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Evolving epidemiology of HCC in Spain

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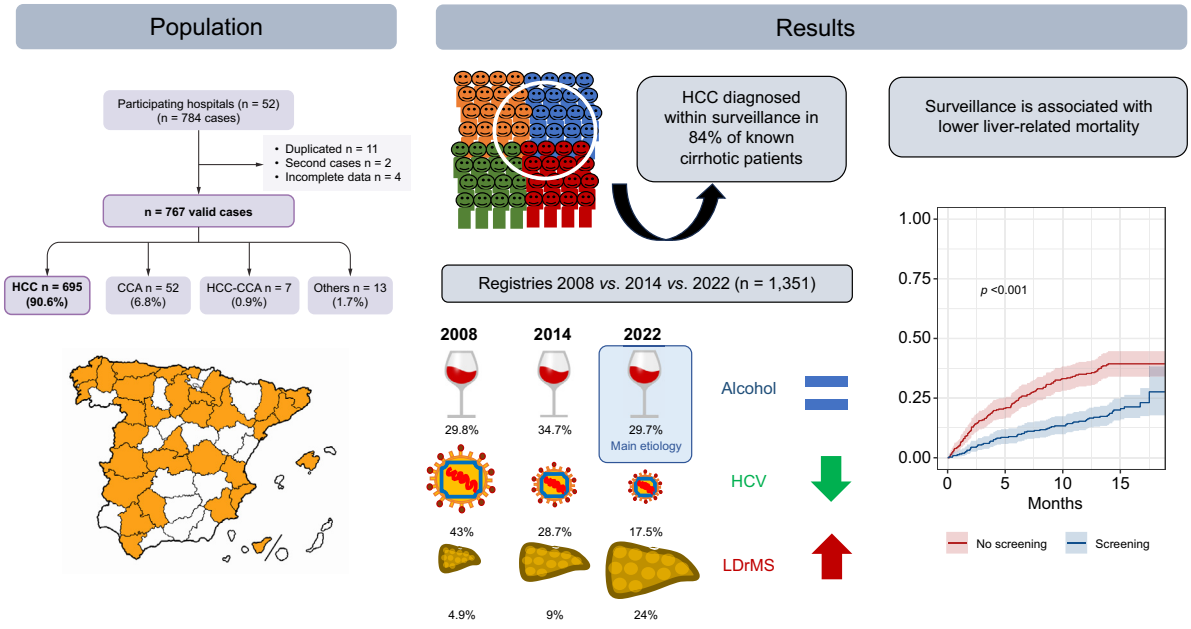
Graphical abstract



HCC, hepatocellular carcinoma; CCA, cholangiocarcinoma; HCV, hepatitis C virus; LDrMS: Liver Disease related to Metabolic Syndrome

Highlights:

- The epidemiological landscape of HCC in Europe is evolving.
- This study is a description of the current epidemiology of HCC in Spain.
- There is an increase in HCC associated with liver disease related to metabolic syndrome and HCC in non-cirrhotic livers.
- Hepatitis C-related HCCs are decreased and alcohol-related HCCs remain stable.
- There is a need for improved screening and prevention strategies.

Impact and implications:

Our study showcases the involvement of numerous reference centers across Spain and examines over 1,300 patients to track the changing epidemiology of hepatocellular carcinoma (HCC) over 14 years. In patients with known liver cirrhosis, more than 80% of HCC diagnoses were made through screening leading to early-stage identification and curative treatment opportunities. Notably, there has been a shift in HCC etiology within the registries from hepatitis C to liver disease related to metabolic syndrome, with an increase in cases without cirrhosis. Findings indicate a need for the prevention and early detection of HCC, particularly focusing on alcohol and liver disease related to metabolic syndrome, along with greater involvement of health authorities, to improve the participation of at-risk patients in screening programs.

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Research article

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Evolving epidemiology of HCC in Spain

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Background & Aims: The epidemiological landscape of hepatocellular carcinoma (HCC) in Europe is evolving. This study aims to provide an updated description of the current epidemiology of liver cancer in Spain.

Methods: This multicenter prospective study collected demographic and clinical data on primary liver cancer between October 2022 and January 2023. We conducted descriptive and comparative analyses with data collected in 2008 and 2014.

Results: Of the 767 cases of primary liver cancer collected from 52 centers, 91% were diagnosed as HCC. The majority of patients were male (83.3%), average age 68 years, 80.7% had cirrhosis. The primary causes were alcohol (29.9% alone, 55% combined with other etiologies), liver disease related to metabolic syndrome (LDrMS, 23%) and hepatitis C (17.3%). Treatments included ablation (15.7%), systemic therapy (14.7%), and chemoembolization (14.6%). Data from 29 centers (n = 1,351) across three registries revealed a significant increase in LDrMS (from 4.9% to 24%) and HCC in non-cirrhotic livers (from 4.2% to 7.9%). Meanwhile, hepatitis C decreased sharply (from 43% to 17.5%). Alcohol-related cases remained stable. There was a slight increase in male patients and hypertension, diabetes, and obesity. Patients with cirrhosis diagnosed outside of screening programs presented with larger tumors and more advanced disease. This led to fewer evaluations for curative treatments.

Conclusions: Alcohol accounts for 30% of HCC cases and is the main etiology. The registry shows a decrease in hepatitis C-related HCC, an increase in LDrMS and HCC in non-cirrhotic livers. Surveillance was implemented in ∼80% of the recommended population. There is a need for improved screening and prevention strategies, particularly for alcohol abuse and LDrMS, to enhance HCC management.

Introduction and aims

Hepatocellular carcinoma (HCC) ranks as the sixth most common tumor globally and it is the third leading cause of cancer-related deaths.[1] Typically, HCC arises in individuals with cirrhosis, becoming the primary cause of mortality in this group of patients.[2] In 2022, there were 865,000 newly diagnosed cases of HCC, with 757,948 recorded deaths worldwide.[1] As >90% of HCC cases occur in patients with cirrhosis, these patients participate in screening programs aimed to detect the cancer at an early stage, allowing for the implementation of potentially curative treatments that may improve survival.[2]

The primary causes of HCC encompass chronic HBV infection, chronic HCV infection, and alcohol consumption.[3] Nonetheless, the epidemiology and clinical features of HCC have experienced shifts in recent decades because of factors such as improved HCV treatment, increased alcohol consumption, and the rising rates of obesity and type 2 diabetes mellitus (T2DM). Given the worsening obesity pandemic, metabolic-associated liver disease (MASLD) is expected to become the number one cause of liver transplantation (LT) by 2030.[4] This ongoing surveillance is vital for adapting strategies to the evolving landscape of HCC risk factors and prevalence.

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Because of these circumstances, the Spanish Association for the Study of the Liver (AEEH: Asociación Española para el Estudio del Hígado) and the CIBERehd created two national registries of HCC in Spain during the periods 2008–2009 and 2014–2015.[5,6] These registries yielded valuable insights into the status of HCC in Spain, identifying trends in the disease's epidemiology and risk factors, and assessing the effectiveness of screening programs and the disparities between the patients diagnosed within and outside of these programs.

As a result of the evolving epidemiology of HCC and the publication and revision of clinical practice guidelines for HCC,[7,8] it was determined that a third registry should be created to assess the current state of HCC in Spain and compare the registry to previous records. The aims of this article are to present the findings from this third registry, offering an updated perspective on HCC in our country and to assess the disparities in comparison with the initial and subsequent registries (conducted in 2008 and 2014, respectively), particularly in terms of etiology.

Patients, materials and methods

From 1 October 2022 to the 31 January 2023, the demographic, clinical, analytical, and tumor characteristics of patients with primary liver tumors diagnosed *de novo* during this period in Spain were prospectively collected. To achieve this, 107 secondary and tertiary centers, where these patients are routinely treated throughout Spain, were contacted following the same methodology used in previous registries.[5,6] The data collection was carried out in accordance with the Organic Law on Protection of Personal Data and Guarantee of Digital Rights. The data were entered through the online digital platform (REDCap®) in a centralized database through the AEEH, also counting on the collaboration of the Liver Cancer Study Group attached to CIBERehd. These data are securely stored in an encoded electronic file (https://aeeh.es/politica-de-privacidad/) to enable identification of the reference centers without recording the patients' name or medical record number.

The study has been evaluated and approved by the ethics committee of each participating center, and all the patients gave their written consent. All research was carried out in accordance with relevant guidelines/regulations, and the data of all participants included in the study were anonymized to be used for research purposes.

Definitions

1. Case: each of the patients with a *de novo* diagnosis of liver tumor during the period between the 1 October 2022 and 31 January 2023.
2. Other tumors: current presence or history of extrahepatic cancer.
3. Cirrhosis: used as a synonym for chronic advanced liver disease, leading to significant liver dysfunction and associated complications such as portal hypertension and HCC.
4. Non-cirrhotic liver: includes those without significant liver fibrosis and those at stages F2 and F3 according to the METAVIR fibrosis scoring system.
5. Clinically significant portal hypertension was defined as hepatic venous pressure gradient of ≥10 mmHg or estimated by the size of the spleen >15 cm, platelet count <100 × 10^9/L, presence of varices or prior decompensations of liver cirrhosis.
6. Method of diagnosis of HCC: (i) non-invasive diagnosis in patients with advanced chronic liver disease using dynamic computed tomography and/or magnetic resonance imaging tests in accordance with clinical guidelines,[7,8] with contrast uptake in the arterial phase and rapid contrast washout in venous/portal/late phase; (ii) cytology/histology.
7. Macroscopic vascular invasion: defined in imaging tests as venous thrombosis with an expansive appearance (portal, hepatic vein, or vena cava).
8. HCC detection methods: (i) screening program (abdominal ultrasound performed within 6 ± 2 months before tumor detection with no liver lesions); (ii) initial imaging study for chronic liver disease diagnosis; (iii) known chronic liver disease without screening owing to poor patient adherence; (iv) known chronic liver disease without screening based on medical criteria; (v) incidental discovery or owing to symptoms.
9. Screening success was defined arbitrarily as the cases diagnosed in the very early or initial stage defined according to the Barcelona Clinic Liver Cancer (BCLC) Staging System: (BCLC 0 and A), whereas screening failure referred to those diagnosed in intermediate, advanced, or terminal stages (BCLC B, C or D).
10. Treatment with curative intent includes surgical resection, ablation (radiofrequency ablation [RFA], microwave ablation [MWA], percutaneous ethanol injection [PEI]), and LT.
11. Alcohol etiology: quantitatively defined as the consumption of more than 100 g of alcohol per day for over a decade.
12. MetALD: Metabolic dysfunction-associated steatotic liver disease patients who consume greater amounts of alcohol per week (140–350 g/week and 210–420 g/week for females and males, respectively).
13. Liver disease related to metabolic syndrome (LDrMS): includes all patients with etiologies of non-alcoholic-fatty-liver disease (NAFLD), MetALD or MASLD as recorded by investigators across the three registries, in addition to those patients with no other identifiable liver etiology or classified as cryptogenic, who exhibit at least one of the following criteria: a BMI >25 kg/m^2 and/or T2DM.

Collected variables

Demographic variables were collected (age, sex, race) as well as underlying liver disease variables and etiology; form of diagnosis, prior decompensations (ascites, hepatic encephalopathy), presence of clinically significant portal hypertension; comorbidities (arterial hypertension, T2DM, dyslipidemia [DL], obesity or overweight defined according to BMI, presence of extrahepatic tumors, HIV coinfection); current tobacco and alcohol consumption; family history of HCC or cirrhosis; form of detection and diagnostic method; general condition of the patient (defined according to the Eastern Cooperative Oncology Group-Performance Status [ECOG-PS] Index); tumor stage (defined according to the BCLC Staging System); treatment applied, and whether an evaluation for LT was performed. The quantitative variables collected were: serum bilirubin, albumin, creatinine, international normalized ratio, platelets, albumin, alpha-fetoprotein (AFP) and Ca 19.9 (cancer antigen 19.9). Furthermore, we gathered the patient's current status as of 30 March 2024, whether deceased or alive, and the cause of death (hepatic *vs.* extrahepatic). Overall survival was defined

from the date of diagnosis to the last contact or date of death. Before the analysis, the data were reviewed to assess any discrepancies and inconsistencies with the originating centers.

Statistical analysis

Quantitative variables were described with the median with first and third quartiles, whereas categorical variables were expressed as absolute frequencies and percentages.

Patients with HCC who had different characteristics were compared using Pearson's X^2 test or Fisher's exact test in the case of categorical variables, and the Mann–Whitney test in the case of quantitative variables. Patients from the 2008–2009, 2014–2015, and 2022–2023 registries were compared using Pearson's X^2 test or Fisher's exact test in the case of categorical variables, and Kruskal–Wallis' test in the case of quantitative variables. A *post-hoc* analysis was performed applying the Benjamin–Hochberg correction of *p* values. The cumulative incidence function of hepatic death with its 95% CI was estimated in a competing risk framework, where extrahepatic death was considered to be a competing event. The cumulative incidence curve for patients who participated in the screening program and the cumulative incidence curve of patients who did not participate were compared with Gray's test. Statistical analysis was performed using SPSS statistical package, version 23.0 (IBM, Armonk, NY, USA) and R software version 4.3.2 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Within the designated 4-month interval, a cumulative total of 52 centers reported the inclusion of 784 patients. Nevertheless, a subset of 17 patients was subsequently omitted owing to a range of discrepancies: four cases were removed for incomplete or conflicting data, 11 for being duplicates, and two for non-incidental classification. Thus, the revised total number of eligible patients was established at 767 cases. Of this cohort, 695 were diagnosed with HCC (90.6%), 52 with cholangiocarcinoma (CCA, n = 6.7%) and seven with combined CCA-HCC (0.9%), as illustrated in Fig. 1.

The estimated annual incidence of liver tumors in Spain, as reported by GLOBOCAN in 2022, was 6.3 per 10^5 inhabitants, a number slightly below the 6.7 per 10^5 incidence for Southern Europe. Moreover, when considering the incidence data forecasted for the year 2022 by the Spanish Network of Cancer Registries,[9] which anticipates 6,604 new cases, the cases documented in this survey amount to 34.8% of the expected incident cases for the corresponding period in Spain.

We have reconciled inconsistencies and potential errors with the main investigators before analysis, verified accurate BCLC stage classification (7.7% of patients with HCC were wrongly classified) and treatment proposals according to guidelines[7,8] (discrepancies found in 1.29% patients), confirming the registry's high reliability.[10]

Characteristics of patients with HCC

Patient characteristics (n = 695) are described in Table 1. A significant proportion of the cohort were male (83.3%) with a median age of 68 years (IQR 61–75 years). A notable 80.7% of the cases had underlying liver cirrhosis, predominantly classified as Child-Pugh stage A (67.3%). The principal etiologies identified were alcoholic liver disease (ALD) in 29.9% of cases, HCV in 17.3%, ALD + HCV in 11.1%, MASLD in 10.5%, MetALD in 11.1%, and HBV in 4.5%. Other etiologies are detailed in Table S1. Thus, alcohol, either as a solitary factor or concomitant with other etiologies, was the most frequent cause of HCC, implicated in 55% of cases. Geographical analysis indicates that the etiology related to alcohol is prevalent across the majority of the regions in the country.

The prevalence of T2DM among the patients was 38.8%, whereas obesity (BMI >30 kg/m^2) was observed in 29.6%. An extrahepatic tumor was present in 16.3% of patients, with a simultaneous HCC diagnosis in 23% of these patients. The most commonly encountered extrahepatic tumors included colon (n = 26; 23%), prostate (n = 13; 11.5%), renal–bladder (n = 13; 11.5%), hematological malignancies (n = 12; 10.6%), breast (n = 9; 7.9%), and those originating from the otorhinolaryngological region (n = 9; 7.9%), among others.

In the cohort under study, for patients in whom MASLD was not considered a contributing factor to the etiology by the

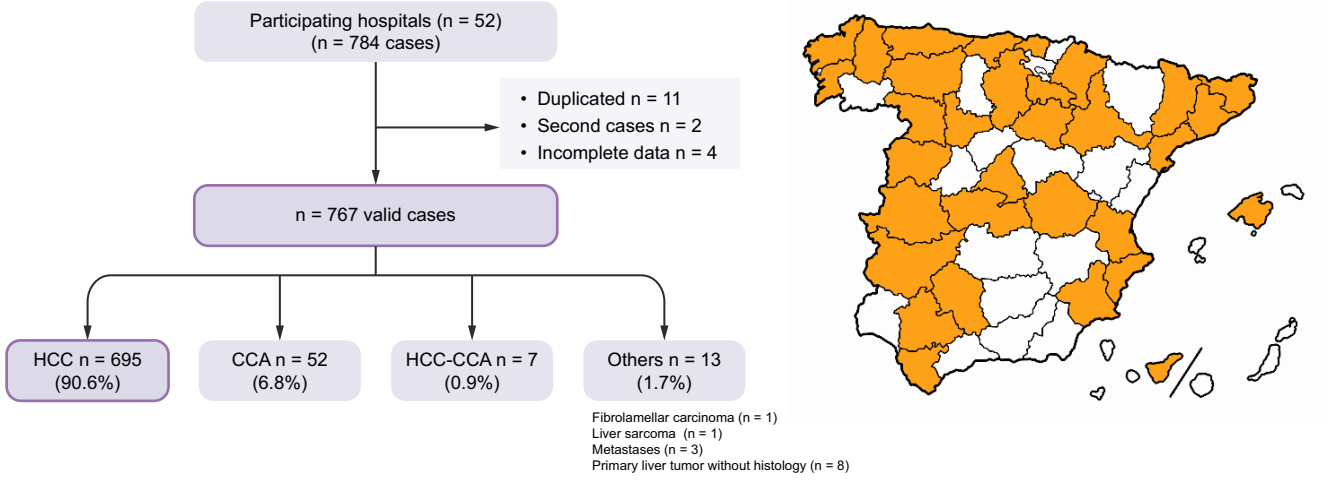

Fig. 1. Flow chart of patients included in the third registry (n = 767) and geographic distribution of the participating hospitals (n = 52).

Table 1. Characteristics of patients with HCC (n = 695).

Variable	HCC (n = 695)
Age, median (IQR), years	68 (61–75)
Male sex, n (%)	579 (83.3)
Underlying liver disease, n (%) (n = 694)	
Non-significant liver fibrosis	60 (8.6)
F2–F3	74 (10.7)
Cirrhosis (n = 694)	560 (80.7)
Etiology, n (%)	
ALD	208 (29.9)
LDrMS	160 (23)
MASLD	73
MetALD	77
Cryptogenic*	10
HCV	120 (17.3)
ALD + HCV	77 (11.1)
HBV	31 (4.5)
Other	99 (14.2)
Arterial hypertension, n (%)	379 (54.5)
Diabetes mellitus, n (%) (n = 694)	269 (38.8)
Dyslipidemia, n (%) (n = 694)	222 (32)
HIV, n (%) (n = 617)	19 (2.7)
BMI, n (%), kg/m^2 (n = 548)	
<25	165 (30.1)
25–30	221 (40.3)
>30	162 (29.6)
Active alcohol consumption, n (%) (n = 694)	197 (28.4)
≤30 g/day	97 (49.2)
>30 g/day	100 (50.8)
Active tobacco consumption, n (%) (n = 692)	461 (66.6)
Non-invasive diagnostic, n (%)	525 (75.5)
AFP categorized, n (%), ng/ml (n = 662)	
<20	398 (60.1)
20–200	123 (18.6)
200–400	20 (3)
>400	121 (18.3)
Tumor size, median (IQR), mm (n = 639)	32 (22–52)
Vascular invasion, n (%)	147 (21.2)
Extrahepatic spread, n (%) (n = 694)	71 (10.2)
ECOG- PS, n (%) (n = 694)	
0	529 (76.2)
1	82 (11.8)
2	40 (5.8)
3	37 (5.3)
4	6 (0.9)
BCLC stage, n (%)	
0	85 (12.2)
A	304 (43.7)
B	86 (12.4)
C	142 (20.4)
D	78 (11.2)
Curative intention treatment†, n (%)	287 (41.4)
Liver resection, n (%)	91 (13.5)
LT evaluation, n (%)	90 (13.2)
Thermal ablation, n (%)	128 (19)
TACE, n (%)	127 (18.8)
TARE, n (%)	35 (5.2)
Systemic therapy, n (%)	104 (15.4)
Symptom management, n (%)	158 (22.8)

ALD, alcohol-related liver disease; AFP, alpha-fetoprotein; BCLC, Barcelona Clinic Liver Cancer; BMI, body mass index; ECOG-PS, Eastern Cooperative Oncology Group-Performance Status; F2, METAVIR stage F2 fibrosis; F3, METAVIR stage F3 fibrosis; HBV, hepatitis B-related liver disease; HCC, hepatocellular carcinoma; HCV, hepatitis C-related liver disease; HIV, human immunodeficiency virus; LDrMS, liver disease related to metabolic syndrome; LT, liver transplantation; MASLD, metabolic dysfunction-associated steatotic liver disease; MELD, model of end-stage liver disease; MetALD, MASLD who consume greater amounts of alcohol per week (140–350 g/week and 210–420 g/week for females and males respectively); TACE, transarterial chemoembolization; TARE, transarterial radioembolization.

*Cryptogenic plus BMI >25 kg/m^2 or diabetes mellitus.

†Curative intention HCC treatment includes resection, thermal ablation, and liver transplantation.

investigators (n = 534), 28.1% had T2DM and 64.7% had a BMI >25 (with 24% having a BMI exceeding 30). Of these patients, 7.2% (n = 51) exhibited a BMI over 25, concurrently with T2DM and DL. Patients with no other identified etiology or classified as cryptogenic who also presented with a BMI >25 kg/m^2 and/or T2DM, together with those diagnosed with MASLD or MetALD, are categorized under the concept of HCC associated with LDrMS. In the third registry this etiology accounted for up to 23%, second only to alcohol.

HCC diagnosis was primarily based on non-invasive criteria for 75.5% of cases. Staging distribution following the BCLC classification was as follows: BCLC 0, 12.2%; BCLC A, 43.7%; BCLC B, 12.4%; BCLC C, 20.4%; and BCLC D, 11.2%. The initial treatment recommended was ablation in 15.7% of cases. Systemic treatment was the second most commonly indicated treatment (14.7%). Transarterial chemoembolization (TACE) was indicated in 14.6% of cases, surgical intervention in 12.4%, transarterial radioembolization (TARE) in 4.8%, and stereotactic body radiotherapy in 0.6%. Ninety patients (13% of the cohort) were evaluated for LT; of these, 35 patients (38.9%) received bridging treatments, predominantly TACE (n = 21, 60%), followed by ablation (n = 12, 34.2%), TARE (n = 1, 2.8%), and resection (n = 1, 2.8%). Ultimately, 41.4% of patients underwent treatment with curative intent, while management for 22.8% was supportive, allowing progression of the natural history of the disease. The distribution of treatment allocation across the BCLC stages is presented in Table S2.

Characteristics of patients with HCC secondary to alcohol

The characteristics of patients with HCC attributable to alcohol are detailed herein. This group, either with alcohol as a sole factor or in conjunction with another etiology, comprised 382 individuals and was contrasted with those having different etiologies (n = 313) as delineated in Table 2. Statistically significant differences emerged in several areas: age (with alcohol-related HCC patients being younger at 66 [IQR 60–73] *vs.*70 [IQR 61–78] years, p <0.001), sex (a higher percentage of men in the alcohol etiology group at 93.7% *vs.* 70.6%, p <0.001), and a greater prevalence of underlying liver disease characterized by cirrhosis (90.8% in the alcohol group *vs.* 68.3%, p <0.001). Additionally, there was a notable increase in tobacco use among the alcohol-related group (79.5% *vs.* 51%, p <0.001). A lower proportion of patients were diagnosed at the BCLC stage 0/A (52.3% *vs.* 60.4%, p = 0.034). No significant differences were found concerning the presence of T2DM (p = 0.252), DL (p = 0.395), arterial hypertension (p = 0.509), BMI >30 kg/m^2 (p = 0.337), or the presence of another primary tumor (p = 0.674).

Narrowing the scope to patients with cirrhosis (n = 560), the proportion of patients at Child-Pugh stage A was lower in the alcohol group (61.7% *vs.* 76.6% in other etiologies, p <0.001). There was also a higher incidence of portal hypertension (78.7% *vs.* 65.7%, p <0.001), more patients presenting with ascites at the time of HCC diagnosis (38.6% *vs.* 24.4%, p = 0.002), and a higher model for end-stage liver disease (MELD) score (10 [IQR 8–13] points *vs.* 9 (IQR 8–13] points; p <0.001).

In the overarching cohort, among those in whom alcohol was not deemed a contributing factor to etiology, 35 were consuming alcohol at the time of HCC diagnosis (11.2%). Conversely, among those with alcohol as a contributing factor, 57.6% (n = 220) were abstinent at the time of HCC diagnosis.

Table 2. Characteristics of patients with HCC secondary to alcohol (n = 382).

Variable	HCC (n = 695)	Alcohol-related HCC (n = 382)	Non-alcohol-related HCC (n = 313)	*p* value
Age, median (IQR), years	68 (61–75)	66 (40–90)	70 (61–78)	<0.001
Male sex, n (%)	579 (83.3)	358 (93.7)	221 (70.6)	<0.001
Underlying liver disease, n (%) (n = 694)				<0.001
Non-significant liver fibrosis	60 (8.6)	3 (0.8)	57 (18.2)	
F2–F3	74 (10.7)	32 (8.4)	42 (13.5)	
Cirrhosis	560 (80.7)	347 (90.8)	213 (68.3)	
Ascites, n (%) (n = 560)				0.002
No	374 (66.8)	213 (61.4)	161 (75.6)	
I–II	163 (29.1)	118 (34)	45 (21.1)	
Refractory	23 (4.1)	16 (4.6)	7 (3.3)	
Encephalopathy, n (%) (n = 560)				0.053
No	511 (91.3)	310 (89.3)	201 (94.3)	
I–II	39 (7)	31 (8.9)	8 (3.8)	
III–IV	10 (1.8)	6 (1.7)	4 (1.9)	
Child-Pugh class, n (%) (n = 551)				<0.001
A	371 (67.3)	211 (61.7)	160 (76.6)	
B	143 (26)	99 (28.9)	44 (21.1)	
C	37 (6.7)	32 (9.4)	5 (2.3)	
MELD, median (IQR) (n = 558)	9 (8-12.8)	10 (8-13)	9 (7-11)	<0.001
Arterial hypertension, n (%)	379 (54.5)	204 (53.4)	175 (55.9)	0.509
Diabetes mellitus, n (%) (n = 694)	269 (38.8)	155 (40.7)	114 (36.4)	0.252
Dyslipidemia, n (%) (n = 694)	222 (32)	117(30.6)	105 (33.7)	0.395
HIV, n (%) (n = 617)	19 (2.7)	7 (2)	12 (4)	0.161
BMI, n (%), kg/m^2 (n = 548)				0.492
<25	165 (30.1)	87 (28.4)	78 (32.2)	
25–30	221 (40.3)	123 (40.2)	98 (40.5)	
>30	162 (29.6)	96 (31.4)	66 (27.3)	
Active alcohol consumption, n (%) (n = 694)	197 (28.4)	162 (42.4)	35 (11.2)	<0.001
Active tobacco consumption, n (%) (n = 692)	461 (66.6)	302 (79.5)	159 (51)	<0.001
Non-invasive diagnostic n, (%)	525 (75.5)	317 (83)	208 (66.5)	<0.001
AFP categorized, n (%), ng/ml (n = 662)				0.973
<20	398 (60.1)	220 (60.6)	178 (59.5)	
20–200	123 (18.6)	68 (18.7)	55 (18.4)	
200–400	20 (3)	11 (3)	9 (3)	
>400	121 (18.3)	64 (17.6)	57 (19.1)	
Tumor size, median (IQR), mm (n = 639)	32 (22–52)	30 (22–50)	33 (22–60)	0.423
Vascular invasion, n (%)	147 (21.2)	83 (21.7)	64 (20.4)	0.681
Extrahepatic spread, n (%) (n = 694)	71 (10.2)	42 (11)	29 (9.3)	0.462
ECOG-PS, n (%) (n = 694)				0.293
0	529 (76.2)	279 (73.2)	250 (79.9)	
1	82 (11.8)	53 (13.9)	29 (9.3)	
2	40 (5.8)	24 (6.3)	16 (5.1)	
3	37 (5.3)	21 (5.5)	16 (5.1)	
4	6 (0.9)	4 (1)	2 (0.6)	
BCLC stage, n (%)				0.150
0	85 (12.2)	44 (11.5)	41 (13.1)	
A	304 (43.7)	156 (40.8)	148 (47.3)	
B	86 (12.4)	54 (14.1)	32 (10.2)	
C	142 (20.4)	78 (20.4)	64 (20.4)	
D	78 (11.2)	50 (13.1)	28 (8.9)	
HCC treatment*, n (%) (n = 693)	535 (77.2)	290 (76.1)	245 (78.5)	0.452

Level of significance p <0.05 (Pearson's X^2 test or Fisher's exact test in the case of categorical variables and the Mann–Whitney test in the case of quantitative variables).
AFP, alpha-fetoprotein; BCLC, Barcelona Clinic Liver Cancer; BMI, body mass index; ECOG-PS, Eastern Cooperative Oncology Group-Performance Status; F2, METAVIR stage F2 fibrosis; F3, METAVIR stage F3 fibrosis; HCC, hepatocellular carcinoma; HIV, human immunodeficiency virus; MELD, model for end-stage liver disease.
*HCC treatment includes curative and palliative therapies.

The implementation of radical treatments and pre-transplant evaluations was less frequent in patients actively consuming alcohol (n = 197) compared with abstainers (n = 497) (33.2% *vs.* 44.8%; p = 0.005 and 4.1% *vs.* 16.9%; p <0.001), with a higher number of active drinkers remaining unmanaged, allowing the progression of the natural history of the disease at the time of HCC diagnosis (28.6% *vs.* 20.4%; p = 0.020).

Characteristics of patients with HCC secondary to HCV

The characteristics of patients with HCC secondary to HCV were examined (n = 208). This group was further stratified into those with ongoing viral replication (viremic, n = 50) and those in sustained virological response (SVR) (n = 158). It was observed that 87% (n = 181) of the anti-HCV positive cohort had cirrhosis at the time of their HCC diagnosis. The median duration from achieving

SVR to the diagnosis of the tumor was 76.74 months (IQR 63.8–89.28). Among the patients with cirrhosis, 74.5% had reached SVR by the time HCC was diagnosed. The analysis sought to discern differences between patients who had viremia and patients with SVR within the overall cohort. It was found that patient with SVR were older (63 [IQR 58–72.8] years compared with 59 [IQR 55–65.5] years, $p = 0.005$), had a higher incidence of arterial hypertension (44.9% *vs.* 26%, $p = 0.017$), and DL (19.7% *vs.* 6%, $p = 0.027$). Additionally, these patients had lower rates of alcohol (17.7% *vs.* 34.7%, $p = 0.012$) and tobacco usage (69% *vs.* 85.7%, $p = 0.021$). Patients with SVR were more often involved in screening programs (68.4% *vs.* 16%, $p < 0.001$) and presented with less advanced HCC (BCLC stages 0–A were 64.5% *vs.* 36%, $p < 0.001$; vascular invasion occurred in 24.1% *vs.* 44%, $p = 0.007$; and extrahepatic spread was found in 7.6% *vs.* 24%, $p = 0.002$). There was a greater implementation of radical treatment in SVR patients (47.5% *vs.* 20%, $p = 0.001$), and fewer patients in this subgroup were unmanaged, allowing the progression of the natural history of the disease (20.9% *vs.* 44%, $p = 0.001$).

Table 3. Characteristics of patients with HCC secondary to HCV (n = 208).

Variable	HCC (n = 208)	SVR-related HCC (n = 158)	Non-SVR-related HCC (n = 50)	*p* value
Age, median (IQR), years	62 (57–70.2)	63 (25–72.8)	59 (55–65.5)	0.015
Male sex, n (%)	163 (74.8)	121 (76.6)	42 (84)	0.267
Underlying liver disease, n (%)				0.425
Non-significant liver fibrosis	5 (2.4)	5 (3.2)	0 (0)	
F2–F3	22 (10.6)	18 (11.4)	4 (8)	
Cirrhosis	181 (87)	135 (85.4)	46 (92)	
Ascites, n (%) (n = 181)				0.003
No	128 (70.7)	104 (77)	24 (52.2)	
I–II	46 (25.4)	28 (20.7)	18 (39.1)	
Refractory	7 (3.9)	3 (2.2)	4 (8.7)	
Encephalopathy, n (%) (n = 181)				0.072
No	169 (93.4)	129 (95.6)	40 (87)	
I–II	9 (5)	5 (3.7)	4 (8.7)	
III–IV	3 (1.6)	1 (0.7)	2 (4.3)	
Child-Pugh class, n (%)				<0.001
A	127 (71.3)	102 (76.7)	25 (55.6)	
B	43 (24.2)	30 (22.6)	13 (28.8)	
C	8 (4.5)	1 (0.7)	7 (15.6)	
MELD, median (IQR) (n = 179)	9 (7-11)	8 (7-10)	10 (8-14)	0.009
Arterial hypertension, n (%)	84 (40.4)	71 (44.9)	13 (26)	0.017
Diabetes mellitus, n (%) (n = 207)	47 (22.6)	40 (25.5)	7 (14)	0.092
Dyslipidemia, n (%) (n = 207)	34 (16.4)	31 (19.7)	3 (6)	0.027
HIV, n (%) (n = 193)	16 (7.7)	16 (10.1)	0 (0)	0.051
BMI, n (%), kg/m^2 (n = 156)				0.212
<25	65 (41.7)	50 (41)	15 (44.1)	
25–30	56 (35.9)	41 (33.6)	15 (44.1)	
>30	35 (22.4)	31 (25.4)	4 (11.8)	
Active alcohol consumption, n (%) (n = 207)	45 (21.6)	28 (17.7)	17 (34.7)	0.012
Active tobacco consumption, n (%) (n = 207)	151 (72.9)	109 (69)	42 (85.7)	0.021
Non-invasive diagnostic, n (%)	169 (81.2)	132 (83.5)	37 (74)	0.132
AFP categorized, n (%), ng/ml (n = 201)				0.005
<20	110 (54.7)	94 (61.4)	16 (33.3)	
20–200	37 (18.4)	25 (16.3)	12 (25)	
200–400	7 (3.5)	4 (2.6)	3 (6.2)	
>400	47 (23.4)	30 (19.6)	17 (35.4)	
Tumor size, median (IQR), mm (n = 186)	30.5 (22–50)	30 (21–46.8)	38.5 (26.5–52.8)	0.024
Vascular invasion, n (%)	60 (28.8)	38 (24.1)	22 (44)	0.007
Extrahepatic spread, n (%) (n = 207)	24 (11.6)	12 (7.6)	12 (24)	0.002
ECOG-PS, n (%)				0.002
0	156 (75)	129 (81.6)	27 (54)	
1	21 (10.1)	11 (7)	10 (20)	
2	13 (6.2)	7 (4.4)	6 (12)	
3	14 (6.7)	8 (5.1)	6 (12)	
4	4 (1.9)	3 (1.9)	1 (2)	
BCLC stage, n (%)				0.008
0	23 (11.1)	19 (12)	4 (8)	
A	97 (46.6)	83 (52.5)	14 (28)	
B	17 (8.2)	12 (7.6)	5 (10)	
C	45 (21.6)	27 (17.1)	18 (36)	
D	26 (12.5)	17 (10.8)	9 (18)	
HCC treatment*, n (%)	153 (73.6)	125 (79.1)	28 (56)	0.001

Level of significance $p < 0.05$ (Pearson's X^2 test or Fisher's exact test in the case of categorical variables and the Mann–Whitney test in the case of quantitative variables).

AFP, alpha-fetoprotein; BCLC, Barcelona Clinic Liver Cancer; BMI, body mass index; ECOG-PS, Eastern Cooperative Oncology Group-Performance Status; F2, METAVIR stage F2 fibrosis; F3, METAVIR stage F2 fibrosis; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HIV, human immunodeficiency virus; MELD, model of end-stage liver disease; SVR, sustained virological response.

*HCC treatment includes curative and palliative therapies.

Focusing solely on patients with cirrhosis (n = 181), those who were non-viremic exhibited better liver function, evidenced by a higher proportion in Child-Pugh class A (76.7% *vs.* 55.6%, p <0.0001), a lower occurrence of ascites (52.2% *vs.* 77%, p = 0.003), and a lower MELD score (8 [IQR 7–10] *vs.* 10 [IQR 8–14], p = 0.009). However, no difference was found in the presence of clinically significant portal hypertension (67.4% in SVR *vs.* 78.3% in viremia, p = 0.165), as noted in Table 3.

Characteristics of patients with HCC and non-cirrhotic liver

A total of 134 patients without cirrhosis were diagnosed with HCC, which includes 60 patients without significant liver fibrosis and 74 with liver stage F2 or F3 fibrosis. These patients had a median age of 73 years (IQR 64–78.8 years). The etiologies attributed include MASLD in 28 cases (20.9%), HCV in 18 cases (13.4%), MetALD in 18 cases (13.4%), and alcohol in 10 cases (7.5%). The characteristics of these patients are provided in Table 4.

When compared with patients with HCC and liver cirrhosis (n = 560), those with non-cirrhotic livers (n = 134) where significantly older (median 73 [IQR 64–78.8] *vs.* 65.5 [IQR 60–74] years; p <0.001). Furthermore, they more frequently presented MASLD as an underlying cause (20.9% *vs.* 8%, p <0.001), had a higher incidence of other primary tumors (26.1% *vs.* 14%; p <0.001), larger tumor sizes (median diameter of 50

Table 4. Characteristics of patients with HCC with non-cirrhotic liver (n = 134).

Variable	HCC (n = 695)*	Non-cirrhosis-related HCC (n = 134)	Cirrhosis-related HCC (n = 560)	*p* value
Age, median (IQR), years	68 (61–75)	73 (64–78.8)	66.5 (60–74)	<0.001
Male sex, n (%)	579 (83.3)	111 (82.8)	468 (83.6)	0.837
Etiology, n (%)				<0.001
ALD	208 (29.9)	10 (7.5)	198 (35.4)	
LDrMS	160 (23)	46 (34.3)	114 (20.4)	
MASLD	73	28	45	
MetALD	77	18	59	
Cryptogenic†	10	—	10	
HCV	120 (17.3)	18 (13.4)	102 (18.2)	
ALD + HCV	77 (11.1)	5 (3.7)	72 (12.9)	
HBV	31 (4.5)	8 (6)	23 (4.1)	
Other	99 (14.2)	47 (35.1)	51 (9)	
Active alcohol consumption, n (%) (n = 694)	197 (28.4)	37 (27.8)	160 (28.6)	0.863
Active tobacco consumption, n (%) (n = 692)	461 (66.6)	85 (63.9)	376 (67.1)	0.445
Arterial hypertension, n (%)	379 (54.5)	86 (64.2)	292 (52.1)	0.012
Diabetes mellitus, n (%) (n = 694)	269 (38.8)	51 (38.1)	218 (39)	0.841
Dyslipidemia, n (%) (n = 694)	222 (32)	59 (44.4)	163 (29.1)	<0.001
BMI, n (%), kg/m^2 (n = 548)				0.139
<25	165 (30.1)	42 (37.8)	123 (28.1)	
25–30	221 (40.3)	40 (36)	181 (41.4)	
>30	162 (29.6)	29 (26.1)	133 (30.4)	
AFP categorized ng/ml, n (%) (n = 662)				0.171
<20	398 (60.1)	83 (65.9)	315 (58.9)	
20–200	123 (18.6)	17 (13.5)	106 (19.8)	
200–400	20 (3)	6 (4.8)	14 (2.6)	
>400	121 (18.3)	20 (15.8)	100 (18.7)	
Tumor size, median (IQR), mm (n = 639)	32 (22–52)	50 (30–77)	30 (21.8–48)	<0.001
Vascular invasion, n (%)	147 (21.2)	30 (22.4)	116 (20.7)	0.669
Extrahepatic spread, n (%) (n = 694)	71 (10.2)	16 (11.9)	55 (9.8)	0.471
ECOG-PS, n (%) (n = 694)				0.571
0	529 (76.2)	105 (78.4)	424 (75.8)	
1	82 (11.8)	18 (13.4)	64 (11.4)	
2	40 (5.8)	4 (3)	36 (6.4)	
3	37 (5.3)	6 (4.5)	30 (5.4)	
4	6 (0.9)	1 (0.7)	5 (0.9)	
BCLC stage, n (%)				0.021
0	85 (12.2)	11 (8.2)	74 (13.2)	
A	304 (43.7)	66 (49.3)	238 (42.5)	
B	86 (12.4)	13 (9.7)	73 (13)	
C	142 (20.4)	36 (26.8)	106 (18.9)	
D	78 (11.2)	8 (6)	69 (12.3)	
HCC treatment‡, n (%) (n = 693)	535 (77.2)	113 (84.3)	422 (75.6)	0.031

Non-cirrhotic liver includes those without significant liver fibrosis and those F2 and F3 according to the METAVIR scoring system. Level of significance p <0.05 (Pearson's X^2 test or Fisher's exact test in the case of categorical variables and the Mann–Whitney test in the case of quantitative variables).

AFP, alpha-fetoprotein; ALD, alcohol-related liver disease; BCLC, Barcelona Clinic Liver Cancer; BMI, body mass index; ECOG-PS, Eastern Cooperative Oncology Group-Performance Status; F2, METAVIR stage F2 fibrosis; F3, METAVIR stage F3 fibrosis; HBV, hepatitis B-related liver disease; HCC, hepatocellular carcinoma; HCV, hepatitis C-related liver disease; HIV, human immunodeficiency virus; LDrMS, liver disease related to metabolic syndrome; MASLD, metabolic dysfunction-associated steatotic liver disease; MELD, model of end-stage liver disease; MetALD, MASLD who consume greater amounts of alcohol per week (140–350 g/week and 210–420 g/week for females and males, respectively).

*One case is excluded because cirrhosis *vs*. non-cirrhosis status was not completed by local investigators.

†Cryptogenic plus BMI ≥25 kg/m^2 or diabetes mellitus.

‡HCC treatment includes curative and palliative therapies.

[IQR 30–77] mm *vs.* 30 IQR [21.8–48] mm; p <0.001), and were less frequently evaluated for LT (3.8% *vs.* 15.3%; p <0.001).

Characteristics of patients with HCC with liver cirrhosis

From a total of 560 patients with HCC and cirrhosis, advanced chronic liver disease was known before the diagnosis of HCC in 66.8% of the cases (n = 374), with 84% (n = 314) of these patients enrolled in a screening program. HCC was an incidental finding in 121 patients and was detected concurrently with the underlying liver disease in 65 patients.

Among patients with known cirrhosis not included in the screening program (n = 60), the predominant cause for non-inclusion was patient non-adherence (n = 45). Overall, only 56.1% of HCC cases were detected within the screening program, with the main reason for non-detection being unawareness of the underlying liver disease (Fig. 2).

Comparison or characteristics between patients with known and unknown liver disease are detailed in Table S3.

The screening program successfully detected early or very early-stage disease in 223 patients (71%), which was associated with better liver function (absence of ascites in 77.1% *vs.* 57.1%; p <0.001), and lower MELD score (median 9 [IQR 7–11] *vs.* 10 [IQR 8–14]; p <0.002). However, this did not correlate with lower BMI (p = 0.768). Table 5 presents the characteristics of patients with cirrhosis diagnosed both within and outside of screening programs. Statistically significant differences were found in etiology (higher alcohol-related cases in non-screened patients, p = 0.011), current alcohol and tobacco consumption (higher in non-screened patients, p <0.001 and p = 0.004, respectively), and level of liver disease at diagnosis. This included a higher proportion of decompensated patients at the time of presentation (p = 0.006), higher MELD scores (p = 0.014), more advanced tumor stages (p <0.001), higher AFP levels (p <0.001), less frequent indication for curative intention treatment (p <0.001), and less frequent evaluation for LT (p <0.001) in patients outside of screening programs. No significant differences were found in age (p = 0.247), sex (p = 0.088), BMI (p = 0.427), HIV coinfection (p = 0.994), presence of T2DM (p = 0.083), or presence of other tumors (p = 0.348) between the two patient groups.

Survival

After a mean follow-up of 15.4 months (95% CI: 14.7–16.0), the median survival has not yet been reached. A total of 35.8% of patients had died (30% owing to hepatic causes and 5.8% to non-hepatic causes), 42.4% in the non-screening group and 28.7% in the screening group (p <0.001 with survival being longer in those patients detected via the screening program (median overall survival of 14.3 [IQR 12–15.7] months *vs.* 13 [IQR 5.5–15.7] months; p <0.001). Regarding the causes of death, patients diagnosed with HCC outside of the screening program more frequently died because of hepatic causes (liver failure and/or tumor progression) compared with those within the screening program, who less frequently died and mainly did as a result of extrahepatic causes. These differences were statistically significant (p <0.001; Figs. S1 and S2).

Comparative analysis: first registry (2008–2009) and second registry (2014–2015) *vs.* third registry (2022–2023)

In this third registry, the number of participating centers has decreased, while the number of cases registered per center has increased. The characteristics from the three study periods of the registries were compared. For this purpose, only hospitals that participated in all three registries (n = 29) were included, with a total of 1,351 patients (first registry, n = 432; second registry, n = 427; third registry, n = 492), as shown in Table 6. Comparing the three time periods, differences in etiology were observed: alcohol continues to be the primary cause (29.7% in third registry *vs.* 34.7% in the second and 29.8% in the first), with a decrease in HCV (17.5% in the third *vs.* 28.7% in the second and 43% in the first) and an increase in LDrMS (24% in the third *vs.* 9% in the second and 4.9% in the first; p <0.0001). Furthermore, variations were noted in the underlying liver disease (p = 0.002), with a higher proportion of patients with livers

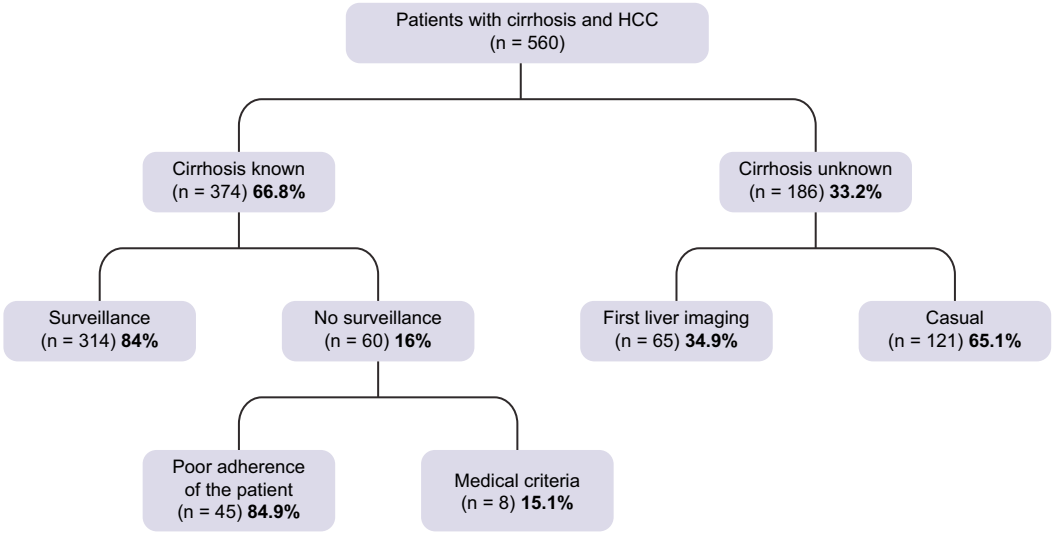

Fig. 2. Flow chart of HCC diagnosis in patients with cirrhosis (n = 560). CCA, cholangiocarcinoma; HCC, hepatocellular carcinoma; HCC-CCA, mixed hepatocellular carcinoma.

Table 5. Characteristics of patients with HCC and cirrhosis diagnosed both within and outside of screening programs (n = 560).

Variable	HCC (n = 560)	HCC diagnosed in surveillance (n = 314)	HCC diagnosed out of surveillance (n = 246)	*p* value
Age, median (IQR), years	66.5 (60–74)	67 (61–74)	66 (59–74)	0.247
Male sex, n (%)	468 (83.6)	255 (81.2)	213 (86.6)	0.088
Etiology, n (%)				
ALD	198 (35.4)	116 (36.9)	82 (33.3)	
LDrMS	114 (20.3)	53 (16.9)	61 (24.8)	
MASLD	45	21	24	0.001
MetALD	59	27	32	
Crypto*	10	5	5	
HCV	102 (18.2)	72 (22.9)	30 (12.2)	
ALD + HCV	72 (12.9)	30 (9.6)	42 (17.1)	
HBV	23 (4.1)	13 (4.1)	10 (4.1)	
Other	51 (9.1)	30 (9.6)	21 (8.5)	
Alcohol (alone or associated with other etiologies)	347 (62)	180 (57.3)	167 (67.9)	0.011
Ascites, n (%)				0.006
No	374 (66.8)	224 (71.3)	150 (61)	
I–II	163 (29.1)	83 (26.4)	80 (32.5)	
Refractory	23 (4.1)	7 (2.2)	16 (6.5)	
Encephalopathy, n (%)				0.062
No	511 (91.2)	284 (90.4)	227 (92.3)	
I–II	39 (7)	27 (8.6)	12 (4.9)	
III–IV	10 (1.8)	3 (1)	7 (2.8)	
Child-Pugh class, n (%) (n = 551)				0.007
A	371 (67.3)	222 (72.8)	149 (60.6)	
B	143 (26)	68 (22.3)	75 (30.5)	
C	37 (6.7)	15 (4.9)	22 (8.9)	
MELD, median (IQR) (n = 558)	9 (8-12.8)	9 (7-12)	10 (8-13)	0.014
Arterial hypertension, n (%)	292 (52.1)	164 (52.2)	128 (52)	0.963
Diabetes mellitus, n (%) (n = 559)	218 (39)	132 (42.2)	86 (35)	0.083
Dyslipidemia, n (%)	163 (29.1)	91 (29)	72 (29.3)	0.941
HIV, n (%) (n = 496)	17 (3)	9 (2.9)	8 (3.3)	0.966
BMI, n (%), kg/m^2 (n = 437)				0.427
<25	123 (28.1)	66 (26)	57 (31.1)	
25–30	181 (41.4)	106 (41.7)	75 (41)	
>30	133 (30.4)	82 (32.3)	51 (27.9)	
Active alcohol consumption, n (%)	160 (28.6)	57 (18.2)	103 (41.9)	<0.001
Active tobacco consumption, n (%) (n = 558)	376 (67.4)	195 (62.3)	181 (73.9)	0.004
Non-invasive diagnostic, n (%)	481 (85.9)	290 (92.4)	191 (77.6)	<0.001
AFP categorized, n (%), ng/ml (n = 535)				< 0.001
<20	315 (58.9)	196 (65.3)	119 (50.6)	
20–200	106 (19.8)	64 (21.3)	42 (17.9)	
200–400	14 (2.6)	4 (1.3)	10 (4.3)	
>400	100 (18.7)	36 (12)	64 (27.2)	
Tumor size, median (IQR), mm (n = 516)	30 (21.8–48)	26 (20–36)	40 (27–70)	<0.001
Vascular invasion, n (%)	116 (20.7)	37 (11.8)	79 (32.1)	<0.001
Extrahepatic spread, n (%) (n = 559)	55 (9.8)	8 (2.5)	47 (19.2)	<0.001
ECOG-PS, n (%) (n = 559)				<0.001
0	424 (75.8)	272 (86.9)	152 (61.8)	
1	64 (11.4)	23 (7.3)	41 (16.7)	
2	36 (6.4)	11 (3.5)	25 (10.2)	
3	30 (5.4)	7 (2.2)	23 (9.3)	
4	5 (0.9)	0 (0)	5 (2)	
BCLC stage, n (%)				<0.001
0	74 (13.2)	58 (18.5)	16 (6.5)	
A	238 (42.5)	165 (52.5)	73 (29.7)	
B	73 (13)	35 (11.1)	38 (15.4)	
C	106 (18.9)	37 (11.8)	69 (28)	
D	69 (12.3)	19 (6.1)	50 (20.3)	
Curative intention therapy†, n (%)	230 (41.2)	171 (54.6)	59 (24.1)	<0.001
Liver resection, n (%)	51 (9.4)	34 (11.4)	17 (7.1)	0.088
LT evaluation, n (%)	85 (15.5)	65 (21.5)	20 (8.2)	<0.001
Thermal ablation, n (%)	112 (20.7)	85 (28.2)	27 (11.2)	<0.001
TACE, n (%)	108 (19.9)	67 (22.2)	41 (17)	0.134
TARE, n (%)	25 (4.6)	15 (5)	10 (4.2)	0.653

(*continued on next page*)

Table 5. (*continued*)

Variable	HCC (n = 560)	HCC diagnosed in surveillance (n = 314)	HCC diagnosed out of surveillance (n = 246)	*p* value
Systemic therapy, n (%)	75 (13.8)	31 (10.3)	44 (18.2)	0.008
Symptomatic treatment, n (%)	136 (24.4)	44 (14.1)	92 (37.6)	<0.001

Level of significance p <0.05 (Pearson's X^2 test or Fisher's exact test in the case of categorical variables and the Mann–Whitney test in the case of quantitative variables).
AFP, alpha-fetoprotein; ALD, alcohol-related liver disease; BCLC, Barcelona Clinic Liver Cancer; BMI, body mass index; ECOG-PS, Eastern Cooperative Oncology Group-Performance Status; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C-related liver disease; HIV, human immunodeficiency virus; LDrMS, liver disease related to metabolic syndrome; LT, liver transplantation; MASLD, metabolic dysfunction-associated steatotic liver disease; MELD, model of end-stage liver disease; MetALD, MASLD who consume greater amounts of alcohol per week (140–350 g/week and 210–420 g/week for females and males, respectively); TACE, transarterial chemoembolization; TARE, transarterial radioembolization.
*Cryptogenic plus BMI >25 kg/m^2 or diabetes mellitus.
†Curative intention HCC therapy includes surgical resection, thermal ablation, and liver transplantation.

without significant fibrosis (7.9% in the third *vs.* 3.8% in the second and 4.2% in the first) and fewer patients with cirrhosis (79.5% in the third *vs.* 86.9% in the second and 88% in the first). Disparities were also observed in the proportion of patients with arterial hypertension (53.7% in the third *vs.* 45% in the second; p = 0.011), DL (30.5% in third *vs.* 13.1% in the second; p <0.001), T2DM (37.3% in the third *vs.* 38.9% in the second and 28.4% in the first; p = 0.002), BMI >25 (69.1% in the third *vs.* 70.1% in the second *vs.* 57.7% in the first; p <0.001), and obesity (32.2% in the second *vs.* 28.1% in the third and 16.3% in the first; p <0.001); as well as the presence of extrahepatic tumors (15.3% in the third *vs.* 16.4% in the second and 9.3% in the first; p = 0.005), evaluation for LT (13.4% in the third *vs.* 11.9% in the second and 24.9% in the first; p <0.001), and the delivery of radical treatment (40.4% in the third *vs.* 46.9% in the second and 47.9% in the first; p = 0.047). Notably, there has been no variation in the rate of HCC detected by screening (p = 0.933).

Discussion

Liver tumors were the sixth leading cause of death in Spain in 2021 (after lung, colon, pancreas, breast and prostate tumors), with incidence data sourced from the Spanish Network of Cancer Registries,[9] which covers 27% of the population across 16 regions. This number is part of the Global Cancer Incidence in Five Continents report by the International Agency for Research of Cancer.[11] Recognizing the importance of comprehensive data, the AEEH initiated a national liver tumor registry in 2008, which was updated in 2014 and recently in 2022, to collect epidemiological data, including etiology and BCLC tumor stage. Despite known modifiable risk factors such as alcohol, obesity, and viral infections, and the benefit of early-stage detection through screening for effective treatment,[12–14] there still is a lack of emphasis by health authorities on improving screening program detection and participation.[15]

The diagnosis of HCC was made through screening in 48.5% of cases, similar to that reported in previous registries (48.3% in the first and 47.3% in the second). Specifically, in the cohort of patients with cirrhosis in the third registry, 56.1% of patients with HCC were diagnosed within the screening program, which increased to 59.1% in patients with cirrhosis aged under 75 years with Child B <7 points. Globally, data indicate that only about a quarter of patients at risk for HCC are enrolled in a surveillance program,[16–18] with numbers varying by region: 17.8% in the USA and 43.2% in Europe.

The main reason behind a diagnosis outside the screening program is a lack of awareness of the underlying liver disease, mainly in patients with active alcohol and tobacco usage and alcohol-related cirrhosis. Conversely, for patients with known cirrhosis before HCC diagnosis, over 84% of HCCs are detected via screening, and more than 65% were diagnosed at an early/very early stage, increasing the likelihood of receiving radical therapies. Diagnosis outside of the screening program is linked to more advanced tumors and fewer treatments with curative intent, including a higher proportion of males and non-abstinent individuals.[19] Despite the brief follow-up, our study confirms that the mean overall survival is lower in patients with HCC outside of screening programs because of a higher rate of hepatic-related death.

A shift in etiology has been noted across the three registries over these 14 years: a substantial decrease in HCV, from 43% in 2008 to 17.5% in 2022, primarily owing to significant efforts in hepatitis C eradication through the national Spanish plan.[20] The incidence of LDrMS has increased from 4.9% in 2008 to 24% in 2022, notably in non-cirrhotic livers, predominantly affecting older patients, and associated with larger tumor sizes. This may be attributed to a growing recognition of metabolic factors in advancing chronic liver disease.[21–23] Approximately one-third of HCC cases linked to LDrMS arise in non-cirrhotic livers.[24,25] Given that over a quarter of the worldwide adult population is affected by MASLD, pinpointing individuals without cirrhosis at elevated risk for HCC remains crucial for their inclusion in surveillance programs.[26,27] The majority of patients with HCC present with one or more factors of metabolic syndrome. This recent change in terminology[28] regarding the role of the metabolic syndrome in chronic liver disease will facilitate an accurate assessment of the impact of metabolic dysfunction on liver cancer etiology in future registries.

This etiological change aligns with GLOBOCAN data, where alcohol and MASLD were the growing causes of mortality in 2010–2019, while mortality attributable to viral liver disease (HCV and HBV) decreased, mainly because of novel HCV treatments[29–31] and the rise in obesity and T2DM.[32] In Spain, 23.8% of the population suffers from obesity,[33] and the prevalence of T2DM is 14.8%,[34] the second-highest rate in Europe.

Unlike viral diseases such as HCV or HBV, which possess specific serological markers, the identification and follow-up of patients with alcohol use disorder or MASLD require a more deliberate approach, including targeted screening in primary care,[35] endocrinology, and cardiology for MASLD. This is crucial particularly when patients exhibit advanced fibrosis. To address this, the AEEH has endorsed a consensus in our country outlining detection and referral strategies for hidden liver diseases, including MASLD and alcohol-related liver disease.[36,37]

Table 6. Comparative analysis between the three registries (2008–2009) *vs.* (2014–2015) *vs.* (2022–2023) (n = 1,351).

Variable	2008–2009 (n = 432)	2014–2015 (n = 427)	2022–2023 (n = 492)	*p* value
Age, median (IQR), years (n = 1,342)	66.1 (55.4–74.7)	65.4 (57.1–73.7)	67 (61–75)	0.003
Male sex, n (%) (n = 1,349)	337 (78)	346 (81.4)	417 (84.8)	0.031
Underlying liver, n (%) (n = 1,345)				0.002
Non-significant fibrosis	18 (4.2)	16 (3.8)	39 (7.9)	
F2–F3	34 (7.8)	39 (9.3)	62 (12.6)	
Cirrhosis	380 (88)	366 (86.9)	391 (79.5)	
Etiology, n, (%) (n = 1,342)				<0.001
ALD	128 (29.8)	146 (34.7)	146 (29.7)	
HCV	185 (43)	121 (28.7)	86 (17.5)	
ALD + HCV	35 (8.1)	59 (14)	53 (10.8)	
HBV	22 (5.1)	19 (4.5)	28 (5.7)	
LDrMS	21 (4.9)	38 (9)	118 (24)	
Other	39 (9.1)	38 (9)	61 (12.3)	
Ascites, n (%) (n = 1,133)				0.497
No	261 (69.4)	243 (66.4)	257 (65.7)	
I-II	95 (25.3)	104 (28.4)	119 (30.4)	
Refractory	20 (5.3)	19 (5.2)	15 (3.8)	
Encephalopathy, n (%) (n = 1,136)				0.103
No	357 (94.2)	325 (88.8)	356 (91)	
I-II	19 (5)	37 (10.1)	30 (7.7)	
III–IV	3 (0.8)	4 (1.1)	5 (1.3)	
Child-Pugh class, n (%) (n = 948)				0.496
A	138 (62.2)	206 (59.9)	253 (66.2)	
B	68 (30.6)	109 (31.7)	104 (27.2)	
C	16 (7.2)	29 (8.4)	25 (6.5)	
Another primary tumor, n (%) (n = 1,340)	40 (9.3)	69 (16.4)	75 (15.3)	0.005
Arterial hypertension, n (%) (n = 912)	NA	189 (45)	264 (53.7)	0.011
Diabetes mellitus, n (%) (n = 1,333)	120 (28.4)	163 (38.9)	183 (37.3)	0.002
Dyslipidemia, n (%) (n = 910)	NA	55 (13.1)	150 (30.5)	<0.001
HIV, n (%) (n = 1,239)	14 (3.4)	9 (2.4)	15 (3.4)	0.625
BMI, n (%), kg/m^2 (n = 919)				<0.001
<25	111 (42.2)	78 (29.9)	122 (30.9)	
25–30	109 (41.4)	99 (37.9)	162 (41)	
>30	43 (16.3)	84 (32.2)	111 (28.1)	
Active alcohol consumption, n (%) (n = 911)	NA	125 (29.8)	136 (27.7)	0.540
Active tobacco consumption, n (%) (n = 908)	NA	251 (60)	325 (54)	0.059
Non-invasive diagnostic, n (%)	340 (78.7)	322 (76.7)	369 (75)	0.413
AFP categorized, n (%), ng/ml (n = 1,267)				0.569
<20	241 (57.4)	236 (61.8)	277 (59.6)	
20–200	88 (21)	69 (18.1)	79 (17)	
200–400	18 (4.3)	15 (3.9)	16 (3.4)	
>400	73 (17.3)	62 (16.2)	93 (20)	
Tumor size, median (IQR), mm (n = 1,347)	34 (25–56)	30 (22–49)	32 (22–55)	0.186
Vascular invasion, n (%) (n = 1,331)	61 (14.5)	84 (20)	114 (23.2)	0.004
Extrahepatic spread, n (%) (n = 1,315)	44 (10.7)	37 (9)	53 (10.8)	0.618
BCLC stage, n (%) (n = 1,338)				0.010
0	36 (8.4)	44 (10.5)	60 (12.2)	
A	179 (41.8)	183 (43.8)	217 (44.1)	
B	87 (20.3)	76 (18.2)	54 (11)	
C	81 (18.9)	75 (17.9)	111 (22.6)	
D	45 (10.5)	40 (9.6)	50 (10.1)	
Detection method, n (%) (n = 1,343)				0.933
Surveillance program	208 (48.3)	199 (47.3)	238 (48.5)	
First imaging	NA	36 (8.6)	51 (10.4)	
Casual finding	223 (51.7)	121 (28.7)	156 (31.8)	
Cirrhosis without follow-up	NA	65 (15.4)	46 (9.3)	
Curative intention therapy*, n (%) (n = 1,342)	197 (47.9)	186 (46.9)	198 (40.4)	0.047
Evaluation for liver transplantation, n (%) (n = 1,314)	102 (24.9)	51 (11.9)	64 (13.4)	<0.001

Level of significance p <0.05 (Pearson's X^2 test or Fisher's exact test in the case of categorical variables and the Kruskal–Wallis test in the case of quantitative variables).
AFP, alpha-fetoprotein; ALD, alcohol-related liver disease; BCLC: Barcelona Clinic Liver Cancer; BMI, body mass index; F2, METAVIR stage F2 fibrosis; F3, METAVIR stage F3 fibrosis; HBV, hepatitis B-related liver disease; HCV, hepatitis C-related liver disease; HIV, human immunodeficiency virus; LDrMS, liver disease related to metabolic syndrome; NA, not available.
*Curative intention therapy includes surgical resection, thermal ablation, and liver transplantation.

Regrettably, neither steatosis nor some other components characterizing the current definition of MASLD were recorded in the three registries, thus the metabolic etiology (be it NAFLD or MASLD) was directly attributed by the authors of the three registries. Dyson *et al.*[38] have assessed the impact of obesity and T2DM in a cohort of patients with HCC managed in Newcastle from 2000 to 2010. They observed that NAFLD-related HCC experienced a more than 10-fold increase by

2010, reaching 34.8%, with a prevalence of 66.1% of metabolic risk factors, associated with regional increases in obesity and T2DM. Vitale *et al.*[39] have assessed the prevalence of metabolic-associated fatty liver disease (MAFLD) within the ITALICA registry from 2002 to 2019. According to their findings, MAFLD-related HCC has markedly increased from 50.4% in 2002–2003 to 77% in 2018–2019. In addition, they established that single-etiology MAFLD exhibited advanced fibrosis/cirrhosis in 90% of cases.

The strengths of our work are firstly, the high number of participating centers, all of which are reference centers for liver cancer treatment in Spain with extensive geographic distribution; secondly, the significant number of centers that have engaged in all three registries, providing over 1,300 patients to assess HCC epidemiological shifts over these 14 years. The third strength of our study is the demonstration that there are no pure etiologies of HCC as the majority of patients with either alcohol or viral etiology also exhibit one or more components of metabolic syndrome.[40]

The primary weakness of our study is the short follow-up and lack of direct data monitoring. The second weakness of our study is that this is not a nationwide registry but rather a voluntary participation of academic centers in a scientific society setting. Therefore, despite acknowledging its merits, there could be a selection bias. The third weakness identified is the lack of consistent recording of steatosis and other components characterizing the current definition of MASLD across the three registries. As a result, the metabolic etiology may have been underestimated in the first and second registries; however, the 'liver disease related to metabolic syndrome' definition provides a framework that could help in clarifying this aspect.

Although this study focuses on the epidemiological shifts of HCC over the past 14 years in our country, it is posited that the findings may be applicable to the Western context, in light of the progressively homogenized customs and lifestyle practices on a global scale.

There is a pressing need to improve HCC diagnosis through screening programs by improving at-risk patient detection and retention in the system, offering more patient information and motivation. National campaigns promoted by health authorities, similar to those for colon, breast, or cervical cancer, could help achieve better adherence or inclusion in screening programs for at-risk individuals. There is a crucial need for close collaboration between health policymakers and primary care physicians, and a need to increase societal awareness to spotlight the significant issue of unrecognized advanced chronic liver disease.

In conclusion, the results of this prospective multicenter third registry reflect the evolving epidemiology of HCC in Spain. These findings provide valuable insights to guide policies aimed at enhancing prevention, early detection, and ultimately improving survival rates, with a particular focus on alcohol-related and MASLD-related HCC.

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Abbreviations

AEEH, Spanish Association for the Study of the Liver; AFP, alpha-fetoprotein; ALD, alcoholic liver disease; BCLC, Barcelona Clinic Liver Cancer; Ca 19.9, cancer antigen 19.9; CCA, cholangiocarcinoma; DL, dyslipidemia; ECOG-PS, Eastern Cooperative Oncology Group-Performance Status; HCC, hepatocellular carcinoma; INR, international normalized ratio; LDrMS, liver disease related to metabolic syndrome; LT, liver transplantation; MAFLD, metabolic-associated fatty liver disease; MASLD, metabolic-associated liver disease; MELD, Model for End-Stage Liver Disease; MetALD, metabolic dysfunction-associated steatotic liver disease patients who consume greater amounts of alcohol per week; MWA, microwave ablation; NAFLD, non-alcoholic fatty liver disease; PEI, percutaneous ethanol injecton; RFA, radiofrequency ablation; SBRT: stereotactic body radiotherapy; SVR, sustained virological response; T2DM, type 2 diabetes mellitus; TACE, transarterial chemoembolization; TARE, transarterial radioembolization.

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Conflicts of interest

MS: travel expenses and congress registrations Roche, Astra-Zeneca; SP: conferences for Roche, Astra-Zeneca, consultant for Astra-Zeneca, Roche, travel expenses and congress registrations Roche; AM: conferences for EISAI-MSD, Roche, Boston, Sirtex, consultant for Roche, EISAI-MSD; MC: consultant for Roche; MTF: Gilead (Grant), conferences for Gilead, EISAI, consultant for EISAI, travel expenses and congress registrations Gilead, Roche, EISAI; JLM: consultant for Roche, EISAI, Advance, Gilead, Abbvie; AGue: conferences for Roche, Astra-Zeneca, travel expenses and congress registrations Roche; BM: Laboratorios Viñas (Grant), conferences for Merck-EISAI, Roche, Astra-Zeneca, consultant for Merck-EISAI, Roche, Astra-Zeneca, travel expenses and congress registrations Astra-Zeneca, Roche, Merck-EISAI; LC-G: conferences for Roche, EISAI, consultant for EISAI, travel expenses and congress registrations EISAI, Gilead, Chiesi; NV-S: travel expenses and congress registrations Gilead; AC: travel expenses and congress registrations Astra-Zeneca; CP: conferences for Roche; JJUP: conferences for EISAI, Gilead, Roche, travel expenses and congress registrations Roche, Gilead, Abbvie; CJL-T: conferences for EISAI, MSD, Roche, travel expenses and congress registrations EISAI, MSD, Roche; SM: travel expenses and congress registrations Roche, EISAI; AGui: conferences for EISAI, Roche; MV: conferences for EISAI, Roche, consultant for Astra-Zeneca, travel expenses and congress registrations Roche, Gilead; AMF-L: Gilead, Abbvie, Roche, Astra-Zeneca (Grants), conferences for Abbvie, travel expenses and congress registrations Gilead, Abbvie, Roche, Astra-Zeneca, Salvat; TH-A: travel expenses and congress registrations Roche, Astra-Zeneca; SC travel expenses and congress registrations Roche; SR: Abbvie, Gilead, EISAI, Roche (Grants), conferences for Gilead, travel expenses and congress registrations Gilead, Abbvie, ESAI, Roche, SESCAM; GP: travel expenses and congress registrations Roche; RR: travel expenses and congress registrations Roche; PCG: travel expenses and congress registrations Roche; MLB: travel expenses and congress registrations Norgine; MG-R: conferences for EISAI, Merck, travel expenses and congress registrations Roche, EISAI, Merck; MR: Bayer, IPSEN (Grants), conferences for Astra-Zeneca, Bayer, BMS, Eli Lilly, Gilead, Roche, Biotoscana Farma, consultant for Astra-Zeneca, Bayer, MSD, Eli Lilly, Geneos, IPSEN, Merck, Roche, Universal DX, Boston, Engitix Therapeutics, Parabilis Medicines, travel expenses and congress registrations Astra-Zeneca, Roche, Bayer, BMS, Lilly, Ipsen; ÁG: travel expenses and congress registrations EISAI; JLL: conferences for Roche, Astra-Zeneca, EISAI, consultant for Roche, Astra-Zeneca and EISAI, travel expenses and congress registrations Roche; AL: conferences for Astra-Zeneca, Advanz Pharma, EISAI, Roche, travel expenses and congress registrations Roche; Manuel Rodríguez conferences for Gilead, travel expenses and congress registrations Gilead, Abbvie; MV: conferences for Boston, Roche, Astra-Zeneca, consultant for Astra-Zeneca, Roche, Boston, travel expenses and congress registration Astra-Zeneca, Roche.

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Authors' contributions

Study design: MV. Supervision: MV. Data provision: all authors apart from MV. Data acquisition: MS, MV. Data analysis and interpretation: MS, MV, VCh. Writing draft preparation: MS. Writing: MV. Critical revision of the manuscript: all authors. Approval of the final version of the manuscript: all authors.

Data availability statement

Registry data will be available to researchers on request.

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During the preparation of this work the author(s) used Liver AI to ensure adherence to British English standards and the guidelines of the journal. After using this tool/service, the author(s) reviewed and edited the content as needed and take(s) full responsibility for the content of the publication.

Supplementary data

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