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Title:
Hepatocellular carcinoma in non-cirrhotic liver: a prospective Spanish multicenter study

Authors:
Marta Romero Gutiérrez, Sonia Pascual, Mariano Gómez-Rubio, Carles Aracil, Laura Márquez, Belén Piqueras, Vanesa Bernal-Monterde, Teresa Ferrer, Mireia Miquel, Cristina Fernández, Jesús Manuel González-Santiago, Diana Horta, Cristina Alarcón, Ana Martín, Raquel Latorre, María Luisa Gutiérrez, Paloma Rendón, Sonia Blanco-Sampascual, Milagros Testillano, Manuel Hernández-Guerra, Marta Tejedor, Carolina Delgado, Ana Matilla, Rafael Gómez Rodríguez

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Hepatocellular carcinoma in non-cirrhotic liver: a prospective Spanish multicenter study.

Study population & Outcomes

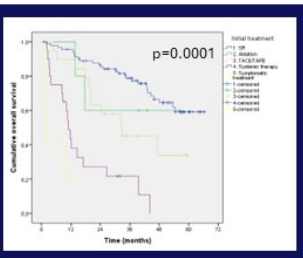
- **Prospective Spanish multicenter study.**
- Inclusion period: May 2018 – October 2022.
- Follow-up until September 2023.

- **HCC diagnosed by cito-histology (n=141 patients).**
- **Liver cirrhosis was excluded by histology** (86.5%), **transient elastography** (7.1%) **or level 2 Mittal criteria** (6.4%).

- ✓ A specific lifestyle questionnaire.
- ✓ We analyzed all study cohort, surgically treated patients and patients treated with systemic therapy.
- ✓ Patients´ baseline characteristics, tumor features and predictors of recurrence and mortality.

Results

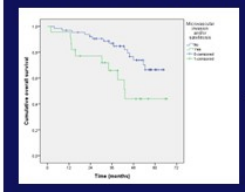
Epidemiological characteristics (n=141)	
Age (median and IQR) years	70 (63 – 77)
Male	85.1%
Healthy liver	22.7%
Underlying liver disease:	77.3%
- MASLD+MetALD	27.6%
- HCV +/- alcohol	16.3%
- HBV	8.5%
- Alcohol	13.5%
- Others	7.1%
- Unknown	4.3%
Other cancers	29.1%
Fibrosis stage:	
- F 0-1	53.2%
- F 2	17%
- F 3	16.3%
- Unknown	13.5%
PAGE B score (low risk group)	0
aMAP score (low risk group)	8.5%
BCLC stage:	
- 0-A	70.2%
- B	17.7%
- C	11.3%
- D	0.7%



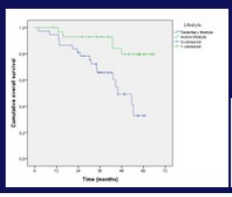
Survival according to initial treatment (median; months):

- Surgical resection and ablation: not assessable.
- TACE/TARE: 32.8 (95% CI: 10.5-55.3).
- Systemic therapy: 10 (95% CI: 6-14).
- Best supportive care: 1.4 (95% CI: 0.6-2.3).

Surgically treated patients (n=90): SURVIVAL. Independent predictors of mortality.



mVI/S [HR: 3.03 (1.18–7.75), p=0.021].



Active lifestyle [HR: 0.27 (0.09–0.8), p=0.018].

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Hepatocellular carcinoma in non-cirrhotic liver: a prospective Spanish multicenter study

Marta Romero-Gutiérrez[1,2], Sonia Pascual[3,4], Mariano Gómez-Rubio[5], Carles Aracil[6], Laura Márquez[7], Belén Piqueras[8], Vanesa Bernal-Monterde[9], Teresa Ferrer[10], Mireia Miquel[11], Cristina Fernández[12], Jesús Manuel González-Santiago[13], Diana Horta[14], Cristina Alarcón[15], Ana Martín[16], Raquel Latorre[17], María Luisa Gutiérrez[18], Paloma Rendón[19], Sonia Blanco-Sampascual[20], Milagros Testillano[21], Manuel Hernández-Guerra[22], Marta Tejedor[23,24], Carolina Delgado[1], Ana Matilla[2,7], Rafael Gómez[1].

1 Complejo Hospitalario Universitario de Toledo, Hepatology Department, Toledo, Spain. 2 Faculty of Medicine, University of Castilla-La Mancha (UCLM), Toledo, Spain. 3 Hospital Universitario Doctor Balmis, Hepatology Department. Instituto de Investigación Sanitaria y Biomédica de Alicante (ISABAL), Alicante, Spain. 4 Centro de Investigación Biomédica en Red Enfermedades Hepáticas y Digestivas (CIBERehd), Madrid, Spain. 5 Hospital Universitario de Getafe. Faculty of Medicine, Health and Sports, Universidad Europea (UE), Madrid, Spain. 6 Hospital Universitario Arnau de Vilanova, Lleida, Spain. 7 Hospital General Universitario Gregorio Marañón, Hepatology Department, Madrid, Spain. 8 Hospital Universitario de Fuenlabrada, Hepatology Department, Madrid, Spain. 9 Hospital Universitario Miguel Servet. Adipofat-lab. IISA. Zaragoza, Spain. 10 Hospital Universitario Virgen del Rocío, Sevilla, Spain. 11 Hospital Universitario Parc Taulí, Hepatology Department. Instituto de Investigación e Innovación Parc Taulí (I3PT-CERCA). Universidad Autónoma de Barcelona (UAB), CIBERehd. Departamento de Medicina. Universitat de Vic-Universitat Central de Catalunya (UVic-UCC), Sabadell, Spain. 12 Hospital Universitario de Burgos, Burgos, Spain. 13 Complejo Asistencial Universitario de Salamanca, Laboratorio de Hepatología Experimental y Vectorización de Fármacos (HEVEPHARM), Instituto de Investigación Biomédica de Salamanca (IBSAL), Salamanca, Spain 14 Hospital Universitario Mútua de Terrassa, Barcelona, Spain. 15 Hospital General de Villalba, Madrid, Spain. 16 Hospital Universitario Doce de Octubre, Hepatology Department, Madrid, Spain. 17 Hospital

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Universitario Son Llàtzer, Palma de Mallorca, Spain. 18 Hospital Universitario Fundación de Alcorcón, Madrid, Spain. 19 Hospital Universitario Puerta del Mar, Cádiz, Spain. 20 Hospital Universitario Basurto, OSI, Bilbao Basurto, Spain. 21 Hospital Universitario de Cruces, Vizcaya, Spain. 22 Hospital Universitario de Canarias, La Laguna, Santa Cruz de Tenerife, Spain. 23 Hospital Universitario Infanta Elena. Department of Gastroenterology and Hepatology, Madrid, Spain. 24 Department of Internal Medicine, Gastroenterology and Hepatology, University of Iowa, Iowa City, Iowa, USA.

Corresponding author:

Marta Romero-Gutiérrez, M.D., Ph.D. Mail: m.romero.gutierrez@gmail.com. Hospital Universitario de Toledo. Av. del Río Guadiana, 45007 Toledo (Spain). Telephone number: 0034 925269200 - Ext 44295 ORCID: 0000-0002-2052-1466

Co-authors details:

Sonia Pascual. Mail: pascualbar.son@gmail.com ORCID: 0000-0002-4265-5019

Mariano Gómez-Rubio. Mail: mgomezr6@gmail.com ORCID: 0009-0008-8124-0706

Carles Aracil. Mail: carbla34@gmail.com ORCID: 0000-0002-8228-9041

Laura Márquez. Mail: laura.mqz.perez@gmail.com ORCID: 0000-0003-2582-9870

Belén Piqueras. Mail: bpiqueras.hflr@salud.madrid.org

Vanesa Bernal. Mail: vbernalm@gmail.com ORCID: 0000-0002-4016-2165

Teresa Ferrer. Mail: mteferrer@gmail.com ORCID: 0000-0003-3453-4038

Mireia Miquel. Mail: mmiquelp@yahoo.es ORCID: 0000-0003-4566-4962

Cristina Fernández. Mail: krisfemar@hotmail.com ORCID: 0000-0002-5191-0413

Jesús González. Mail: jmgonzalezsantiago@gmail.com ORCID: 0000-0003-4667-4492

Diana Horta. Mail: diana.horta.s@gmail.com ORCID: 0000-0002-3675-1135

Cristina Alarcón. Mail: crisalarcondelamo@hotmail.com ORCID: 0009-0003-0872-9904

Ana Martín. Mail: analgibez@gmail.com ORCID: 0000-0003-0670-8459

Raquel Latorre. Mail: raquel.latorre.martinez@gmail.com

María Luisa Gutiérrez. Mail: mlgutgar@gmail.com

Paloma Rendón. Mail: prendonu@gmail.com ORCID: 0000-0002-6521-3766

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Sonia Blanco. Mail: SONIA.BLANCOSAMPASCUAL@osakidetza.eus

Milagros Testillano. Mail: mtestillano@gmail.com

Manuel Hernández-Guerra. Mail: mhernand@ull.edu.es ORCID: 0000-0002-3478-9981

Marta Tejedor. Mail: marta-tejedorbravo@uiowa.edu ORCID: 0000-0001-7563-1294

Carolina Delgado. Mail: cdelgadom91@gmail.com ORCID: 0000-0002-0808-4494

Ana Matilla. Mail: anamatillapena@gmail.com ORCID: 0000-0002-6586-2440

Rafael Gómez Rodríguez. Mail: ra.gomez.rodriguez@gmail.com ORCID: 0009-0005-3006-2522

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A list of abbreviations in the order of appearance:

Non-cirrhotic (NC), hepatocellular carcinoma (HCC) metabolic dysfunction–associated steatotic liver disease (MASLD), hepatitis B virus (HBV), surgical resection (SR), microvascular invasion (mVI), satellite nodules (S), overall survival (OS), recurrence free survival (RFS), liver transplantation (LT), systemic therapy (ST), transient elastography (TE), MetALD: MASLD and increased alcohol intake, ALD: alcohol associated liver disease alpha-fetoprotein (AFP), Barcelona Clinic Liver Cancer (BCLC), transarterial chemoembolization (TACE), transarterial radioembolization (TARE), transarterial embolization (TAE), high-risk characteristics (HRC), sorafenib (SOR), lenvatinib (LEN), atezolizumab plus bevacizumab (AB), tyrosine kinase inhibitor (TKI), adverse events (AE).

Lay summary:

- Understanding real-world clinical practice in non-cirrhotic patients is essential.
- We prospectively included 141 patients diagnosed with hepatocellular carcinoma based on cyto-histology, in whom liver cirrhosis was ruled out

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through biopsy, FibroScan® or a combination of laboratory and imaging criteria.

- Our results show that most patients were diagnosed at an early stage, with single but relatively large lesions. Surgical resection was the main treatment, and although recurrence was frequent, many patients were able to undergo further curative treatment.
- In patients who underwent surgery, the presence of mVI/S and a sedentary lifestyle were linked to a higher risk of mortality, highlighting the importance of exploring *ab initio* liver transplantation and lifestyle interventions in the management of NC-HCC.
- Survival in patients treated with systemic therapy was in line with clinical trial results, and the safety profile seemed a bit more favorable.

ABSTRACT

Background and Aims: Prospective data on non-cirrhotic hepatocellular carcinoma (NC-HCC) are scarce, mainly in Western countries. Characteristics, evolution, prognostic factors and outcomes were analyzed.

Method: One hundred and forty-one NC-HCC diagnosed by histology were included in a Spanish multicenter prospective registry (2018–2023) involving 23 centers. Liver cirrhosis was excluded by histology, transient elastography or level 2 Mittal criteria.

Results: Underlying chronic liver disease was present in 77% of patients, mainly MASLD/MetALD and viral. Using the aMAP risk score less than 10% of patients were classified in the low-risk group. Fibrosis stage was 0-1 in 53%. A single nodule was detected in 75%. The BCLC stage was 0 in 6.5%, A in 63.8%, B in 17.7%, C in 11.3% and D in 0.7%. Initial treatment was surgical resection in 63.9%, ablation in 4.2%, TACE/TARE in 13.5%, systemic therapy in 14.9%, and symptomatic treatment in 3.5%. Median follow-up was 34.1 (IQR: 15.5–49.5) months. Median overall survival was 47.9 months (95% CI: not assessable), and global 1-, 3- and 5-year survival rate were 85%, 62.4% and 49.1%, respectively. AFP level (<20/≥20ng/ml) [HR: 2.63 (1.3–5.3), p=0.007] was an independent predictor of survival.

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In surgically treated patients, the 5-year recurrence rate and 5-year survival rate were 55.1% and 59.1%, respectively. Active lifestyle (HR 0.27 [95% CI: 0.09–0.8]) and microvascular invasion and/or satellite nodules (HR 3.03 [95% CI: 1.18–7.75]) were independent predictors of mortality.

Conclusions: Despite the lack of routine screening, most patients with NC-HCC were diagnosed at early stages and treated with surgery. The main underlying etiology was MASLD/MetALD and a sedentary lifestyle was associated with mortality, so interventions to improve this aspect are essential.

Keywords: Hepatocellular carcinoma. MASLD. BCLC staging. Surgical resection. Lifestyle, Systemic therapy.

INTRODUCTION

Hepatocellular carcinoma (HCC) occurs mostly in patients with liver cirrhosis[1,2], in whom screening is recommended in clinical guidelines[1-3]. Screening in selected non-cirrhotic (NC) patients is an emerging trend, prompted by increased risk in those with metabolic dysfunction–associated steatotic liver disease (MASLD)-related or hepatitis B virus (HBV)-related liver disease[1,2,4-7], and by the global rise in MASLD prevalence[4,7].

Surgical resection (SR) is the main HCC treatment in NC patients due to the possibility of more extensive hepatectomies[1-3,8,9]. Generally, SR achieves good results in selected patients with a 5-year survival rate of 51-60%[10-12], but 5-year recurrence rate is high at 40-60%[11-13]. Microvascular invasion (mVI) and satellite nodules (S)[14,15] are the main factors associated with recurrence[9,10,13,16,17].

Most historical reports find that NC-HCC were predominantly solitary (80-81%) with a median size of 6.5–9.3 cm[9,18] and those patients had better overall survival (OS) compared to cirrhotic HCC[11,18-20]. However, two recent studies, among the patients who underwent surgery, did not find significant differences for recurrence free survival (RFS) and OS[9,21].

There is scarce information on the therapeutic possibilities and outcomes of these patients. Previous studies are retrospective and mainly consist of surgical series. Moreover, strategies such as *ab initio* liver transplantation (LT) in patients with high-risk of aggressive recurrence[16] or the efficacy and safety of systemic therapy (ST) have not been studied in NC-HCC patients specifically.

MATERIAL AND METHODS

Patient cohort and study design: We performed a prospective Spanish multicenter study in NC patients with HCC diagnosed by cyto-histology, in accordance with international consensus diagnostic criteria[1-3], involving 23centers. The inclusion period was May 2018–October 2022. The patients were enrolled consecutively with the aim of obtaining a representative sample of our country and censored at death, last medical contact or end of follow up until September 2023. Liver cirrhosis was excluded by histology, according to METAVIR score[22]; by transient elastography (TE) (FibroScan®, Echosens, Paris, France), using a cut-off value of <9kPa to exclude advanced fibrosis/cirrhosis in chronic liver disease due to HBV and <10 kPa in other etiologies[23]; or by level 2 Mittal criteria, which include laboratory and abdominal imaging data[18,24]. Interim analyses were conducted periodically to monitor data quality and recruitment progress. During follow-up, data were successfully retained for most included patients — only 6 patients were lost to follow-up. Figure 1.

Etiological study of underlying liver disease was conducted[25-27]. A liver without fibrosis (fibrosis 0) and no underlying liver disease was considered a healthy liver.

At diagnosis, patients were asked to complete a lifestyle questionnaire assessing smoking, coffee and tea intake, physical activity level (classified as sedentary or active, with “active” defined as walking at least 3 times per week for a minimum of 30 minutes at an intensity higher than normal walking), dietary habits (processed meat and fruit/vegetable intake), and residential history (rural vs. urban). Completion was done independently or with physician assistance (n=95/141 all group, n= 67/90 surgical group).

Surveillance risk scores were calculated: aMAP in all patients[28], and PAGE-B in patients with HBV patients[5,6].

HCC was diagnosed either through follow-up ultrasonography at non-fixed intervals or incidentally, via imaging for unrelated reasons or symptoms.

Therapeutic strategies were individualized following guidelines recommendations[1-3]. The selection of ST depended on the therapeutic options available during the study period, influenced by national funding policies in Spain.

Outcomes: We analyzed patients´ baseline characteristics to identify potential risk factor, tumor features, and predictors of survival and recurrence. Covariates included in the multivariate model were selected based on clinical relevance and statistical significance in univariate analysis ($p < 0.05$). To avoid collinearity, variables that were closely related—such as BCLC stage and ECOG—were not included in the same multivariate model.

In surgically treated patients, surgical technique, complications (Clavien-Dindo classification[29]) and surgical pathology of HCC[30], included mVI/S[14-16] were described. Biopsies were examined by an expert pathologist at each center.

In patients treated by ST we reviewed safety profile and survival benefit.

Ethical considerations: The study was performed in accordance with the Declaration of Helsinki, as reflected in a priori approval by the Clinical Research Ethics Committee of Toledo (CEIM HUT/2018/261).

Statistical analysis: Quantitative variables were summarized as median (IQR), and qualitative variables as counts and percentages. Survival and recurrence were analyzed using Kaplan-Meier curves with medians and 95% CIs; group differences were assessed with the log-rank test. Cox regression was used to estimate HRs and 95% CIs for factors associated with OS and recurrence. All tests were two-sided, with $p < 0.05$ considered significant. Analyses were performed using IBM SPSS Statistics v22.0 (IBM Corp., Armonk, NY).

RESULTS

One hundred and forty-one patients with NC-HCC were included. Liver cirrhosis was excluded by histology in 86.5%, TE in 7.1% and level 2 Mittal criteria in 6.4%.

Patients´ baseline characteristics.

Among all HCC patients in the study cohort, median age was 70 years, 85.1% were male, 37.6% had diabetes and 29.1% had other cancers.

An underlying liver disease was identified in 77.3% of patients: 27.6% MASLD/MASLD and increased alcohol intake (MetALD), 25.5% viral markers (17% HCV, 8.5% HBV) with/without alcohol associated liver disease (ALD), 13.5% ALD only, 4.3% hereditary hemochromatosis, 2.1% other causes, and 4.3% unknown. Eighty-one percent of viral hepatitis cases were untreated before HCC diagnosis. The aMAP score classified 8.5% as low risk. Fibrosis stage was 0-1 in 53.2%, 2 in 17%, 3 in 16.3%, and unknown in 13.5%. Table 1.

Tumor features.

<u>All study cohort (n=141).</u>

In 19.9% the diagnosis was made by follow-up ultrasonography, 56% was incidental and 24.1% by symptoms.

A single nodule was detected in 75.2%. The median size of the main nodule was 59 (IQR 32.5 – 87) mm. Only 9.2% had macrovascular invasion and 2.8% had extrahepatic spread. The differentiation degree was: 32.6% well-differentiated, 53.9% moderately differentiated, 7.1% poorly differentiated, 1.4% undifferentiated, and 5% other histologic variants. Only 26.9% had alpha-fetoprotein (AFP) >20ng/ml and 18.4% >200 ng/ml. The Barcelona Clinic Liver Cancer (BCLC) stage was 0 in 6.5%, A in 63.8%, B in 17.7%, C in 11.3% and D in 0.7%.

<u>Surgically treated patients (n=90 patients).</u>

A single nodule was detected in 85.6%. The median size of the main nodule was 49 (IQR 26–88.5) mm. AFP level was >20ng/ml in 21.1%. Table 1.

Treatment.

<u>All study cohort (n=141).</u>

The main initial treatment was SR in 63.8% (n=90). Other initial treatments were transarterial chemoembolization (TACE) or radioembolization (TARE) in 13.5 (n=19), ST in 15% (n=21), percutaneous ablation in 4.2% (n=6) and best supportive care in 3.5% (n=5).

Surgically treated patients: Operative data, postoperative complications, and surgical pathology (n=90 patients).

SR was performed in 90 patients (63.8%), of whom 7 previously had TACE/transarterial embolization (TAE).

Resection was anatomical in 85.6% (40% laparoscopy and 45.6% laparotomy) and non-anatomical in 14.4% (1.1% laparoscopy and 13.3% laparotomy), with major liver resection in 22.2% and Pringle maneuver in 46.6%. Thirty-day hospital readmission was required in 6.7%, mainly due to infections. Postoperative complications occurred in 18.7% of patients: 9.9% grade II, 3.3% grade III, 3.3% grade IV, and 2.2% grade V (perioperative mortality), according to the Clavien-Dindo classification.

The surgical specimen had mVI/S in 25.3%, presence of high-risk characteristics (HRC)[17] in 63.2% and capsule in 36.8%.

Survival and recurrence.

All study cohort (n=141): survival.

Median follow-up was 34.1 (IQR: 15.5–49.5) months, with 33.3% of patients in remission (n= 47) and 44.7% of patients died (n=63), 31.2% (n= 44) of them due to liver-related causes. Median OS was 47.9 months (95% CI: not assessable). The global 1-, 2-, 3-, 4- and 5-years survival rate was 85%, 70.9%, 62.4%, 49.1% and 49.1%, respectively.

Lifestyle, ALBI score, APRI index, differentiation degree, ECOG, AFP level, BCLC stage, and initial treatment, were predictors of mortality in the univariate analysis, but only AFP level (<20/≥20ng/ml) [HR: 2.63 (1.3–5.3), p=0.007] and surgical resection as initial treatment [HR: 0.09 (0.01–0.79), p=0.003] were independent predictors of mortality. Table 2. Figure 2.

Surgically treated patients (n=87): recurrence and survival.

After a median follow up of 40.4 months (IQR: 27.2–54.5), 52.9% (n=46) of patients remained in remission, 44.8% (n=39) experienced recurrence and 2.3% (n=2) died during the perioperative period. The median time to recurrence was 48.4 months (95% CI: 32–64.7). The 1-, 3- and 5-year recurrence rates were 16.5%, 38.2% and 55.1%, respectively. Median RFS was 37.9 months (95% CI: 25.8–50.1).

Sequential therapy due to first recurrence was administered in 87.2% (n=34/39), while 12.8% (n=5/39) received only symptomatic treatment. About half of the patients were managed with curative-intent approaches, including repeat SR (33,3%) or ablation (10.3%) – four of them received a LT and remained in remission at the end of follow-up. The remaining patients received TACE (12.8%), ST (25.6%), or other modalities (5.1%).

28.7% of patients (n=25) died, 19.5% (n=17) of them due to liver-related causes and 9.2% (n=8) due to non–liver-related causes (2 cardiovascular, 2 infections, 1 metabolic, 1 other cancer, 2 unknown) in 6 patients with MASLD/MetALD/ALD and 2 with other underlying liver diseases.

The 1-, 2-, 3-, 4- and 5-year survival rate was 95.6%, 85.3%, 78.8%, 64.5%, and 59.1% in the surgical group, respectively. Figure 2.

Predictive factors of recurrence and mortality in the surgically treated patients.

Lifestyle, AFP level, mVI/S, and presence of HRC[17] were predictive factors for recurrence in the univariate analysis, but only active lifestyle [HR: 0.16 (0.05–0.49), p=0.013] and HRC [HR: 3.26 (1.34–7.96), p=0.009] were independent predictive factors of relapse.

Differentiation degree, mVI/S and lifestyle were predictors of mortality in the univariate analysis, and mVI/S [HR: 3.03 (1.18–7.75), p=0.021] and active lifestyle [HR: 0.27 (0.09–0.8), p=0.018] were independent predictors of mortality. Table 2. Figure 3.

Systemic therapy (n=47).

Forty-seven patients out of 141 (33.3%) were treated with ST in our series: 21 patients (44.7%) at diagnosis (BCLC C 25.6%, BCLC B 19.1%); 26 patients (55.3%) due to progression/recurrence.

First line (1L) drugs were sorafenib (SOR) 59.6%, lenvatinib (LEN) 14.9%, atezolizumab plus bevacizumab (AB) 19.1% or others 6.4%. Twenty-nine percent and 8.5% were treated with 2 or 3 lines, respectively. AFP level was higher than 200ng/ml in 25.5% at initiation ST.

The median follow-up was 29.1 (IQR 10–43) months. The median treatment time was 9 months (95% IC: 4.4 – 13.6): 7 months (95% CI: 0–14) in tyrosine kinase inhibitor (TKI) (SOR/LEN) group and 16 months (95% CI: 0–35) in AB group; p=0.3. The median OS

from ST initiation was 16.3 months (95% CI: 9.8–22.7), and no significant difference was observed between the different 1L drugs: TKI 13.4 months (95% CI: 8–19) and AB 26.3 months (95% CI: 13–39) (p=0.35).

Regarding safety data, adverse events (AE) of any grade were 77.8% for SOR, 80% for LEN, and 62.5% for AB. First-line treatment was discontinued in 34% due to symptomatic progression, 14.9% radiological progression, and 12.8% severe AEs; 38.3% continued treatment.

DISCUSSION

This is the first prospective multicenter study on NC-HCC, which accounts for 14-20% of all HCC cases[1-4,19,20].

In our series, the patients were predominantly male, with a mean age of 70 years, and almost 40% had diabetes. A lifestyle questionnaire showed that over 50% of patients had a sedentary lifestyle, about 75% were active/ex-smokers and over 50% were active/ex-drinkers. Our findings are in keeping with what has been reported in the literature: male gender, smoking, alcohol consumption, older age and type 2 diabetes were independent risk factors for developing NC-HCC, in addition to certain high-risk genetic variants[10,19].

The main risk factors related to NC-HCC were the presence of chronic liver disease due to MASLD/MetALD and viral etiology[4,19,20] and 23% of patients had a healthy live. HCC in MASLD is characterized by a lower percentage of underlying cirrhosis compared to other liver diseases[9,31]. However, the risk is too low to justify the use of universal surveillance[31], especially since abdominal ultrasound has a lower sensitivity[7] in this population. The aMAP system, which identifies increased HCC risk in patients with any liver disease[25], classified under 10% of our patients as low risk. The PAGE-B score, used for chronic HBV[5,6], correctly classified all HBV patients as intermediate/high risk.

Although 80% of cases were symptom-based or incidental diagnoses, stage 0-A predominated (70.2%), with a high rate of single lesions (75%), which were nevertheless large (median size of 6 cm). Larger early-stage single lesions have been described by other studies[9,19,20] and might reflect a distinct tumour biology in NC-HCC, characterized by a greater propensity for intrahepatic growth, and a high proportion of

well and moderately differentiated tumors[10,18,19]. Several epidemiologic studies have reported a higher proportion of early-stage HCC in NC patients[9,19]. However, other retrospective studies[11,18] have shown a higher proportion of advanced stages. In our series, periodic imaging – whether for the evaluation of other cancers or irregular ultrasound follow-up of liver disease – may have contributed to the low rates of macrovascular invasion (<10%) and extrahepatic spread (<5%).

Median OS in our series was 47.9 months, and 3- and 5-year survival rates were 62.5% and 49.1% respectively, longer than what was reported in an American[19] and a French multicenter study in MASLD patients[9].

AFP level (≥20ng/ml) was a predictor of worse survival independent of BCLC in all patients group. Our new findings in NC-HCC should prompt specific future research, especially in patients with underlying viral hepatitis and MASLD, etiologies in which AFP levels were higher.

SR is the cornerstone of NC-HCC management[19,20], due to the absence of portal hypertension and a preserved liver function[8]. Our surgical cohort achieved 3- and 5-year survival rates of ~ 80% and 60%, respectively, similar to the current series[10] and higher than older series probably due to improvements in surgical technique and better perioperative management. There was a low perioperative mortality (2.2%), similar[8] or lower[10,21] to other series. Mortality from non-liver-related causes was 32%, mainly in patients with MASLD/MetALD, who have high cardiovascular risk.

Recurrence remains a major challenge in NC-HCC, with reported 3- and 5-year rates of 33–52% and 40–60%, respectively[11-13]. In our cohort, recurrence occurred in 38.2% at 3 years and 55.1% at 5 years, with a median time to recurrence of 48.4 months and median RFS of 37.9 months. Multivariate analysis identified mVI/S as an independent predictor of mortality, consistent with its strong association with recurrence reported in the literature[9,10,13-17].

Sequential therapy was administered to 87.2% of patients with recurrence and approximately half of the patients were retreated with curative intention (new SR, LT, or ablation). Similarly, a French study reported 86.6% retreatment, 32.6% with curative intent[10]. Repeat resection in recurrence has been linked to a 67% 5-year survival[32]. Four of our patients with recurrence were treated with salvage LT. Moreover, the risk-

benefit balance of *ab initio* LT should be specifically evaluated in NC-HCC, as its single but important advantage is the prevention of potentially incurable tumor recurrence. A study is needed to evaluate the benefit of *ab initio* LT in these NC patients, defining selection criteria—including mVI/S—and comparing this strategy to individualized close follow-up for patients at high risk of recurrence to increase the probability of sequential curative treatment, including salvage LT. Currently, in the absence of data, the individual risk of aggressive tumor recurrence must be weighed against the risk of post-transplant mortality due to common comorbidities in MASLD patients or complications related to immunosuppression.

We used a simple questionnaire to classify participants as active or sedentary to facilitate efficient data collection. A more active lifestyle was independently associated with improved overall survival. In an experimental model using PTEN-deficient mice, exercise reduced HCC growth and incidence, but not steatosis[33]. These findings are hypothesis-generating and highlight physical activity as a potential target for risk stratification and behavioral intervention.

In our series, ST was more frequently required for recurrence/progression than as first-line therapy for advanced disease. A limited group of patients opted for 2nd and 3rd ST lines, probably because the same type of ST was continued beyond radiological progression, mainly with SOR at the beginning of the study. Median OS was similar to clinical trials data and safety profile was slightly better[34,35], being severe AE an uncommon reason for discontinuation.

This study has some limitations. Firstly, histological assessment was performed at each participating center, but previous data support high interobserver agreement[19] and METAVIR score is well-standarized. Secondly, the absence of cirrhosis was not assessed exclusively by histopathological criteria; non-invasive data were also used[18,23,24] in some non-surgical patients, which may imply possible misclassification of non-cirrhotic status. Nevertheless, this approach has allowed us to collect a representative series reflecting the current epidemiological situation in our country. Thirdly, we employed a non-validated physical activity questionnaire. Finally, the main ST used was TKI reflecting the treatment era, but we have been able to explore the efficacy and safety of newer therapies.

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Conclusion

In this multicenter prospective study on NC-HCC, most patients were diagnosed at an early stage, with single but relatively large lesions and underwent SR. MASLD/MetALD was the leading etiology, and a sedentary lifestyle was linked to higher mortality. These findings underscore the importance of lifestyle interventions at all stages of disease. Our series highlight the need for further studies regarding *ab initio* LT in NC-HCC and cost-effectiveness of screening in NC patients with different underlying liver diseases.

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REFERENCES

1. European Association for the Study of the Liver. EASL Clinical Practice Guidelines on the management of hepatocellular carcinoma. *J Hepatol* 2025;82(2):315-374.
2. Singal AG, Llovet JM, Yarchoan M, et al. AASLD Practice Guidance on prevention, diagnosis, and treatment of hepatocellular carcinoma. *Hepatology* 2023;78(6):1922-1965.

3. Reig M, Forner A, Ávila MA, et al. Update of the consensus document of the AEEH, AEC, SEOM, SERAM, SERVEI, and SETH. *Med Clin (Barc)* 2021;156(9):463.e1-463.e30.
4. Sala M, Pascual S, Rota Roca MR, et al. Evolving epidemiology of HCC in Spain. *JHEP Rep* 2025;7(5):101336.
5. Papatheodoridis G, Dalekos G, Sypsa V, et al. PAGE-B predicts the risk of developing hepatocellular carcinoma in Caucasians with chronic hepatitis B on 5-year antiviral therapy. *J Hepatol* 2016;64(4):800–806.
6. Kim JH, Kim YD, Lee M, et al. Modified PAGE-B score predicts the risk of hepatocellular carcinoma in Asians with chronic hepatitis B on antiviral therapy. *J of Hepatol* 2018;69(5):1066-73.
7. EASL–EASD–EASO Clinical Practice Guidelines on the management of metabolic dysfunction-associated steatotic liver disease (MASLD). *J Hepatol* 2024;81(3):492-542.
8. Gupta M, Davenport D, Orozco G, et al. Perioperative outcomes after hepatectomy for hepatocellular carcinoma among patients with cirrhosis, fatty liver disease, and clinically normal livers. *Surg Oncol* 2024;56:102114.
9. Vitellius C, Desjonqueres E, Lequoy M, et al. MASLD-related HCC: Multicenter study comparing patients with and without cirrhosis. *JHEP Rep* 2024;6(10):101160.
10. Maulat C, Truant S, Hobeika C, et al. Prognostication algorithm for non-cirrhotic non-B non-C hepatocellular carcinoma-a multicenter study under the aegis of the French Association of Hepato-Biliary Surgery and liver Transplantation. *Hepatobiliary Surg Nutr* 2023;12(2):192-204.
11. Grazi GL, Cescon M, Ravaioli M, et al. Liver resection for hepatocellular carcinoma in cirrhotics and noncirrhotics. Evaluation of clinicopathologic features and comparison of risk factors for long-term survival and tumour recurrence in a single centre. *Aliment Pharmacol Ther* 2003;17 Suppl 2:119-129.
12. Shimada M, Rikimaru T, Sugimachi K, et al. The importance of hepatic resection for hepatocellular carcinoma originating from nonfibrotic liver. *J Am Coll Surg* 2000;191(5):531-537.

13. Ruiz E, Honles J, Fernández R, et al. A preoperative risk score based on early recurrence for estimating outcomes after resection of hepatocellular carcinoma in the non-cirrhotic liver. *HPB (Oxford)* 2024;26(5):691-702.
14. Sumie S, Kuromatsu R, Okuda K, et al. Microvascular invasion in patients with hepatocellular carcinoma and its predictable clinicopathological factors. *Ann Surg Oncol* 2008;15(5):1375-1382.
15. Fuster-Anglada C, Mauro E, Ferrer-Fàbrega J, et al. Histological predictors of aggressive recurrence of hepatocellular carcinoma after liver resection. J Hepatol 2024;81(6):995-1004.
16. Ferrer-Fàbrega J, Forner A, Liccioni A, et al. Prospective validation of ab initio liver transplantation in hepatocellular carcinoma upon detection of risk factors for recurrence after resection. *Hepatology* 2016;63(3):839-849.
17. Hack SP, Spahn J, Chen M, et al. IMbrave 050: a Phase III trial of atezolizumab plus bevacizumab in high-risk hepatocellular carcinoma after curative resection or ablation. *Future Oncol* 2020;16(15):975-989.
18. Gawrieh S, Dakhoul L, Miller E, et al. Characteristics, aetiologies and trends of hepatocellular carcinoma in patients without cirrhosis: a United States multicentre study. *Aliment Pharmacol Ther* 2019;50(7):809-821.
19. Donica WRF, Stephens KR, Martin RCG 2nd, et al. Changes in Incidence of Cirrhotic and Noncirrhotic Hepatocellular Carcinoma in the United States. *J Surg Res* 2024;302:641-647.
20. van Meer S, van Erpecum KJ, Sprengers D, et al. Hepatocellular carcinoma in cirrhotic versus noncirrhotic livers: results from a large cohort in the Netherlands. *Eur J Gastroenterol Hepatol* 2016;28(3):352-359.
21. Zeindler J, Hess GF, von Heesen M, et al. Anatomic versus non-anatomic liver resection for hepatocellular carcinoma-A European multicentre cohort study in cirrhotic and non-cirrhotic patients. *Cancer Med* 2024;13(5):e6981.
22. The French METAVIR Cooperative Study Group. Intraobserver and interobserver variations in liver biopsy interpretation in patients with chronic hepatitis C. *Hepatology* 1994;20(1):15-20.

23. European Association for the Study of the Liver. EASL Clinical Practice Guidelines on non-invasive tests for evaluation of liver disease severity and prognosis - 2021 update. *J Hepatol* 2021;75(3):659-689.
24. Mittal S, El-Serag HB, Sada YH, et al. Hepatocellular carcinoma in the absence of cirrhosis in United States Veterans is associated with nonalcoholic fatty liver disease. *Clin Gastroenterol Hepatol* 2016;14(1):124-131.
25. European Association for the Study of the Liver (EASL); European Association for the Study of Diabetes (EASD); European 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):1388-1402.
26. Rinella ME, Lazarus JV, Ratziu V, et al. NAFLD Nomenclature consensus group. A multisociety Delphi consensus statement on new fatty liver disease nomenclature. *J Hepatol* 2023;79(6):1542-1556.
27. Song SJ, Lai JC, Wong GL, et al. Can we use old NAFLD data under the new MASLD definition? *J Hepatol* 2024:80(2):e54-e56.
28. Fan R, Papatheodoridis G, Sun J, et al. aMAP risk score predicts hepatocellular carcinoma development in patients with chronic hepatitis. *J Hepatol* 2020;73(6):1368-1378.
29. Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. *Ann Surg* 2004;240(2):205-213.
30. Paradis V. Histopathology of hepatocellular carcinoma. *Recent Results Cancer Res* 2013;190:21-32.
31. Plaz Torres MC, Bodini G, Furnari M, et al. Surveillance for Hepatocellular Carcinoma in Patients with Non-Alcoholic Fatty Liver Disease: Universal or Selective? *Cancers* 2020;12(6):1422.
32. Bège T, Le Treut YP, Hardwigsen J, et al. Prognostic factors after resection for hepatocellular carcinoma in nonfibrotic or moderately fibrotic liver. A 116-case European series. *J Gastrointest Surg* 2007;11(5):619-625.
33. Piguet AC, Saran U, Simillion C, et al. Regular exercise decreases liver tumors development in hepatocyte-specific PTEN-deficient mice independently of

steatosis. *J Hepatol* 2015;62(6):1296-1303.

34. Finn RS, Qin S, Ikeda M, et al. Atezolizumab plus Bevacizumab in Unresectable Hepatocellular Carcinoma. *N Engl J Med* 2020;382(20):1894-1905.
35. Kudo M, Finn RS, Qin S, et al. Lenvatinib versus sorafenib in first-line treatment of patients with unresectable hepatocellular carcinoma: a randomised phase 3 non-inferiority trial. *Lancet* 2018;391(10126):1163-1173.

Table 1. Epidemiological, clinical and tumor features of all study cohort patients and surgical treated patients.

CHARACTERISTICS	ALL STUDY COHORT NC-HCC PATIENTS (n=141)	SURGICALLY TREATED NC-HCC (n=90)
Age (years), median (IQR)	70 (63-77)	70.4 (62-77)
Male, n (%)	120 (85.1%)	75 (83.3%)

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Caucasian race, n (%)	137 (97.2%)	87 (96.7%)
BMI (kg/m^2), median (IQR)	26 (24-30)	26 (24-30)
AHT, n (%)	84 (59.6%)	51 (56.7%)
DM, n (%)	53 (37.6%)	32 (35.6%)
Metabolic syndrome, n (%)	51 (36.2%)	68 (75.6%)
≥ 1cardiovascular risk factor, n (%)	109 (77.3%)	32 (35.6%)
No HCC family history, n (%)	3 (2.1%)	3 (2.1%)
HIV, n (%)	3 (2.1%)	1 (1.1%)
Toxic habits, n (%): - Smoker/past smoker - Drinker/past drinker	 105 (74.2%) 74 (52.2%)	 64 (71.3%) 41 (45.9%)
Other cancers, n (%) ≥2 other cancers, n (%)	41 (29.1%)* 8 (5.7%)	23 (25.6%) 4 (4.4%)
Coffee drinkers, n/total (%)	71/93 (76.3%)	50/67 (74.6%)
Active lifestyle, n/total (%)	45/95 (47.4%)	37/67 (55.2%)
Urban area n/total (%)	85/116 (73.3%)	53/77 (69%)
Hepatology follow-up, n (%)	22 (31%)	22 (24.4%)
Healthy liver, n (%)	32 (22.7%)	17 (18.9%)
Underlying liver disease, n (%): -MASLD † -MetALD -HCV -HCV +/- ALD -HBV -HBV+HCV+ALD ‡ -ALD -HH +/- ALD -Others § -Unknown	109 (77.3%) 34 (24.1%) 5 (3.5%) 19 (13.5%) 4 (2.8%) 12 (8.5%) 1 (0.7%) 19 (13.5%) 6 (4.3%) 3 (2.1%) 6 (4.3%)	73 (81.1%) 22 (24.4%) 4 (4.5%) 12 (13.3%) 4 (4.5%) 7 (7.8%) 0 12 (13.3%) 5 (5.5%) 3 (3.3%) 4 (4.5%)
Fibrosis stage, n (%): -F0-1	 75 (53.2%)	 52 (57.8%)

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-F2	24 (17%)	18 (20%)
-F3	23 (16.3%)	17 (18.9%)
-Unknown	19 (13.5%)	3 (3.3%)
PAGE B score n/total (%)		
-Low risk group (<10 points)	0	0
-Intermediate risk group (10-17)	8/12 (66.7%)	5/7 (71.4%)
-High risk group (≥18 points)	4/12 (33.3%)	2/7 (28.6%)
Modified PAGE-B score n/total (%)		
-Low risk group (<8 points)	0	0
-Intermediate risk group (8-13)	3/12 (25%)	2/7 (28.6%)
-High risk group (>13 points)	9/12 (75%)	5/7 (71.4%)
aMAP risk score, n (%)		
-Low risk group (<50 points)	12 (8.5%)	8 (8.9%)
-Intermediate-risk group (50-60)	52 (36.9%)	37 (41.1%)
-High risk group (>60 points)	77 (54.6%)	45 (50%)
APRI, n (%):		
-Low risk group (<1)	121 (85.8%)	82 (91.1%)
-Intermediate-risk group (1-2)	15 (10.6%)	6 (6.7%)
-High risk group (>2)	5 (3.5%)	2 (2.2%)
FIB-4, n (%)		
-Low risk group (<1.6)	42 (29.8%)	28 (31.1%)
-Intermediate-risk group (1.6-3.6)	84 (59.6%)	55 (61.1%)
-High risk group (>3.6)	15 (10.6%)	7 (7.8%)
Elastography (kPa), total n	(n=49)	(n=33)
Median (IQR)	6.75 (5.63-8.8)	6.8 (5.7-8.9)
ALBI score, n (%):		
-Grade 1 (≤-2.6)	95 (67.4%)	65 (72.2%)
-Grade 2 (-2.6 – -1.39)	39 (27.6%)	23 (25.6%)
-Grade 3 (>-1.39)	7 (5%)	2 (2.2%)
Bilirubin (mg/dl), median (IQR)	0.7 (0.49-1)	0.7 (0.49-1)
Albumin (g/dl), median (IQR)	4.1 (3.8-4.4)	4.1 (3.9-4.4)

Creatinine (mg/dl), median (IQR)	0.87 (0.7-1.08)	0.9 (0.7-1.06)
Sodium (mEq/L), median (IQR)	140 (138-142)	140 (138-142)
Platelets (x10^{12}/L), median (IQR)	202 (175-247)	200 (176-240)
Prothrombin time (%), median (IQR)	93 (81-100)	95 (83-100)

*Cancer types: colorectal cancer (11), others in digestive system (2), head and neck cancer (9), urologic cancers (renal 5, prostate 5, others 5), lung cancer (5), basocellular skin carcinoma (2), breast cancer (2), others (lymphoma 1, thyroid 1, endometrium 1, retroperitoneal sarcoma 1). †1 MASLD+occult HBV. ‡Antiviral treatment before HCC diagnosis: none 80.9%, oral antiviral agents for chronic hepatitis B 6.4%, direct-acting antivirals for chronic hepatitis C 9.9%, peginterferon and ribavirin 2.1%, antivirals VHB + direct-acting antivirals HCV 0.7%. §Other etiologies: 1 primary biliary cholangitis, 1 overlap primary biliary cholangitis+autoimmune hepatitis, 1 drug induced liver injury.

TUMOR FEATURES	ALL STUDY COHORT NC-HCC PATIENTS (n=141)	SURGICALLY TREATED NC-HCC PATIENTS (n=90)
HCC diagnosis, n (%): • Follow-up US*	28 (19.9%)	21 (23.3%)

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• Incidental • Symptoms	79 (56%) 34 (24.1%)	51 (56.7%) 18 (20%)
Ruptured HCC, n (%)	7 (5%)	4 (4.4%)
Number of nodules, n (%): • Single nodule • 2 nodules • >2nodules	 106 (75.2%) 16 (11.3%) 19 (13.5%)	 77 (85.6%) 11 (12.2%) 2 (2.2%)
Size (mm) median (IQR)	59 (32.5-87)	49 (26-88.5)
Macrovascular invasion, n (%)	13 (9.2%)	2 (2.2%)
Extrahepatic spread, n (%)	4 (2.8%)	1 (1.1%)
Differentiation degree, n (%): • WD • MD. • PD • U • Others	 46 (32.6%) 76 (53,9%) 10 (7,1%) 2 (1,4%) 7 (5%) ‡	 26 (29%) 55 (61.1%) 4 (4.4%) 1 (1.1%) 4 (4.4%) §
AFP ng/ml (total n) Median (IQR): • ≥20ng/ml, n (%) • ≥200ng/ml, n (%)	(n=135) 4.4 (2.1-41) 38 (26.9%) 26 (18.4%)	(n=85) 3.6 (2-13.6) 19 (21.1%) || 11 (12.9%)
Typical hallmarks CT/MRI†, n (%)	83 (58.9%)	54 (60%)
ECOG, n (%): • 0 • 1 • 2 • 3	 112 (79.4%) 25 (17.7%) 3 (2.1%) 1 (0.7%)	 80 (88.9%) 10 (11.1%) 0 0
BCLC stage, n (%): • 0 • A • B	 9 (6.4%) 90 (63.8%) 25 (17.7%)	 7 (7.8%) 72 (80%) 9 (10%)

• C • D	16 (11.3%) 1 (0.7%)	2 (2.2%) fj 0

*Periodicity according to the physician responsible. †The combination of hypervascularity in late arterial phase and washout on portal venous and/or delayed phases ‡Fibrolamellar (2); clear cell HCC (1); §surgically treated cases: clear cell HCC (2), hepatocholangiocarcinoma (1), mixed neuroendocrine-non neuroendocrine neoplasm with a component of HCC (1). ||Liver disease etiology: 9 viral (4 HCV and 5 HBV), 5 MASLD, 3 ALD, 2 others. fj 1 patient with vascular invasion and tumour involvement of the diaphragm, treated surgically due to severe secondary pain; 1 patient with unclear vascular invasion prior to surgery, later confirmed.

ABBREVIATIONS: NC-HCC: non-cirrhotic hepatocellular carcinoma, BMI: body mass index, AHT: Arterial hypertension, DM: Diabetes mellitus, HIV: human immunodeficiency virus, MASLD: Metabolic dysfunction associated steatotic liver disease, MetALD: MASLD and increased alcohol intake, ALD: alcohol associated liver disease, HH: Hereditary haemochromatosis, US: ultrasonography, WD: Well-differentiated, MD: Moderately differentiated, PD: Poorly differentiated, U: Undifferentiated. kPa: kilopascals. AFP: alpha-fetoprotein, CT: computed tomography, ECOG: Eastern Cooperative Oncology Group, BCLC: Barcelona Clinic Liver Cancer.

Table 2 (A). Univariate and multivariate analyses of mortality risk factors in all study cohort patients.

UNIVARIATE ANALYSIS OF MORTALITY RISK FACTORS (all group)	**Death**		**HR (95%CI)**	**p value**
	No (n=78)	**Yes (n=63)**		
	Median (IQR) **n (%)**	**Median (IQR)** **n (%)**		

Age at diagnosis (years)	70.5 (63 – 77)	70 (62 – 77)	0.99 (0.97 – 1.02)	0.47
Sex (male)	63 (80.8%)	57 (90.5%)	0.61 (0.26 – 1.42)	0.25
BMI (kg/m^2)	26 (24 – 30)	27 (24 – 29)	0.97 (0.91 – 1.03)	0.36
AHT (yes)	43 (58.1%)	41 (67.2%)	1.32 (0.77 – 2.26)	0.31
DM (yes)	26 (33.3%)	27 (42.9%)	1.36 (0.82 – 2.24)	0.23
Toxic habits: Smoker (yes) Drinker (yes)	 53 (71.6%) 32 (43.2%)	 48 (77.4%) 39 (62.9%)	 1.11 (0.61 – 2.01) 1.53 (0.91 – 2.56)	 0.74 0.11
Other cancers (yes)	20 (25.6%)	21 (33.3%)	1.3 (0.78 – 2.23)	0.3
Coffee drinkers (yes)	40 (78.4%)	31 (73.8%)	0.79 (0.4 – 1.59)	0.53
Active lifestyle (yes)	**29 (55.8%)**	**16 (37.2%)**	**0.53 (0.28 – 0.99)**	**0.048**
Underlying liver	19 / 43 / 16	19/31/13	1.16	0.34

disease: viral/non-viral/healthy liver	(55.1/24.4/20.5 %)	(30.2/49.2/20.6%)	(0.85 – 1.58)	
Fibrosis stage: F0-1/ F2-3	47 / 25 (60.3/32.1%)	28 / 22 (56 / 44%)	1.33 (0.76 – 2.33)	0.31
APRI index: Low / intermediate / high risk	**70 / 6 / 2 (89.7 / 7.7 / 2.6%)**	**51 / 9 / 3 (81 / 14.3 / 4.8%)**	**1.65 (1.01 – 2.68)**	**0.045**
FIB-4 index low/ intermediate / high risk	27 / 44 / 7 (34.6/56.4/9%)	15 / 40 / 8 (23.8/63.5/ 12.7%)	1.37 (0.9 – 1.09)	0.14
ALBI score: 1 / 2 / 3	**55 / 22 / 1 (70.5 / 28.2 / 1.3%)**	**40 / 17 / 6 (63.5 / 27 / 9.5%)**	**1.55 (1.009 – 2.37)**	**0.045**
Platelets ($x10^{12}$/L)	210 (176 – 240)	192 (163 – 267)	1 (0.997–1.00 4)	0.78
HCC diagnosis: Follow-up US/incidental/sympto ms	16 / 48 / 14 (20.5/61.5/17.9 %)	12/31/20 (19/49.2/31.7%)	1.28 (0.89 – 1.86)	0.19
Differentiation degree: WD/MD vs PD/U	**74 / 2 (97.4 / 2.6%)**	**48 / 10 (82.8 / 17.2%)**	**3.44 (1.73 – 6.82)**	**0.000 1**
AFP (ng/ml): <20/≥20	**59 / 14 (80.8 / 19.2%)**	**31 / 25 (59.7/40.3%)**	**2.64 (1.58 – 4.4)**	**0.000 1**
AFP level (ng/ml)	**3 (1 – 8.3)**	**8.5 (2.4 – 246)**	**1 (1 – 1)**	**0.000 1**
ECOG: 0/≥1	**74 / 4 (94.9/5.1%)**	**38 / 25 (60.3/39.7%)**	**3.86**	**0.000 1**

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			(2.34 – 6.42)	
BCLC staging system: Stage 0-A / B / C / D	66 / 9 / 3 / 0 (84.6/11.5/3.8%)	33 / 16 / 13 / 1 (52.4/25.4/20.6/1 .6%)	**3.55 (2.55 – 4.94)**	**0.000 1**
Initial treatment: SR/ablation/locoregi onal/ST/symptomatic	**62 / 3 / 8 / 4 / 1 (79.4/3.8/10.3/ 5.1/ 1.3%)**	**28 / 2 / 11 / 17 / 4 (44.4/3.2/17.5/2 7/ 6.3%)**	**2.04 (1.67 – 2.49)**	**0.000 1**

MULTIVARIATE ANALYSIS OF MORTALITY RISK FACTORS (all group)	**HR (95%CI)**	**p value**
Active lifestyle	0.66 (0.31 – 1.4)	0.28
APRI index	1.02 (0.5 – 2.1)	0.97
ALBI score	0.9 (0.47 – 1.72)	0.75
Differentiation degree	1.14 (0.38 – 3.4)	0.81
AFP (ng/ml): <20/≥20	**2.63 (1.3 – 5.3)**	**0.007**
BCLC staging system: Stage 0-A / B / C / D	1.15 (0.5 – 2.66)	0.74
Initial treatment: • **SR** • Ablation • Locoregional • ST • Symptomatic	 **0.09 (0.01 – 0.79)** 0.25 (0.01 – 4.8) 0.22 (0.03 – 1.86) 0.73 (0.12 – 4.3) Ref.	 **0.03** 0.36 0.17 0.73

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Table 2 (B). Univariate and multivariate analyses for recurrence and mortality risk factors in surgical treated patients.

UNIVARIATE ANALYSIS FOR RECURRENCE (surgical group)	**Recurrence**		**HR (95%CI)**	**p value**
	No (n=48)	**Yes (n=39)**		
	Median (IQR) n (%)	**Median (IQR) n (%)**		
Age at diagnosis (years)	72 (63.5 – 77.7)	67 (60 – 75)	0.98 (0.95 – 1.01)	0.205
Sex (male)	43 (89.6%)	29 (74.4)	2.44 (1.18 – 5.03)	0.015
BMI (kg/m^2)	26 (24 – 30)	26.5 (24 – 30)	1.02 (0.94 – 1.104)	0.61
AHT (yes)	24 (51.1%)	24 (61.5%)	1.66 (0.85 – 3.27)	0.14
DM (yes)	17 (35.4%)	14 (35.9%)	1.01	0.96

			(0.53 – 1.95)	
Toxic habits: • Never smoker/smoker. • Never drinker/drinker.	35 (74.5%) 24 (51.1%)	24 (64.9%) 15 (40.5%)	0.59 (0.3 – 1.18) 0.67 (0.35 – 1.3)	0.14 0.24
Other cancers (yes)	11 (22.9%)	12 (30.8%)	1.5 (0.76 – 2.97)	0.24
Coffee drinkers (yes)	28 (58.3%)	20 (69%)	0.504 (0.23 – 1.12)	0.092
Active lifestyle (yes)	**20 (55.6%)**	**9 (30%)**	**0.39 (0.17 – 0.85)**	**0.019**
Underlying liver disease: viral/non-viral/healthy liver	12 / 28 / 8 (25/58.3/16.7%)	11 / 22 / 6 (28.2/56.4/15.4%)	1.13 (0.73 – 1.73)	0.59
Fibrosis stage: F0-1 / F2-3	30 / 17 (63.8/36.2%)	21 / 16 (56.8 / 43.2%)	1.2 (0.63 – 2.3)	0.58
APRI: Low / intermediate / high risk group.	43 / 3 / 2 (89.6/6.3/4.2%)	36 / 3 (92.3 / 7.7%)	0.64 (0.22 – 1.87)	0.42
FIB-4: low / intermediate / high risk group.	15 / 30 / 3 (31.3/62.5/6.3%)	12 / 23 / 4 (30.8/59/10.3%)	1.04 (0.61 – 1.77)	0.9
ALBI score: 1 / 2 / 3	35 / 13	28 / 9 / 2	1.31	0.41

	(72.9 – 27.1%)	(71.8/23.1/5.1%)	(0.69 – 2.48)	
Platelets ($x10^{12}$/L)	203 (176 – 236)	191 (176 – 246)	1 (0.99 – 1.004)	0.88
HCC diagnosis: Follow-up US/incidental/symptoms	12 / 28 / 8 (25/58.3/16.7%)	9 / 23 / 7 (23.1/59/17.9%)	1.04 (0.65 – 1.67)	0.86
Differentiation degree: WD/MD vs PD/U	45 / 2 (95.7/4.3%)	34 / 3 (91.9/8.1%)	2.45 (0.75 – 8.03)	0.14
AFP (ng/ml): <20/≥20	38 / 7 (84.4/15.6%)	27 / 10 (73/27%)	1.7 (0.83 – 3.56)	0.14
AFP level (ng/ml)	**3 (2 – 8.6)**	**4.6 (2 – 37.5)**	**1 (1 – 1)**	**0.004**
Main nodule size (cm)	42.5 (25 – 77)	50 (30 – 91)	1.005 (0.99 – 1.011)	0.17
ECOG: 0/≥1	43 / 5 (89.6 / 10.4%)	37 / 2 (94.9 / 5.1%)	0.51 (0.12 – 2.13)	0.36
Type of surgical resection: • Anatomical laparoscopy • Anatomical laparotomy • Non-anatomical laparotomy	 19 (39.6%) 23 (47.9%) 6 (12.5%)	 16 (41%) 18 (46.2%) 5 (12.8%)	0.89 (0.61 – 1.31)	0.57
Major liver resection	12 (25%)	6 (16.2%)	0.88 (0.37 – 2.11)	0.77

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ASA physical status classification system: 1-2 / 3-4.	23 / 25 (47.9/52.1%)	25 / 12 (67.5/ 32.5%)	0.82 (0.57 – 1.17)	0.27
mVI/S	**10 (20.8%)**	**12 (31.6%)**	**2.08 (1.05 – 4.14)**	**0.037**
HRC	**25 (52.1%)**	**30 (78.9%)**	**2.95 (1.35 – 6.45)**	**0.007**

MULTIVARIATE ANALYSIS FOR RECURRENCE (surgical group)	**HR (95%CI)**	**p value**
Active lifestyle	**0.16 (0.05 – 0.49)**	**0.013**
AFP level	1 (1 – 1)	0.15
mVI/S	1.59 (0.67 – 3.79)	0.29
HRC	**3.26 (1.34 – 7.96)**	**0.009**

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UNIVARIATE ANALYSIS OF MORTALITY RISK FACTORS (surgical group)	**Death**		**HR (95%CI)**	**p value**
	No (n=62)	**Yes (n=25)**		
	Median (IQR) n (%)	**Median (IQR) n (%)**		
Age at diagnosis (years)	69.5 (62.5 – 76)	72 (60.5 – 77)	0.49 (0.11 – 2.07)	0.33
Sex (male)	49 (79%)	23 (92%)	0.99 (0.95 – 1.03)	0.72
BMI (kg/m^2)	26 (24 – 30)	27 (25 – 31)	1.07 (0.98 – 1.18)	0.146
AHT (yes)	32 (54.2%)	16 (64%)	1.64 (0.72 – 3.73)	0.24
DM (yes)	19 (30.6%)	12 (48%)	2.17 (0.98 – 4.79)	0.055

Toxic habits: • Smoker (yes). • Drinker (yes).	41 (69.5%) 24 (40.7%)	18 (72%) 15 (60%)	0.89 (0.37 – 2,16) 1.46 (0.66 – 3.27)	0.81 0.35
Other cancers (yes)	13 (21%)	10 (40%)	2.08 (0.93 – 4.63)	0.074
Coffee drinkers (yes)	34 (79.1%)	14 (56%)	0.52 (0.21 – 1.29)	0.159
Active lifestyle (yes)	**24 (54.5%)**	**5 (22.7%)**	**0.239 (0.87 – 0.66)**	**0.006**
Underlying liver disease: viral/non-viral/healthy liver	16 / 35 / 11 (25.8/56.5/17.7%)	7 / 15 / 3 (28/60/12%)	0.9 (0.52 – 1.57)	0.72
Fibrosis stage: F0-1 / F2-3	39 / 21 (65 / 35%)	12 / 12 (50 / 50%)	1.68 (0.75 – 3.74)	0.204
APRI: Low / intermediate / high risk group.	57 / 4 / 1 (91.9/6.5/1.6%)	22 / 2 / 1 (88/8/4%)	1.12 (0.44 – 2.88)	0.81
FIB-4: low / intermediate / high risk group.	20 / 36 / 6 (32.3/58.1/9.7%)	7 / 17 / 1 (28 / 68 / 4%)	0.5 (0.2 – 1.4)	0.21
ALBI score: 1 / 2 / 3	47 / 15 / 0 (75.8 / 24.2%)	16 / 7 / 2 (64/28/8%)	1.75 (0.86 – 3.59)	0.125

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Platelets (x10^{12}/L)	205 (175 – 239)	192 (177 – 249)	1.001 (0.99 – 1.006)	0.58
HCC diagnosis: Follow-up US/incidental/symptoms	13 / 37 / 12 (21/59.7/19.4%)	8 / 14 / 3 (32 / 56 / 12%)	0.67 (0.37 – 1.21)	0.18
Differentiation degree: WD/MD vs PD/U	**59 / 1 (98.3 / 1.7%)**	**20 / 4 (83.3 / 16.7%)**	**3.92 (1.34 – 11.52)**	**0.013**
AFP (ng/ml): <20/≥20	47 / 11 (81 / 19%)	18 / 6 (75/25%)	1.39 (0.55 – 3.5)	0.48
AFP (ng/ml)	3 (2 – 9.45)	4.8 (1.8 – 29.5)	1 (0.99 – 1.001)	0.54
Size (mm)	46.5 (25.7 – 70)	45 (25.5 – 96.5)	1.004 (0.99 – 1.01)	0.35
ECOG: 0/≥1	59 / 3 (91.9 / 8.1%)	22 / 3 (88% / 12%)	1.72 (0.59 – 5.03)	0.32
Type of surgical resection: • Anatomical laparoscopy • Anatomical laparotomy • Non-anatomical laparotomy	 24 (38.7%) 30 (48.4%) 8 (12.9%)	 11 (44%) 11 (44%) 3 (12%)	 0.9 (0.56 – 1.43)	0.66
Major liver resection	14 (23%)	4 (16.7%)	0.88 (0.301 – 2.59)	0.82
ASA physical status classification system: 1-2 / 3-4.	37 / 24 (60.7/39.3%)	11 / 13 (45.8/54.2%)	1.4 (0.88 – 2.22)	0.157

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mVI/S	**12 (19.7%)**	**10 (40%)**	**2.61 (1.68 – 5.83)**	**0.019**
HRC	37 (60.7%)	18 (72%)	1.69 (0.71 – 4.07)	0.24

MULTIVARIATE ANALYSIS OF MORTALITY RISK FACTORS (surgical group)	**HR (95%CI)**	**p value**
Active lifestyle	**0.27 (0.09 – 0.8)**	**0.018**
mVI/S	**3.03 (1.18 – 7.75)**	**0.021**
Differentiation degree	1.46 (0.44 – 4.85)	0.53

ABBREVIATIONS: BMI: Body Mass Index, AHT: Arterial hypertension, DM: Diabetes mellitus, HCC: hepatocellular carcinoma, US: ultrasonography, WD/MD: Well-differentiated/Moderately differentiated., PD/U: Poorly differentiated /Undifferentiated AFP: alpha-fetoprotein, ECOG: Eastern Cooperative Oncology Group, BCLC: Barcelona Clinic Liver Cancer, SR: surgical resection, ST: systemic therapy, mVI/S: microvascular invasion and/or satellitosis, HRC: high-risk characteristics[17].

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Legends for all figures

FIGURE 1

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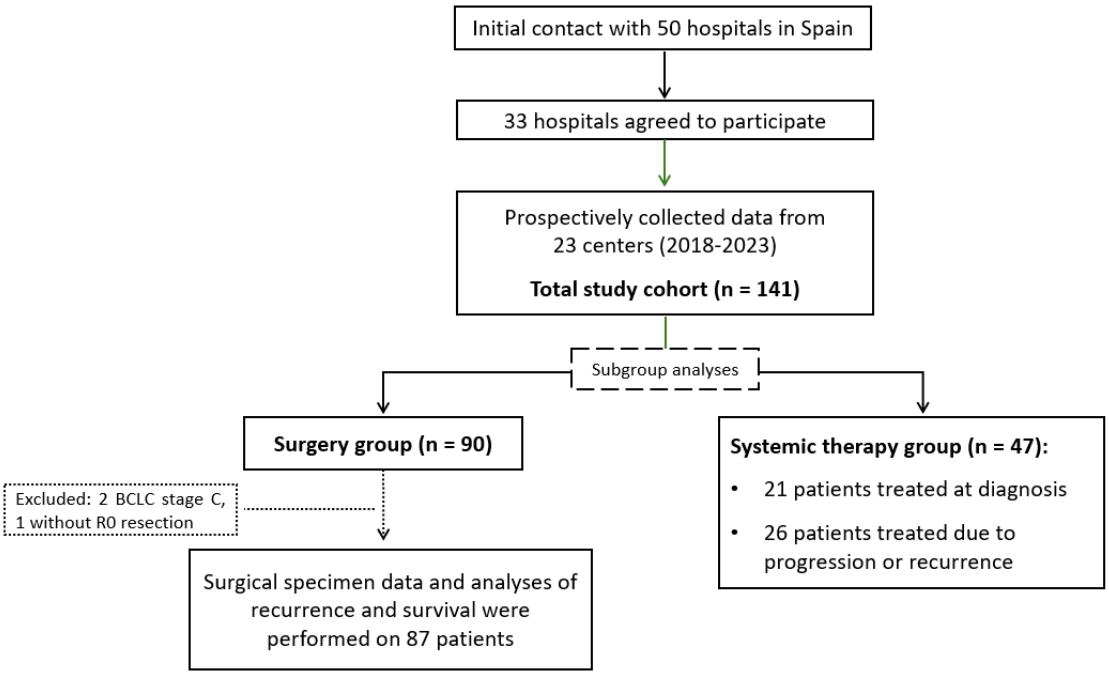

Figure 1. Flow diagram of patient selection and subgroup analyses.

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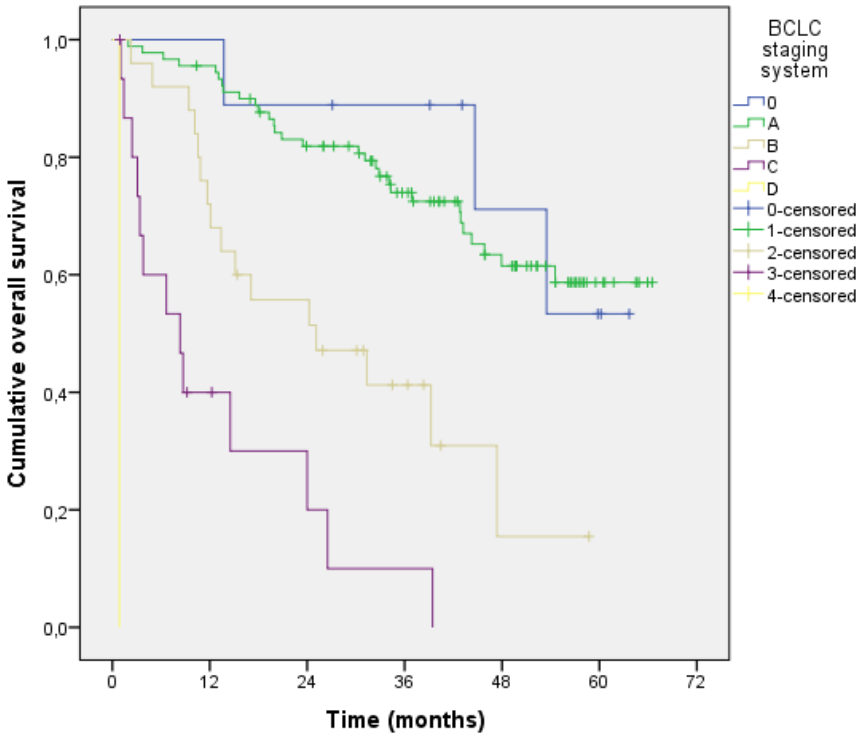

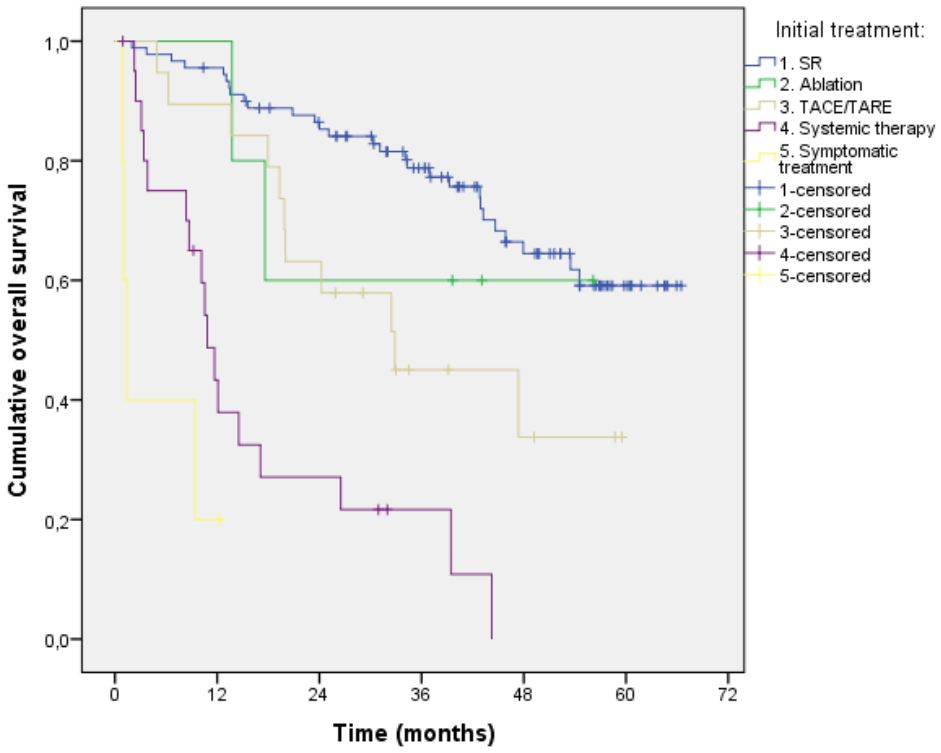

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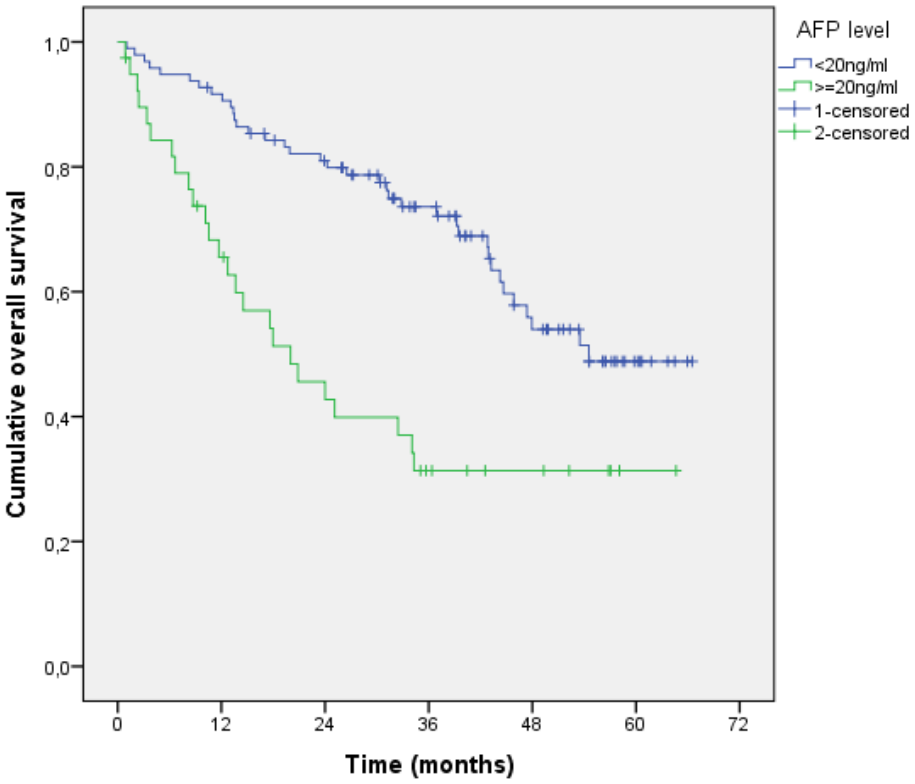


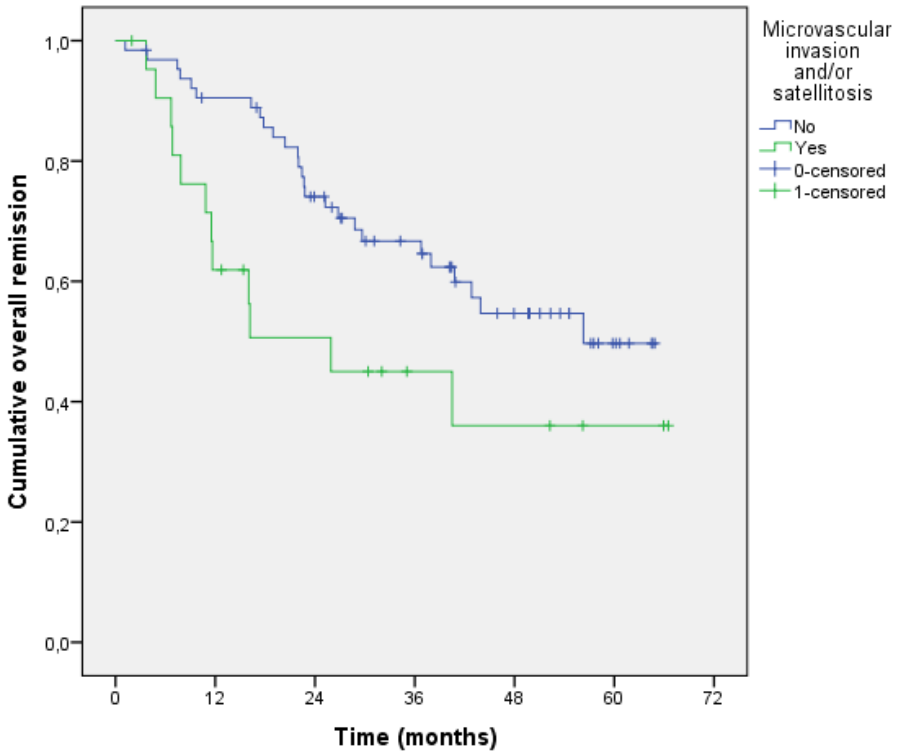
Figure 2. Cumulative overall survival in all study cohort according to BCLC staging system, initial treatment and AFP level.

Median OS according to BCLC staging system (n=141, 63 events): 0 and A median OS not assessable, B 25.1 months (CI95%: 5.5-44.7), C 8.3 months (95%CI: 2.2-14.5), D 0.9 months; p=0.0001.

Median OS according to initial treatment (n=141, 63 events): loco-regional treatment (TACE/TARE) 32.8 months (95%CI: 10.5-55.3), systemic therapy 10 months (95%CI: 6-14) and symptomatic treatment 1.4 months (95%CI: 0.6-2.3); SR and ablation: median OS not assessable; p=0.0001.

Median OS according to AFP level (n= 135, 62 events): <20ng/ml 54.3 months (95%CI: not assessable) and AFP≥20 ng/ml 20 months (CI95%: 9.2-30.8); p=0.0001.

ABBREVIATIONS: BCLC: Barcelona Clinic Liver Cancer, SR: surgical resection, TACE: transarterial chemoembolization, TARE: transarterial radioembolization, AFP: alpha-fetoprotein.



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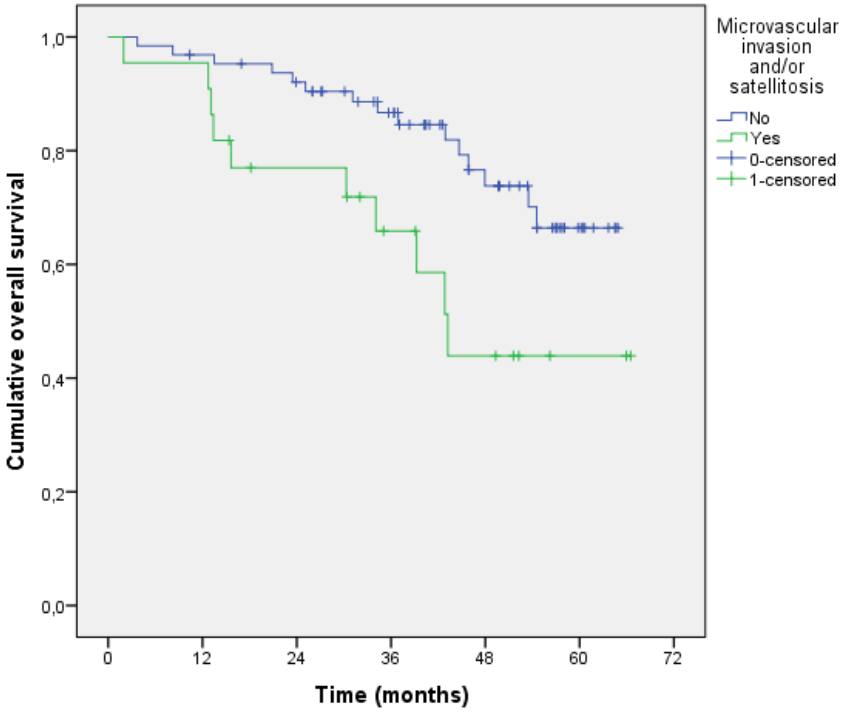

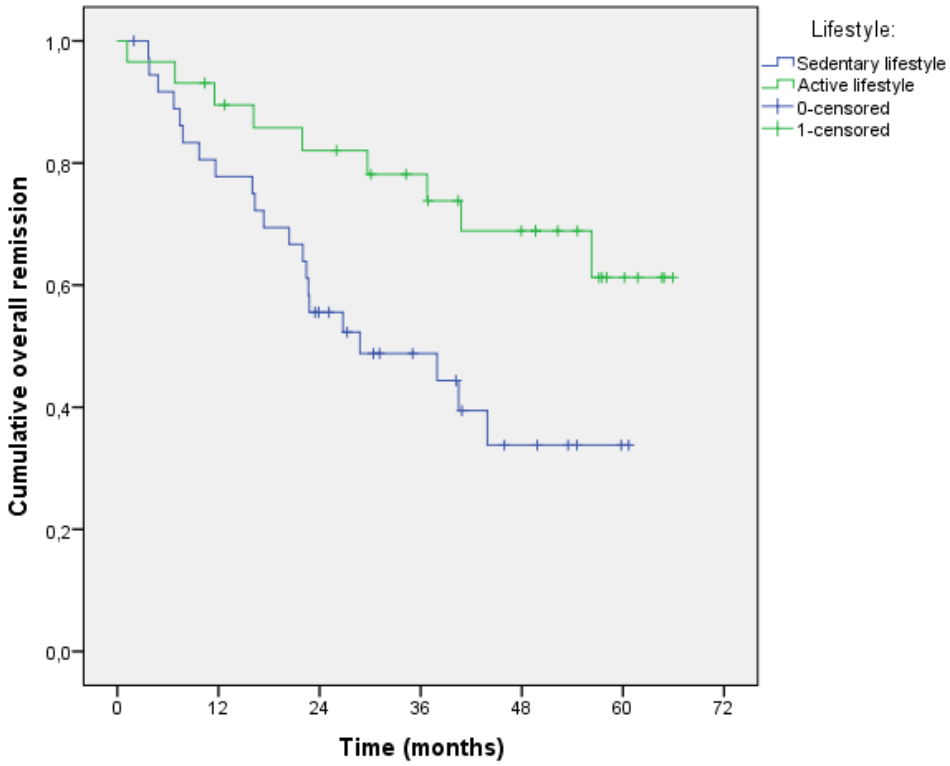

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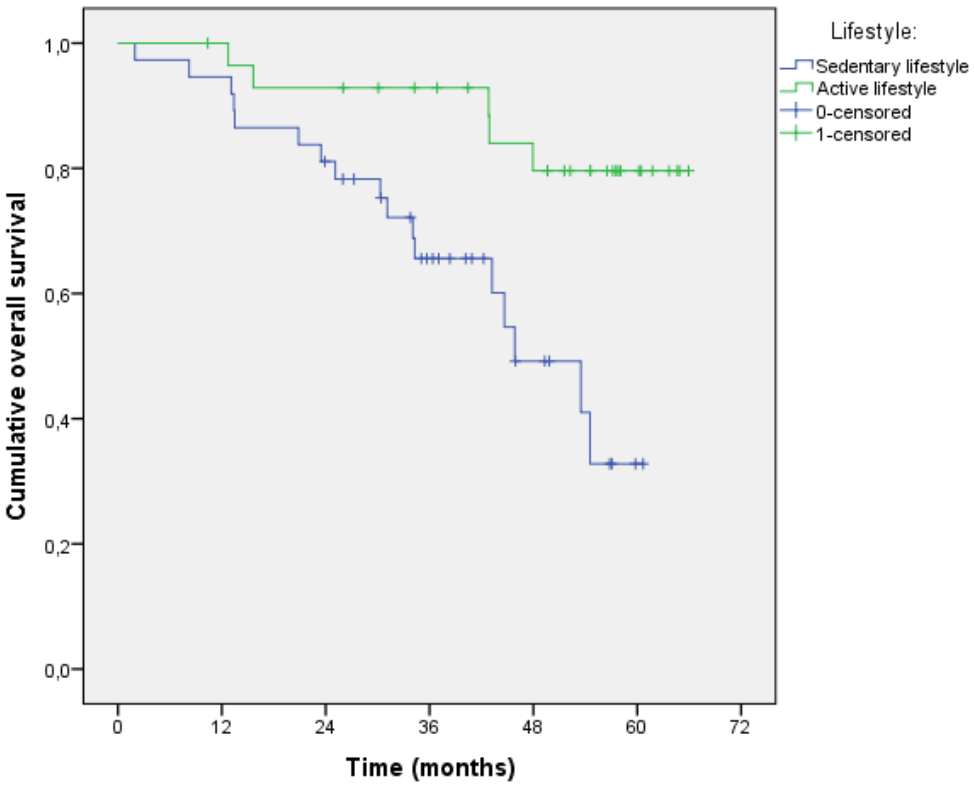

Figure 3. Recurrence and survival in surgically treated patients according to mVI/S and lifestyle.

Median time to recurrence (n= 86, 38 events) was 56.3 months (95%CI: not assessable) in patients without mVI/S and 25.9 months (95%CI: 0.001 – 52.8) in patients with mVI/S.

Recurrence at 1-, 2- and 4-years was 38.1, 49.4% and 64% in patients with mVI/S and 9.5%, 25.9 and 45.3% in patients without mVI/S, respectively; p=0.033.

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Median OS (n=86, 25 events) was 43.2 months (95%CI: 36.6 – 49.9) in patients with mVI/S and not assessable in patients without mVI/S. Survival at 1-, 2- and 4-years was 95.5%, 77% and 43.9% in patients with mVI/S and 96.9%, 92.1% and 73.8%, in patients without mVI/S and respectively; p=0.015.

Median time to recurrence (n= 66, 30 events) was 28.8 months (95%CI: 6 – 51) in patients with sedentary lifestyle and not assessable in patients with active lifestyle. Recurrence at 1-, 2- and 4-years was 22.2%, 44.4% and 66.2%, in patients with sedentary lifestyle and 10.5%, 17.9% and 31.1% in patients with active lifestyle, respectively; p=0.015.

Median OS (n=66, 22 events) was 45.9 months (95%CI: 35 – 56) in patients with sedentary lifestyle and not assessable in patients with active lifestyle. Survival at 1-, 2- and 4-years was 94.6%, 81.1% and 49.2% in patients with sedentary lifestyle and 100%, 92.9% and 79.6% in patients with active lifestyle, respectively; p=0.003.

ABBREVIATIONS: mVI/S: microvascular invasion and/or satellitosis.