in exacerbating the clinical picture and prognosis of patients with SLD-related HCC should strengthen the current recommendations of complete alcohol abstinence in patients with metabolic chronic liver disease.

Appendix

Collaborators of the Ita.Li.Ca. group: Department of Experimental and Clinical Medicine, University of Florence, Italy: Lucia Ragozzino, Alessio Mastro, Tancredi Li Cavoli, Tommaso Zurli. Department of Surgery, Oncology, and Gastroenterology, University of Padova, Italy: Filippo Pelizzaro, Elisa Pinto. Liver Injury and Transplant Unit, Polytechnic University of Marche, Ancona Italy: Gloria Allegrini. Division of Internal Medicine, Hepatobiliary Diseases and Immunoallergology, University of Bologna, Bologna, Italy: Fabio Piscaglia, Alessandro Granito, Luca Muratori, Vito Sansone, Francesco Tovoli. UOC Clinica Medica 5 Azienda Ospedale Università Padova: Pietro Guerra, Silvia Cagnin, Antonio Bonato. Gastroenterology & Hepatology Unit, Department of Health Promotion, Mother & Child Care, Internal Medicine & Medical Specialties, PROMISE, University of Palermo, Palermo, Italy: Ciro Celsa, Paolo Giuffrida, Caterina Stornello, Mauro Grova, Carmelo Marco Giacchetto, Gabriele Rancatore, Maria Vittoria Grassini. Department of Medical and Surgical Sciences, University of Bologna, Bologna, Italy: Laura Bucci, Lorenzo Lani, Paolo Caraceni. Gastroenterology Unit, Belcolle Hospital, Viterbo, Italy: Valentina Lauria, Giorgio Pelecca. Department of Internal Medicine, Ospedale per gli Infermi

di Faenza, Faenza, Italy: Vittoria Bevilacqua, Alberto Borghi, Andrea Casadei Gardini, Fabio Conti, Anna Chiara Dall'Aglio, Giorgio Ercolani, Federica Mirici. Department of Clinical Medicine and Surgery, Diseases of the Liver and Biliary System Unit, University of Naples "Federico II", Naples, Italy: Maria Guarino, Valentina Cossiga, Mario Capasso. Department of Medicine and Surgery, Infectious Diseases and Hepatology Unit, University of Parma and Azienda Ospedaliero-Universitaria of Parma, Parma, Italy: Gabriele Missale, Andrea Olivani, Elisabetta Biasini. Department of Clinical and Experimental Medicine, Unit of Medicine and Hepatology, University of Messina, Messina, Italy: Irene Cacciola, Roberto Filomia, Maria Stella Franzè, Concetta Pitrone, Giovanni Raimondo. Department of Clinical and Experimental Medicine, Hepatology and Liver Physiopathology Laboratory, University Hospital of Pisa, Pisa, Italy: Veronica Romagnoli. Gastroenterology Unit, IRCCS Azienda Ospedaliero-Universitaria di Bologna, Bologna, Italy: Elton Dajti, Giovanni Marasco, Federico Ravaioli. Gastroenterology and Digestive Endoscopy Unit, Foggia University Hospital, Foggia, Italy: Ester Marina Cela, Antonio Facciorusso. Gastroenterology Unit, Ospedale Sacro Cuore Don Calabria, Negrar, Italy: Alessandro Inno, Fabiana Marchetti. Department of Medical, Surgical and Experimental Sciences, Clinica Medica Unit, University of Sassari, Azienda Ospedaliero-Universitaria di Sassari, Sassari, Italy: Marco Arru, Assunta Sauchella, Maria Grazia Serra. Gastroenterology Unit, Department of Internal Medicine, University of Genoa, Genoa, Italy: Andrea Pasta, Giulia Pieri, Sara Labanca, Simona Marenco.

Statement of Ethics

The Institutional Review Board of the ITA.LI.CA Coordinating Center approved the use of this database for scientific research (approval No. 99/2012/O/Oss) and the study was conducted in accordance with the ethical principles outlined in the 1975 Declaration of Helsinki. Written informed consent was obtained from the enrolled participants.

Conflict of Interest Statement

Alessandro Vitale and Edoardo G. Giannini were members of the journal's Editorial Board at the time of submission.

Funding Sources

This study was not supported by any sponsor or funder.

Author Contributions

Stefano Gitto, Alessandro Vitale, Gianluca Svegliati-Baroni, Giulio Marchesini, Francesco Paolo Russo, Luca Miele conceived the study, analyzed data, wrote the paper. Claudia Campani, Valentina Adotti, Martina Rosi recorded data and contributed to analysis. Francesco Vizzutti, Mariarosaria Marseglia, Andrea Martini, Angelo Sangiovanni, Giuseppe Cabibbo, Giacomo Zaccherini, Giorgia Ghittoni, Mariella Di Marco, Francesco Giuseppe Foschi, Filomena Morisco, Sara Grasselli, Carlo Saitta, Francesca Romana Ponziani, Maurizia Rossana Brunetto, Donatella Magalotti, Francesco Azzaroli, Andrea Mega, Rodolfo Sacco, Gerardo Nardone, David Sacerdoti, Sara Boninsegna, Gianpaolo Vidili provided data and revised the final work. Franco Trevisani and Edoardo Giovanni Giannini critically revised the discussion. Fabio Marra coordinated the work, critically revised the manuscript and participated in the paper's writing.

Data Availability Statement

The data that support the findings of this study are not publicly available due to privacy reasons but are available from the corresponding author OR the coordinator of the study group upon reasonable request.

References

1 European Association for the Study of the Liver EASLEuropean Association for the Study of Diabetes EASDEuropean Association for the Study of Obesity EASO. EASL-EASD-EASO Clinical Practice Guidelines for the management of non-alcoholic fatty liver disease. J Hepatol. 2016;64(6):1388–402. https://doi.org/10.1016/j.jhep.2015.11.004

2 Global Burden of Disease Liver Cancer Collaboration, Akinyemiju T, Abera S, Ahmed M, Alam N, Alemayohu MA, et al. The burden of primary liver cancer and underlying etiologies from 1990 to 2015 at the global, regional, and national level: results from the global burden of disease study 2015. JAMA Oncol. 2017;3(12):1683–91. https://doi.org/10.1001/jamaoncol.2017.3055

3 Pimpin L, Cortez-Pinto H, Negro F, Corbould E, Lazarus JV, Webber L, et al. Burden of liver disease in Europe: epidemiology and analysis of risk factors to identify prevention policies. J Hepatol. 2018;69(3):718–35. https://doi.org/10.1016/j.jhep.2018.05.011

4 Rinella ME, Lazarus JV, Ratziu V, Francque SM, Sanyal AJ, Kanwal F, et al. A multisociety Delphi consensus statement on new fatty liver disease nomenclature. J Hepatol. 2023;79(6):1542–56. https://doi.org/10.1016/j.jhep.2023.06.003

5 Farinati F, Vitale A, Spolverato G, Pawlik TM, Huo T, Lee YH, et al. Development and validation of a new prognostic system for patients with hepatocellular carcinoma. Plos Med. 2016;13(4):e1002006. https://doi.org/10.1371/journal.pmed.1002006

6 Sangro B, Argemi J, Ronot M, Paradis V, Meyer T, Mazzaferro V, et al. EASL clinical practice guidelines on the management of hepatocellular carcinoma. J Hepatol. 2025;82(2):315–74. https://doi.org/10.1016/j.jhep.2024.08.028

7 Goodyear MDE, Krleza-Jeric K, Lemmens T. The declaration of Helsinki. BMJ. 2007;335(7621):624–5. https://doi.org/10.1136/bmj.39339.610000.BE

8 Reig M, Forner A, Rimola J, Ferrer-Fàbrega J, Burrel M, Garcia-Criado Á, et al. BCLC strategy for prognosis prediction and treatment recommendation: the 2022 update. J Hepatol. 2022;76(3):681–93. https://doi.org/10.1016/j.jhep.2021.11.018

9 Trevisani F, Vitale A, Kudo M, Kulik L, Park JW, Pinato DJ, et al. Merits and boundaries of the BCLC staging and treatment algorithm: learning from the past to improve the future with a novel proposal. J Hepatol. 2024;80(4):661–9. https://doi.org/10.1016/j.jhep.2024.01.010

10 Fine JP, Gray RJ. A proportional hazards model for the subdistribution of a competing risk. J Am Stat Assoc. 1999;94(446):496–509. https://doi.org/10.1080/01621459.1999.10474144
11 Austin PC, Lee DS, Fine JP. Introduction to the analysis of survival data in the presence of competing risks. Circulation. 2016;133(6):601–9. https://doi.org/10.1161/CIRCULATIONAHA.115.017719
12 Austin PC, Fine JP. Practical recommendations for reporting fine-gray model analyses for competing risk data. Stat Med. 2017;36(27):4391–400. https://doi.org/10.1002/sim.7501
13 Lee KJ, Simpson JA. Introduction to multiple imputation for dealing with missing data. Respirology. 2014;19(2):162–7. https://doi.org/10.1111/resp.12226
14 Liver Cancer Study Group of Japan. The general rules for the clinical and pathological study of primary liver cancer. Jpn J Surg. 1989;19(1):98–129. https://doi.org/10.1007/BF02471576
15 Estes C, Razavi H, Loomba R, Younossi Z, Sanyal AJ. Modeling the epidemic of nonalcoholic fatty liver disease demonstrates an exponential increase in burden of disease. Hepatology. 2018;67(1):123–33. https://doi.org/10.1002/hep.29466
16 Younossi ZM, Stepanova M, Ong J, Trimble G, AlQahtani S, Younossi I, et al. Nonalcoholic steatohepatitis is the Most rapidly increasing indication for liver transplantation in the United States. Clin Gastroenterol Hepatol. 2021;19(3):580–9.e5. https://doi.org/10.1016/j.cgh.2020.05.064
17 Tampaki M, Tsochatzis E, Lekakis V, Cholongitas E. Prevalence, characteristics and outcomes of patients with metabolic and alcohol related/associated liver disease (MetALD): a systematic review and meta-analysis. Metabolism. 2025;163:156101. https://doi.org/10.1016/j.metabol.2024.156101
18 Aglago EK, Ramos I, Keski-Rahkonen P, Chatziioannou C, Freisling H, Fedirko V, et al. Alcohol and smoking habits in association with hepatocellular carcinoma risk. Int J Cancer. 2025;157(4):644–57. https://doi.org/10.1002/ijc.35401
19 Kim GA, Jeong S, Jang H, Lee DH, Joo SK, Kim W. Metabolic dysfunction-associated steatotic liver disease and metabolic dysfunction-associated steatotic liver disease with increased alcohol intake increase the risk of developing hepatocellular carcinoma and incident or decompensated cirrhosis: a Korean nationwide study. Liver Cancer. 2024;13(4):426–37. https://doi.org/10.1159/000535943
20 Chaudhari R, Fouda S, Sainu A, Pappachan JM. Metabolic complications of hepatitis C virus infection. World J Gastroenterol. 2021;27(13):1267–82. https://doi.org/10.3748/wjg.v27.i13.1267
21 Piscaglia F, Svegliati-Baroni G, Barchetti A, Pecorelli A, Marinelli S, Tiribelli C, et al. HCC-NAFLD Italian Study Group Clinical patterns of hepatocellular carcinoma in nonalcoholic fatty liver disease: a multicenter prospective study. Hepatology. 2016;63(3):827–38. https://doi.org/10.1002/hep.28368
22 Mittal S, Sada Y, El-Serag HB, Kanwal F, Duan Z, Temple S, et al. Temporal trends of nonalcoholic fatty liver disease-related hepatocellular carcinoma in the Veteran Affairs Population. Clin Gastroenterol Hepatol. 2015;13(3):594–601.e1. https://doi.org/10.1016/j.cgh.2014.08.013
23 Reggidori N, Bucci L, Santi V, Stefanini B, Lani L, Rampoldi D, et al. Landscape of alcohol-related hepatocellular carcinoma in the last 15 years highlights the need to expand surveillance programs. JHEP Rep. 2023;5(8):100784. https://doi.org/10.1016/j.jhepr.2023.100784
24 Israelsen M, Torp N, Johansen S, Hansen CD, Hansen ED, Thorhauge K, et al. Validation of the new nomenclature of steatotic liver disease in patients with a history of excessive alcohol intake: an analysis of data from a prospective cohort study. Lancet Gastroenterol Hepatol. 2024;9(3):218–28. https://doi.org/10.1016/S2468-1253(23)00443-0
25 Oh R, Kim S, Cho SH, Kim J, Lee YB, Jin SM, et al. Metabolic dysfunction-associated steatotic liver disease and all-cause and cause-specific mortality. Diabetes Metab J. 2025;49(1):80–91. https://doi.org/10.4093/dmj.2024.0042
26 Ochoa-Allemant P, Hubbard RA, Kaplan DE, Serper M. Cause-specific mortality in patients with steatotic liver disease in the United States. J Hepatol. 2025;83(4):860–9. https://doi.org/10.1016/j.jhep.2025.05.013
27 Li M, Xie W. Are there all-cause mortality differences between metabolic dysfunction-associated steatotic liver disease subtypes? J Hepatol. 2024;80(2):e53–4. https://doi.org/10.1016/j.jhep.2023.07.012
28 Yun B, Park H, Ahn SH, Oh J, Kim BK, Yoon JH. Liver cancer risk across metabolic dysfunction-associated steatotic liver disease and/or alcohol: a nationwide study. Am J Gastroenterol. 2025;120(2):410–9. https://doi.org/10.14309/ajg.0000000000002920
29 Åberg F, Byrne CD, Pirola CJ, Männistö V, Sookoian S. Alcohol consumption and metabolic syndrome: clinical and epidemiological impact on liver disease. J Hepatol. 2023;78(1):191–206. https://doi.org/10.1016/j.jhep.2022.08.030
30 Seitz HK, Stickel F. Molecular mechanisms of alcohol-mediated carcinogenesis. Nat Rev Cancer. 2007;7(8):599–612. https://doi.org/10.1038/nrc2191
31 Vitale A, Svegliati-Baroni G, Ortolani A, Cucco M, Dalla Riva GV, Giannini EG, et al. Epidemiological trends and trajectories of MAFLD-associated hepatocellular carcinoma 2002-2033: the ITA.LI.CA database. Gut. 2023;72(1):141–52. https://doi.org/10.1136/gutjnl-2021-324915
32 Koh YX, Tan HJ, Liew YX, Syn N, Teo JY, Lee SY, et al. Liver resection for nonalcoholic fatty liver disease-associated hepatocellular carcinoma. J Am Coll Surg. 2019;229(5):467–78.e1. https://doi.org/10.1016/j.jamcollsurg.2019.07.012
33 Hingorani AD, Windt DA, Riley RD, Abrams K, Moons KG, Steyerberg EW, et al. PROGRESS Group. Prognosis research strategy (PROGRESS) 4: stratified medicine research. BMJ. 2013;346:e5793. https://doi.org/10.1136/bmj.e5793