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Treatment patterns and outcomes in hepatocellular carcinoma: Real-world experience in Greece from the retrospective OPAL study

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Abstract

Background Newer advances involving immunotherapies are changing the hepatocellular carcinoma (HCC) landscape. In the multinational OPAL study, we described the characteristics of patients with HCC during 2014-2021 in Greece.

Methods This was a retrospective chart review study of adults (alive/dead) with newly diagnosed HCC between 2014-2021.

Results Of 406 patients, 37.7%, 33.0%, 25.9% and 3.4% had Barcelona Clinic Liver Cancer (BCLC) stage 0/A, B, C and D, respectively. Common etiologies were hepatitis B virus (32.9%), alcohol use (31.6%), hepatitis C virus (27.6%), and metabolic dysfunction-associated steatotic liver disease (26.3%); viral+non-viral: 15.5%. The first treatment was resection, embolization, ablation, systemic therapy and transplant, in 35.5%, 30.7%, 22.9%, 3.3% and 0.7% of BCLC-0/A; 14.9%, 48.5%, 9.0%, 15.7% and 0% of BCLC-B; and 4.8%, 18.1%, 3.8%, 49.5% and 0% of BCLC-C patients; 7.2%, 11.9% and 23.8% of patients in the respective BCLC groups remained untreated. Tyrosine-kinase inhibitor monotherapy was the commonest systemic therapy (76.7%). Among BCLC-0/A, BCLC-B, and BCLC-C patients, median progression-free survival was 15.8, 8.0 and 3.2 months, and overall survival (OS) was 45.7, 21.8 and 7.9 months from treatment initiation, respectively. Among BCLC-D patients, median OS was 3.4 months from HCC diagnosis. By multivariate Cox regression analysis, hepatitis B virus etiology (P=0.016) and Eastern Cooperative Oncology Group performance status ≥1 (P=0.015) were independent factors associated with poorer OS among BCLC-C patients.

Conclusion Real-life clinical practice in Greece is aligned with European guidelines, while poor clinical outcomes underscore the need for implementation of new therapies.

Keywords Hepatocellular carcinoma, risk factors, survival, treatment patterns

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Introduction

Liver cancer was the sixth most commonly diagnosed cancer and the third leading cause of cancer death worldwide in 2022 [1], with an estimated 1699 incident cases and 1468 deaths in Greece [2]. Hepatocellular carcinoma (HCC) is the most common type of liver cancer [3], mainly associated with infection by hepatitis B (HBV) or C (HCV), alcohol misuse, and metabolic dysfunction-associated steatotic liver disease (MASLD), among other etiological factors of cirrhosis, with wide geographical variations [3]. Since 2000, a decrease in HBV-related HCC has been observed in Greece, with a

concomitant increase in non-viral HCC cases [4,5], reflecting the implementation of national HBV immunization programs, as well as HCV eradication programs through the use of direct acting antivirals, and the epidemic of the metabolic syndrome in Western countries [3,4,6].

The Barcelona Clinic Liver Cancer (BCLC) classification system is the most widely used staging system worldwide, comprising primary tumor characteristics, liver function and performance status [7-11]. BCLC guidelines divide HCC into 5 stages: BCLC 0 (very early, usually a single nodule <2 cm with no vascular invasion and performance status [PS] 0); A (early, usually 1-3 nodules <3 cm with no macrovascular invasion and PS 0); B (intermediate, usually multiple nodules with no macrovascular invasion and PS 0); C (advanced, usually extrahepatic spread [N1, M1] with macrovascular invasion and PS 1-2); and D (terminal) HCC, which are linked to prognosis and treatment recommendations. Early-stage HCC is susceptible to curative therapies—e.g., liver resection (LR), liver transplantation (LTX) and/or ablation—while intermediate stage HCC (iHCC) may require locoregional treatments, such as embolization and radiation therapy, or systemic therapy in cases of diffuse, infiltrative, extensive HCC liver involvement. Systemic anticancer treatment (SACT) has been the mainstay treatment for advanced-stage HCC patients (aHCC), aiming to improve survival and/or maintain quality of life without curative intent. End-stage patients are offered best supportive care (BSC) options, while LTX is also a curative procedure for those patients with end-stage liver function and HCC within the Milan criteria. Median overall survival (mOS) may range from 5 years in early-stage patients to 3 months in end-stage patients [7-11].

For advanced/unresectable HCC, sequential treatment with multikinase inhibitors was the standard of care (SOC) until the advent of immune-oncology (IO) agents in 2021 [7-11]. IO+anti-VEGF (atezolizumab+bevacizumab) now constitutes the SOC in the first-line (1L) treatment of advanced HCC, with a growing body of real-world evidence to support its utility [10-13]; a dual-IO regimen (durvalumab+tremelimumab) was recently granted European Medicines Agency (EMA) approval for unresectable/advanced HCC [14-17]; and multiple IO-based therapies are being investigated in ongoing trials across all HCC stages [18-21].

With the changing treatment landscape, and in the absence of a nationwide liver cancer registry in Greece, this study aimed to comprehensively describe the real-life management, clinical characteristics and outcomes of patients diagnosed with HCC in Greece over a period immediately preceding this new era. The evidence generated will serve as a benchmark for future studies addressing the uptake and clinical utility of the new therapeutic armamentarium.

Patients and methods

Study design and population

OPAL was a non-interventional, retrospective, observational study conducted in England, Italy, Spain, France, Denmark, Sweden, Switzerland, Greece and Portugal. Herein we present data retrieved from medical charts of patients treated in Greece. Eligible patients were adults with newly diagnosed HCC from January 1, 2014, until December 31, 2021 (referred to as the "index period"). Informed consent was obtained from patients who were alive at the time of their inclusion in the study; a consent waiver was granted for deceased patients by the competent institutional review boards of the participating study sites.

The retrospective observation period extended from the date of initial HCC diagnosis to the date of informed consent or death, with the latter representing the end of surveillance (EOS).

The study was designed, conducted and reported according to the Declaration of Helsinki, the Guidelines for Good Pharmacoepidemiology Practice of the International Society for Pharmacoepidemiology, the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines where applicable, the European Union General Data Protection Regulation, and the local regulations.

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Study objectives and definitions

The primary objectives were to describe patients' demographic and clinical characteristics, and treatment patterns. Secondary objectives included real-world overall survival (rw-OS), real-world progression free survival (rw-PFS) for locoregional or advanced disease, and recurrence free survival (rw-RFS) for early-stage disease from initiation of curative treatment.

To address the study objectives, patients were divided into subgroups by BCLC stage at initial HCC diagnosis, i.e., BCLC stages 0/A, B, C and D.

Non-systemic treatment (NST) refers to any surgical or non-surgical curative and/or locoregional treatment including LTX, LR, ablation, stereotactic body/external beam radiation therapy (SBRT/EBRT), transarterial chemoembolization (TACE), transarterial radioembolization (TARE), and transarterial embolization (TAE). BSC includes any therapy other than SACT received for the management of pain, nutritional and psychological support. For safety data, specific treatment-related adverse events were recorded.

Statistical analysis

A sample size of 400 patients was considered sufficient to ensure the precision of primary outcome measures with an error margin of 5.0%—with a 95% confidence interval (CI) using the Clopper-Pearson exact method ranging between 45.0% and 55.0%—for the estimation of a frequency of 50% where the width of the CI is greatest. Categorical variables are presented as absolute and relative frequencies, and continuous variables as mean (standard deviation) in the case of a normally distributed data, or median (interquartile range; IQR). The normality of distribution was examined using the Shapiro-Wilk test. Time-to-event analyses were conducted using the Kaplan-Meier (KM) method. Patients alive at chart abstraction were censored at the date informed consent was obtained. The log-rank test was used to compare the survival distribution between subgroups. The effect of potential confounders on rw-OS was examined using univariable and multivariate Cox regression models for BCLC-C patients. The final multivariate models were selected through a stepwise procedure based on the minimization of Akaike's information criterion. Variables with $P \leq 0.05$ in the univariate analysis, as well as those judged to be clinically significant, were included in the initial step of the stepwise procedure. All statistical tests were 2-sided and performed at a significance level of $P<0.05$. Statistical analyses were performed using SAS® software Version 9.4 (SAS Institute Inc., Cary, NC, USA).

Results

Patient disposition and BCLC stage distribution

From June 24, 2022, to March 14, 2023, 408 patients were enrolled in the study by 3 public academic hospital clinics (Attica: 1, Crete: 1, Thessaloniki: 1). Two patients did not meet all eligibility criteria; thus, the analysis was performed in 406 patients (Fig. 1A) with 69.5% (282/406) enrolled in Attica.

The study index period was 8.0 years, extending from January 1, 2014, to December 22, 2021. The proportion of patients diagnosed each year ranged from 7.1% (29/406) in 2014 to 17.0% (N=69/406) in 2021 (Fig. 1A). HCC was initially diagnosed at BCLC Stage 0/A, B, C, and D in 37.7%, 33.0%, 25.9% and 3.4% of patients, respectively (Fig. 1A).

At study inclusion, 74.4% of eligible patients (302/406) were deceased. The cause of death was related to HCC progression, non-HCC liver disease progression or treatment toxicity in 45.0% (136/302), 22.5% (68/302) and 2.0% (6/302) respectively. In 5.3% (16/302) the cause of death was unrelated to HCC, treatment toxicity or other liver condition. The median (IQR) length of the retrospective observation period (from initial HCC diagnosis to EOS) was 1.6 (0.7-3.2) years; 2.6 (1.8-4.4) for living and 1.3 (0.5-2.6) years for deceased patients. The proportion of deceased patients increased with advancing stage, whereas the length of the retrospective observation period decreased with advancing stage (Fig. 1A).

The frequency distribution of HCC BCLC stages by year is summarized in Fig. 1B. The proportion of BCLC-0/A cases were higher before 2017. Starting in 2017, a small shift in stage distribution was observed, which remained relatively constant throughout the subsequent years. BCLC-0/A cases represented 45.5% (56/123) of 2014-2016 HCC cases and 34.3% (97/283) of 2017-2021 cases. Conversely, the respective proportions of BCLC-C cases were 19.5% (24/123) and 28.6% (81/283), while BCLC-B and D patients were equally diagnosed between these 2 periods: 32.5% (40/123) vs. 33.2% (94/283), and 2.4% (3/123) vs. 3.9% (11/283), respectively.

Initial Child-Pugh (CP) classification data were not recorded in 42 patients. CP class A, B and C were reported in 68.6% (247/360), 26.1% (94/360) and 5.3% (19/360) of patients with available data, respectively, without notable variations through the years (Fig. 1C). However, CP classification differed significantly between the early-to-intermediate (0/A/B) and advanced BCLC (C/D) stages. The majority of BCLC-0/A/B patients were classified as CP-A, while only 52.7% of BCLC-C patients and 15.2% of BCLC-D patients were classified as CP-A (Fig. 1D).

Demographic and clinical characteristics of HCC patients

The study population was predominantly Caucasian (99.3%), male (84.0%), and aged ≥65 years (59.4%). Smoking and alcohol use were reported in approximately half of the patients with available data (Table 1). Sociodemographic characteristics in each BCLC stage are shown in Table 1.

The most common HCC etiologies were HBV (single infection) in 32.9% (125/380), alcohol use in 31.6% (120/380), HCV (single infection) in 27.6% (105/380), MASLD in 26.3% (100/380), while other factors were each reported in fewer than 8 patients (<2%). Combinations are summarized in Fig. 2A and B, showing an even distribution between viral vs. non-viral etiologies in the overall HCC population, with

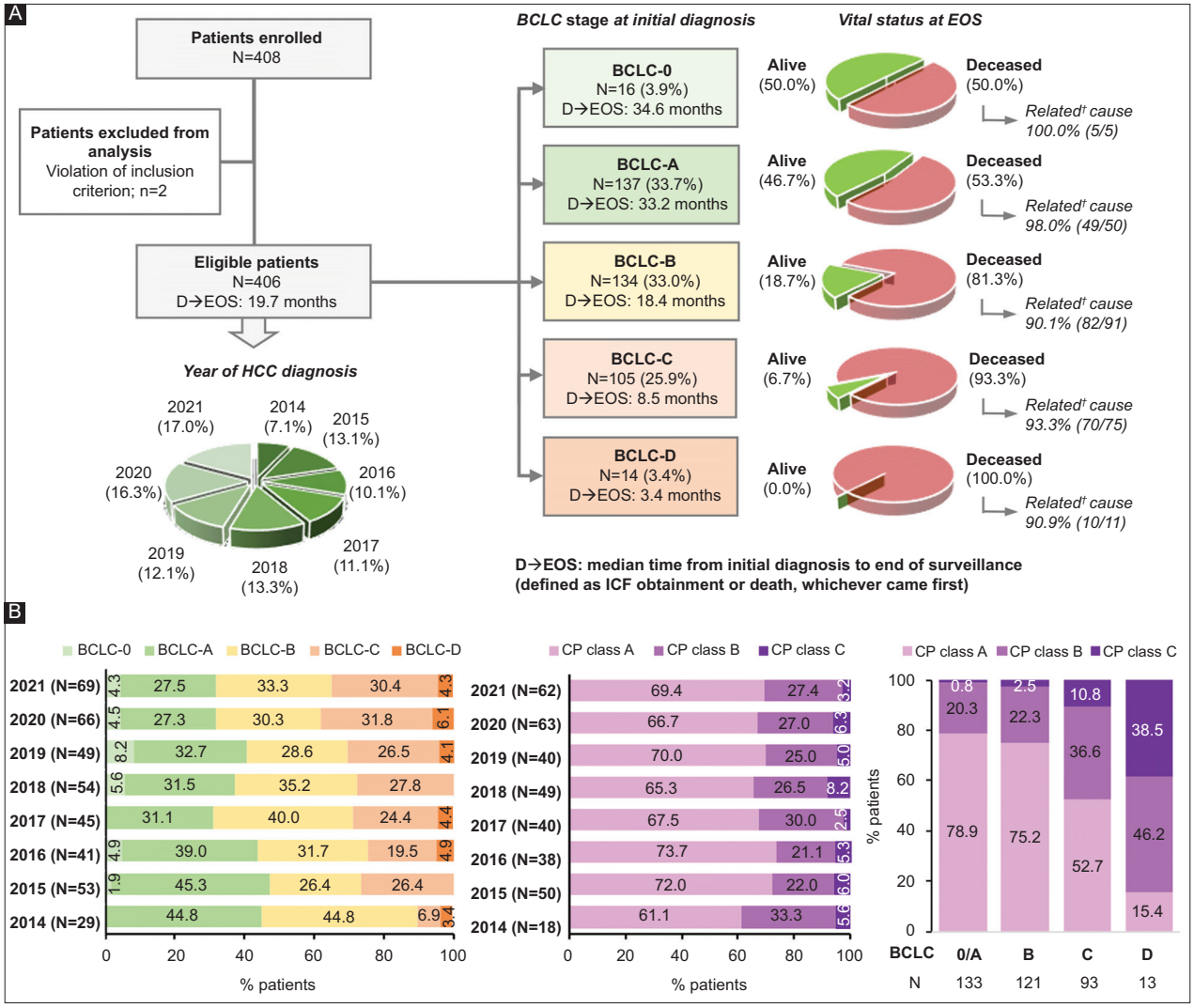


Figure 1 (A) Patient disposition by year and BCLC stage at initial diagnosis, and vital status at EOS; distribution of (B) BCLC stage and (C) CP class, per year of HCC diagnosis; (d) distribution of CP class per BCLC stage, throughout the index period

†Frequency of death related to HCC or Tx toxicity or other liver's affection among deceased patients with known cause of death

Imputation of date of death: for patients with only day missing, if month & year of death were the same as month & year of last follow-up contact, then day was set to day of last follow-up contact. Otherwise, day of death was set to the first day of the month. If both day and month of death were missing but the year was the same as the year of the last contact then the date of death was set to the date of last contact. For patients for whom the death month was missing but the year did not coincide with the year of the last follow-up contact, imputation was not performed. In case the imputation of date of death provided date earlier than the date of last treatment, then it was set to the date of last treatment. It is noted that the full date of death was missing for 42% (127/302) of the deceased patients [month was missing for 19% (58/302)]

BCLC, Barcelona Clinic Liver Cancer; CP, Child–Pugh; D, Diagnosis; EOS, end of surveillance; HCC, hepatocellular carcinoma; ICF, informed consent form; N, number of patients with available data; n, number of patients with variable; Tx, treatment

small variations across stages, mainly driven by differences in the prevalence of HBV (higher in BCLC-0/A/B) and alcohol use (higher in BCLC-B/C) (Fig. 2C). Time trends of HCC risk factors are shown in Fig. 2D, possibly reflecting trends in stage distribution (Fig. 1B).

The most frequent liver disease type was cirrhosis (77.2%) (Table 1). Clinical characteristics reflect an increasing disease severity in each BCLC subgroup, apart from clinically significant comorbidities for which no particular trends were observed across stages (Table 1).

Treatments

During the period from initial HCC diagnosis until EOS, 86.5% (351/406) of the patients received treatment (NST, SACT, or BSC). The most common reason for not receiving any treatment was severity of liver disease/death (37.0%; 17/46), or patient's wish (26.1%; 12/46), among untreated patients with available data (Supplementary Fig. 1A).

The treatment modalities received across different BCLC stages are shown in Fig. 3A. The most frequent NST was

Table 1 Sociodemographic and disease characteristics, overall and by HCC BCLC stage†

Characteristics	Overall (N=406)	Stage 0 (N=16)	Stage A (N=137)	Stage B (N=134)	Stage C (N=105)	Stage D (N=14)
Sociodemographic characteristics at initial HCC diagnosis						
Age at initial HCC diagnosis, mean (SD) years	66.9 (10.2)	68.0 (13.0)	66.9 (9.0)	67.0 (10.9)	66.1 (9.9)	70.4 (12.5)
Age ≥65 years, % (n/N)	59.4 (241/406)	56.3 (9/16)	61.3 (84/137)	61.2 (82/134)	54.3 (57/105)	64.3 (9/14)
Male, % (n/N)	84.0 (341/406)	93.8 (15/16)	83.2 (114/137)	86.6 (116/134)	81.9 (86/105)	71.4 (10/14)
Ever-smokers (current and former), % (n/N)	53.4 (197/369)	57.1 (8/14)	40.2 (51/127)	58.5 (69/118)	65.3 (64/98)	41.7 (5/12)
Ever-alcohol users, % (n/N)	50.1 (191/381)	37.5 (6/16)	39.5 (51/129)	59.7 (74/124)	52.0 (51/98)	64.3 (9/14)
Current moderate/ heavy alcohol users	12.9 (49/380)	6.3 (1/16)	3.9 (5/129)	15.4 (19/123)	20.4 (20/98)	28.6 (4/14)
Ever-parenteral (intravenous) drug use, % (n/N)	6.8 (26/383)	6.3 (1/16)	3.8 (5/131)	6.6 (8/122)	8.9 (9/101)	21.4 (3/14)
Any past or concurrent neoplasia, % (n/N)	10.6 (43/406)	18.8 (3/16)	11.7 (16/137)	9.0 (12/134)	10.5 (11/105)	7.1 (1/14)
Concurrent neoplasia, % (n/N)	1.2 (5/406)	.	0.7 (1/137)	1.5 (2/134)	1.9 (2/105)	.
Disease characteristics at initial HCC diagnosis						
Cirrhosis as liver disease type, % (n/N)	77.2 (302/391)	75.0 (12/16)	72.9 (97/133)	77.0 (97/126)	81.4 (83/102)	92.9 (13/14)
Decompensated	39.4 (114/289)	22.2 (2/9)	29.0 (27/93)	34.0 (32/94)	52.5 (42/80)	84.6 (11/13)
Histologic diagnosis, % (n/N)	44.3 (174/393)	40.0 (6/15)	45.4 (59/130)	45.0 (59/131)	42.7 (44/103)	42.9 (6/14)
Diffuse HCC, % (n/N)	10.1 (39/387)	.	.	10.2 (13/128)	22.1 (23/104)	23.1 (3/13)
Presence of nodules, % (n/N)	97.6 (367/376)	100.0 (12/12)	100.0 (127/127)	97.6 (120/123)	94.1 (95/101)	100.0 (13/13)
Single nodule	56.6 (213/376)	100.0 (12/12)	78.7 (100/127)	43.1 (53/123)	43.6 (44/101)	30.8 (4/13)
≥2cm in maximal diameter	50.0 (188/376)	.	74.8 (95/127)	40.7 (50/123)	38.6 (39/101)	30.8 (4/13)
2-3 nodules	24.2 (91/376)	.	20.5 (26/127)	30.9 (38/123)	20.8 (21/101)	46.2 (6/13)
Any with >3 cm in maximal diameter	16.0 (60/376)	.	2.4 (3/127)	26.8 (33/123)	18.8 (19/101)	38.5 (5/13)
Multiple nodules	16.8 (63/376)	.	0.8 (1/127)	23.6 (29/123)	29.7 (30/101)	23.1 (3/13)
Presence of extrahepatic spread, % (n/N)	6.1 (24/391)	.	.	.	19.2 (20/104)	30.8 (4/13)
Evidence of vascular invasion, % (n/N)	25.8 (101/392)	.	14.4 (19/132)	4.6 (6/130)	68.6 (70/102)	46.2 (6/13)
Portal vein invasion, % (n/N)	20.1 (77/384)	.	0.8 (1/130)	3.1 (4/129)	64.7 (66/102)	46.2 (6/13)
Main portal vein tumor thrombosis, % (n/N)	12.3 (48/391)	.	0.8 (1/130)	0.8 (1/130)	40.8 (42/103)	30.8 (4/13)
Other than main portal vein tumor thrombosis, % (n/N)	7.5 (29/388)	.	.	1.5 (2/130)	23.8 (24/101)	23.1 (3/13)
ECOG PS score % (n/N)						
PS 0	72.3 (248/343)	100.0 (12/12)	92.2 (107/116)	81.9 (95/116)	39.5 (34/86)	.
PS 1	20.4 (70/343)	.	7.8 (9/116)	14.7 (17/116)	47.7 (41/86)	23.1 (3/13)
PS ≥2	7.3 (25/343)	.	.	3.4 (4/116)	12.8 (11/86)	76.9 (10/13)
Tumor burden ≥50% of the total liver volume, % (n/N)	10.6 (40/377)	.	0.8 (1/131)	8.2 (10/122)	25.8 (25/97)	30.8 (4/13)
Distant metastatic disease, % (n/N)	5.6 (19/341)	.	.	.	16.9 (15/89)	30.8 (4/13)
ALBI grade, % (n/N)						
Grade 1	35.2 (113/321)	64.3 (9/14)	50.0 (50/100)	38.6 (39/101)	16.1 (15/93)	.
Grade 2	51.1 (164/321)	35.7 (5/14)	42.0 (42/100)	47.5 (48/101)	67.7 (63/93)	46.2 (6/13)
Grade 3	13.7 (44/321)	.	8.0 (8/100)	13.9 (14/101)	16.1 (15/93)	53.8 (7/13)

(*Contd...*)

Table 1 (*Continued*)

Characteristics	Overall (N=406)	Stage 0 (N=16)	Stage A (N=137)	Stage B (N=134)	Stage C (N=105)	Stage D (N=14)
Significant fibrosis (FIB-4 score >3.25), % (n/N)	59.8 (204/341)	42.9 (6/14)	50.9 (55/108)	59.1 (65/110)	68.8 (66/96)	92.3 (12/13)
MELD score, median (IQR)	10.0 (8.0, 14.0)	8.0 (7.0, 11.0)	9.0 (7.0, 10.5)	10.0 (8.0, 13.0)	11.0 (9.0, 15.0)	15.5 (10.5, 18.5)
Serum AFP ≥400 μg/L, % (n/N)	26.8 (87/325)	7.7 (1/13)	12.1 (12/99)	29.2 (31/106)	42.6 (40/94)	23.1 (3/13)
Any known HCC-related complication, % (n/N)‡	60.5 (199/329)	28.6 (4/14)	48.5 (50/103)	58.7 (61/104)	75.5 (71/94)	92.9 (13/14)
Esophageal varices	42.7 (137/321)	28.6 (4/14)	37.0 (40/108)	42.0 (42/100)	49.4 (44/89)	70.0 (7/10)
Ascites	25.8 (103/400)	6.3 (1/16)	15.7 (21/134)	18.2 (24/132)	44.2 (46/104)	78.6 (11/14)
Renal function impairment	5.5 (22/401)	.	1.5 (2/136)	4.6 (6/131)	10.6 (11/104)	21.4 (3/11)
Hepatic encephalopathy	5.3 (21/398)	.	3.8 (5/133)	3.1 (4/131)	8.7 (9/104)	21.4 (3/11)
Any clinically significant comorbidity, % (n/N)‡	70.7 (266/376)	93.3 (14/15)	68.5 (87/127)	69.8 (88/126)	70.1 (68/97)	81.8 (9/11)
Arterial hypertension	40.0 (161/402)	53.3 (8/15)	35.0 (48/137)	45.0 (59/131)	41.0 (43/105)	21.4 (3/14)
Diabetes mellitus	28.1 (114/405)	37.5 (6/16)	25.5 (35/137)	30.1 (40/133)	27.6 (29/105)	28.6 (4/14)
Hyperlipidemia	14.2 (57/402)	13.3 (2/15)	13.1 (18/137)	17.4 (23/132)	11.5 (12/104)	14.3 (2/14)
Coronary artery disease	10.6 (42/396)	6.7 (1/15)	11.1 (15/135)	8.3 (11/132)	12.0 (12/100)	21.4 (3/14)
Chronic obstructive pulmonary disease	9.5 (38/399)	12.5 (2/16)	8.0 (11/137)	9.2 (12/130)	12.7 (13/102)	.
Heart failure	6.3 (25/400)	6.3 (1/16)	3.7 (5/136)	6.8 (9/132)	5.8 (6/103)	30.8 (4/13)

†Variables with a missing data rate ≤30% are presented; ‡Reported at a frequency ≥10% in any subpopulation

AFP, alpha fetoprotein; ALBI, albumin-bilirubin; BCLC, Barcelona Clinic Liver Cancer; ECOG, Eastern Cooperative Oncology Group; FIB-4, fibrosis-4; HCC, hepatocellular carcinoma; IQR, interquartile range; MELD, Model for End-stage Liver Disease; n, number of patients with variable; N, number of patients with available data; PS, performance status; SD, standard deviation

embolization, followed by LR and ablation across BCLC-0/A/B/C stages (Supplementary Fig. 1B); note that just 1.7% (7/406) of the patients underwent LTX. The most frequent SACT across BCLC-0/A/B/C stages and lines of treatment was tyrosine kinase inhibitor (TKI) monotherapy followed by IO+anti-VEGF (Supplementary Fig. 1C). An increasing frequency of BSC/no treatment was observed with advancing stage (Fig. 3A), with only 1 BCLC-D patient receiving a non-BSC option (LR) (Fig. 3B; Supplementary Fig. 1B).

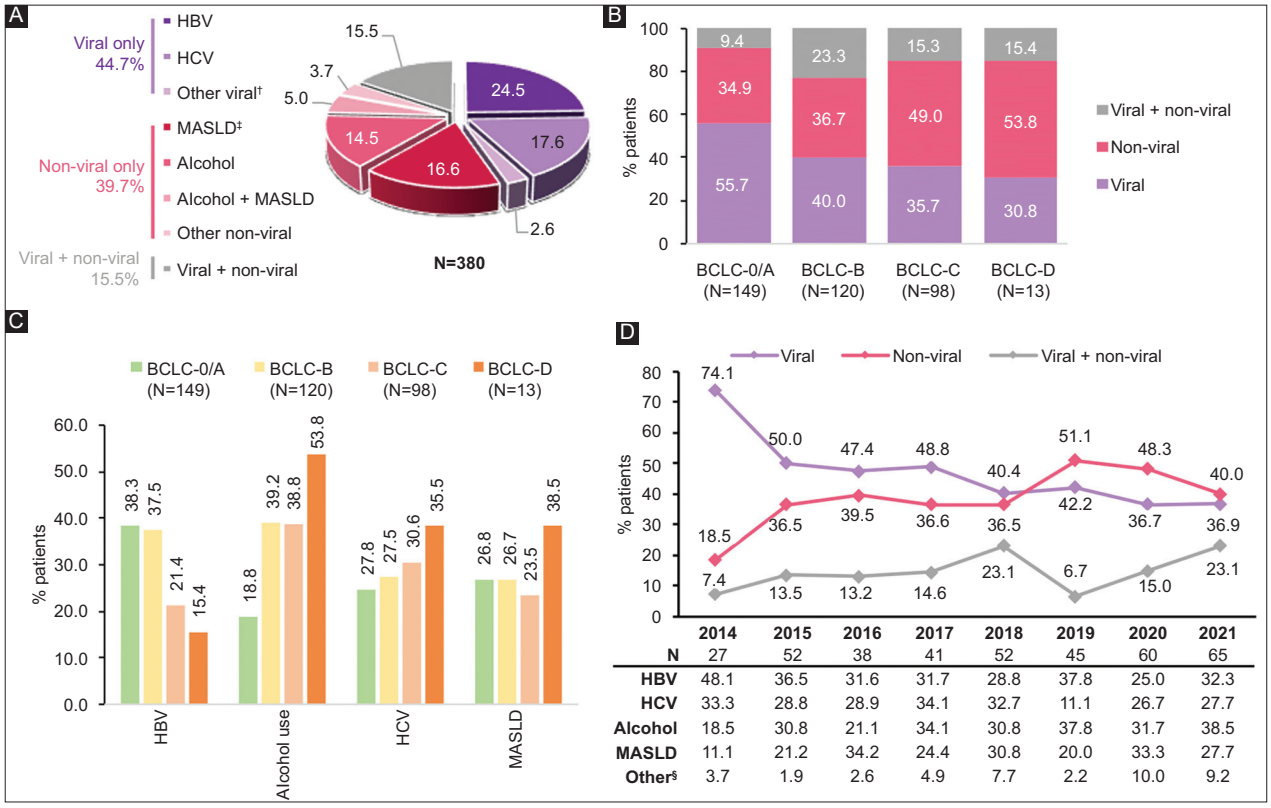
Treatment patterns were highly heterogeneous across BCLC-0/A/B/C stages. In terms of treatment sequences among BCLC-0/A and B patients, NST was the first treatment for 89.5% (137/153) and 72.4% (97/134) (Fig. 3B), of whom 43.8% (60/137) and 48.5% (47/97), respectively, moved on to receive 1L SACT. Five BCLC-A and 21 BCLC-B patients received 1L SACT as their first treatment (Fig. 3B). Among BCLC-0/A/B patients, curative-intent therapies (i.e., ablation/LR/LTX ±TACE) and TACE (excluding curative-intent therapies), were followed by SACT in 44.8% (64/143) and 43.2% (44/102) of cases, respectively (Figs. 3C and D). Overall, 1L SACT was initiated after first relapse/progression in 96.7% (58/60) and 89.5% (51/57) of NST+SACT-treated BCLC-0/A and BCLC-B patients, respectively. Of SACT-treated BCLC-0/A patients with available data, 77.0% (47/61) had progressed to a higher HCC BCLC stage by the time of 1L SACT initiation (Supplementary Fig. 1C).

Treatment sequences for BCLC-C are depicted in Fig. 3E. The first treatment was SACT in 49.5% of patients (52/105) and NST in 26.7% (28/105), which was followed by SACT in 67.9% (19/28) of the latter cases (Fig. 3B and 3E). Overall, 32.4% did not receive any SACT. The majority of patients experienced treatment-related adverse events of special interest during 1L SACT, with fatigue being the most common (Fig. 3F).

No particular trends were observed in key patient and disease characteristics between subgroups by most prevalent first treatment (Supplementary Table 1; Supplementary Fig. 2), apart from vascular invasion in BCLC-0/A/B patients, reported only for those receiving curative treatment and none of those treated with TACE.

Survival

The rw-PFS from HCC diagnosis, overall and by BCLC stage, is shown in Fig. 4A. rw-PFS differed significantly between BCLC stages (P<0.001; Fig. 4A, right panel); median rw-PFS was 19.8, 8.9 and 5.0 months from HCC diagnosis (Fig. 4B) and 15.8, 8.0 and 3.2 months from start of treatment among BCLC-0/A, BCLC-B and BCLC-C patients, respectively (Fig. 4B; Supplementary Fig. 3). For BCLC-0/A, median rw-PFS did not differ significantly between curative-intent therapies and TACE (P=0.051). LTX or LR with surgical margin R0 exhibited significantly longer median RFS compared with ablation (40.4 vs. 13.1 months; P<0.001). For BCLC-B, median rw-PFS was significantly longer (P<0.001) among those receiving curative-intent therapies (20.1 months) as first treatment than those receiving TACE (6.1 months) or SACT (5.7 months). Patient numbers for each treatment



N	2014	2015	2016	2017	2018	2019	2020	2021
	27	52	38	41	52	45	60	65
HBV	48.1	36.5	31.6	31.7	28.8	37.8	25.0	32.3
HCV	33.3	28.8	28.9	34.1	32.7	11.1	26.7	27.7
Alcohol	18.5	30.8	21.1	34.1	30.8	37.8	31.7	38.5
MASLD	11.1	21.2	34.2	24.4	30.8	20.0	33.3	27.7
Other§	3.7	1.9	2.6	4.9	7.7	2.2	10.0	9.2

Figure 2 HCC etiology: patterns, (A) overall and (B) per BCLC stage; (C) most prevalent¶ HCC risk factors per BCLC stage; (D) prevalence of HCC risk factors per year of HCC diagnosis∫

†"Other viral" includes: HBV/HCV coinfection (n=5), HBV/HDV coinfection (n=4), chronic hepatitis (not otherwise specified) (n=1)

‡Including Non-Alcoholic Steatohepatitis (NASH) and Simple steatosis (NAFL), in 85.5% and 14.5% of MASLD cases with known type (N=83), respectively

¶Reported at a frequency ≥10% at any subpopulation

∫The frequency of specific risk factors (regardless of HCC etiology pattern) per year of HCC diagnosis is presented in the data table below the graph; percentages do not add up to 100 since patients may have more than 1 risk factor

§"Other" HCC risk factors include: autoimmune liver disease (n=7), HBV/HDV coinfection (n=5), hemochromatosis (n=4), Alagille syndrome, Budd–Chiari syndrome, chronic hepatitis (not otherwise specified), history of hepatic adenoma and oral contraceptive use, PBC cirrhosis, secondary liver cirrhosis due to biliojejunal anastomosis (n=1, each)

BCLC, Barcelona Clinic Liver Cancer; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; N, number of patients with available data; MASLD, metabolic dysfunction-associated steatotic liver disease; PBC, primary biliary cholangitis

group in BCLC-C patients were too low to draw meaningful inferences; nevertheless, median rw-PFS appeared numerically longer, albeit not statistically significantly so, among those treated with IO+anti-VEGF rather than TKI monotherapy (3.9 vs. 2.9 months; P=0.609) (Fig. 4B; Supplementary Fig. 3).

The rw-OS from HCC diagnosis, overall and by BCLC stage, is shown in Fig. 5A. rw-OS differed significantly between BCLC stages (P<0.001; Fig. 5A, right panel); median rw-OS was 47.0, 20.4 and 8.5 months from HCC diagnosis (Fig. 5B) and 45.7, 21.8 and 7.9 months from start of treatment among BCLC-0/A, BCLC-B and BCLC-C patients, respectively (Fig. 5B; Supplementary Fig. 4). BCLC-D patients had a median rw-OS of 3.4 months from HCC diagnosis.

For BCLC-0/A and B, patients undergoing curative-intent treatment as first treatment had longer median rw-OS than those receiving TACE (62.1 and 49.5 vs. 33.1 and 18.2 months, respectively), while BCLC-B patients initially treated with SACT had the shortest rw-OS of 10.6 months (P=0.006 for BCLC-0/A and P=0.002 for BCLC-B; Fig. 5B; Supplementary Fig. 4). For BCLC-C patients, median rw-OS was significantly longer among patients treated with any NST (13.0 months) compared with IO+anti-VEGF (9.1 months) and TKI monotherapy (5.4 months) (P=0.026; Fig. 5B; Supplementary Fig. 4). Survival outcomes for BCLC-C should be interpreted with caution, given the small sample sizes in each treatment group. Among unresected patients with BCLC-B/C (any CP class and ECOG PS) receiving any HCC-specific treatment (N=158), median rw-OS from start of treatment was 11.9 months (95%CI 9.3-13.7; censoring: 13.3%). Among unresected patients with BCLC-B/C, CP class A, and ECOG PS 0/1, receiving only SACT post-diagnosis (N=25; TKI monotherapy, n=15; IO+anti-VEGF, n= 9; IO+other SACT, n=1), median rw-OS from start of 1L SACT was 7.4 months (95%CI 4.5-10.1; censoring: 4.0%).

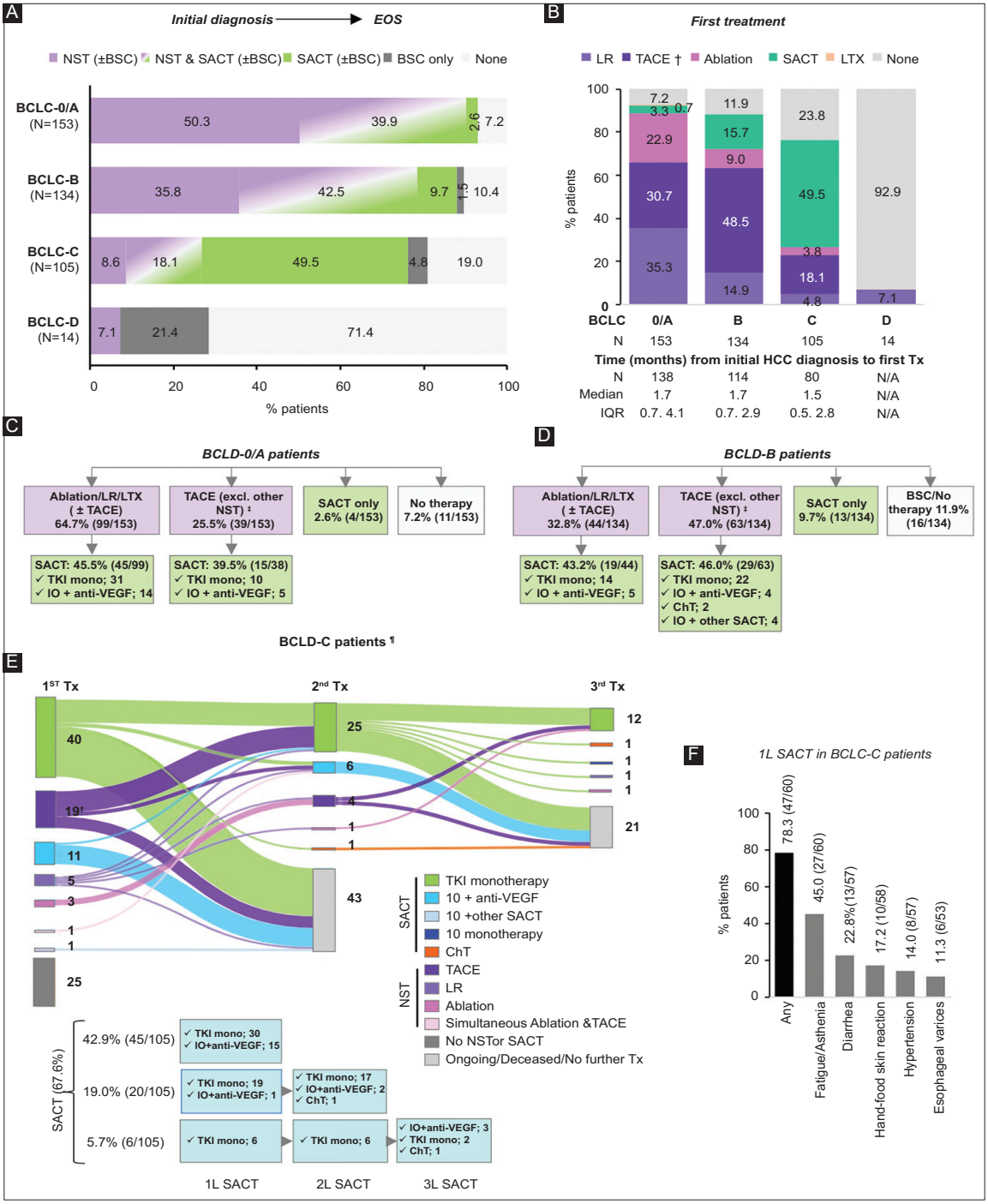


Figure 3 HCC-specific treatments: (A) treatment types from initial HCC diagnosis to EOS, per HCC BCLC stage; (B) initial treatments (excluding BSC), per BCLC stage; treatment sequences from initial HCC diagnosis to EOS among patients with BCLC Stage 0/A (C), B (D) and C; (F) treatment-related AEs of special interest[§] in 1L SACT among patients with BCLC Stage C

[†]For 1 patient (with Stage C) this was TARE

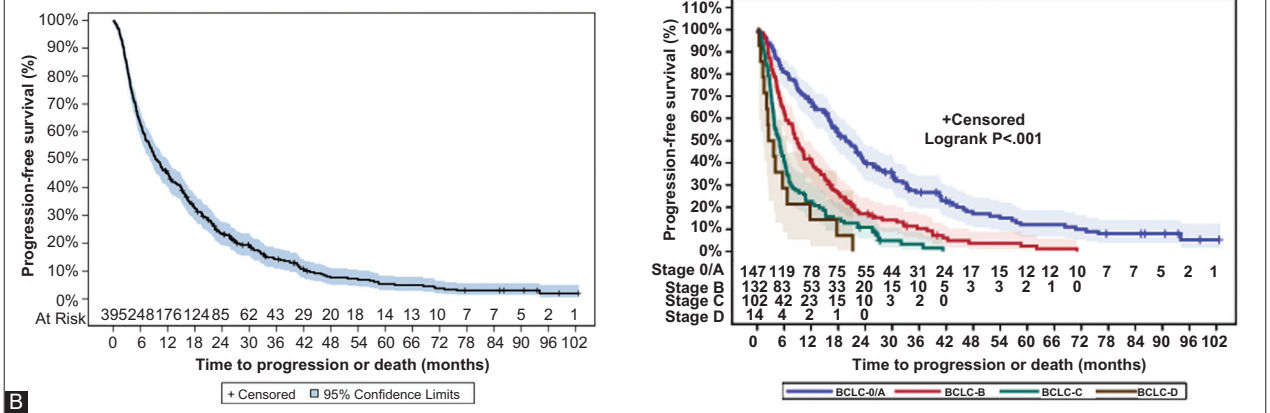
[‡]One patient with Stage A and 7 patients with Stage B, received 1L SACT prior to TACE

[¶]One patient with Stage C, received 4LT during the study observation period, which was IO+IO

[§]Reported at a frequency ≥10%, among pre-specified treatment-related AEs of special interest, namely fatigue/asthenia, hand-foot skin reaction, upper gastrointestinal hemorrhage, lower gastrointestinal hemorrhage, non-gastrointestinal hemorrhage, esophageal varices, neutropenia, colitis, anemia, deep vein thrombosis, pulmonary embolism, diarrhea, hepatitis, hypertension, hyperthyroidism, hypothyroidism, myocarditis, nephritis, pancreatitis, pneumonitis, and thrombocytopenia

1L/2L/3L, first/second/third line; AE, adverse event; BCLC, Barcelona Clinic Liver Cancer; BSC, best supportive care; ChT, chemoradiation; EOS, end of surveillance; HCC, hepatocellular carcinoma; IO, immunotherapy; IQR, interquartile range; LR, liver resection; LTX, liver transplant; N, number of patients with available data; NST, non-systemic treatment; SACT, systemic anticancer treatment; TACE, transarterial chemoembolization; TARE, transarterial radioembolization; Tx, treatment; VEGF, vascular endothelial growth factor

A



B

				KM-estimated time (months)		KM-estimated rates, % (95% CI)				
				Median (95% CI)	$n_{events}/n_{obs.}$	1-year	2-year	3-year	4-year	5-year
RFS	from HCC diagnosis		Any stage	9.6 (8.1-11.9)	360†/395	45.1 (40.1-49.9)	23.5 (19.4-27.8)	14.3 (10.9-18.2)	7.7 (5.1-11.1)	5.4 (3.2-8.4)
			BCLC-O/A	19.8 (16.3-23.3)	123/147	67.3 (59.1-74.3)	40.3 (32.2-48.2)	26.6 (19.4-34.4)	17.0 (10.9-24.3)	12.0 (6.8-18.8)
			BCLC-B	8.9 (7.0-10.5)	124/132	40.9 (32.5-49.1)	17.1 (11.1-24.1)	10.4 (5.7-16.7)	3.6 (1.1-8.9)	2.4 (0.5-7.3)
			BCLC-C	5.0 (3.7-6.0)	99/102	22.5 (15.0-31.0)	10.8 (5.7-17.7)	3.3 (0.8-9.1)	N/A	N/A
			BCLC-D	3.1 (1.3-6.7)	14/14	14.3 (2.3-36.6)	N/A	N/A	N/A	N/A
	from FIRST Tx	0/A	Any	15.8 (10.2-18.7)	109/131	55.2 (46.2-63.3)	33.3 (25.2-41.5)	23.3 (16.2-31.2)	16.4 (10.1-24.1)	11.5 (6.1-18.8)
			Abl/LR/LTX	17.9 (13.1-23.0)	69/86	63.3 (52.1-72.6)	37.3(26.9-47.6)	27.5(18.2-37.7)	18.9 (10.7-28.9)	15.5 (8.0-25.2)
			TACE	9.4 (5.4-18.2)	35/40	45.0 (29.3-59.5)	29.1 (15.9-43.6)	17.6 (7.5-31.4)	14.1 (5.1-27.7)	N/A
		B	Any	8.0 (5.5-11.0)	104/112	39.7 (30.6-48.7)	17.2 (10.&-25.0)	11.4 (6.1-18.7)	3.8 (1.1-9.5)	1.3 (0.1-6.0)
			TACE	6.1 (3.4-9.9)	61/62	33.9 (22.5-45.6)	11.3 (5.0-20.5)	9.4 (3.7-18.3)	N/A	N/A
			Abl/LR	20.1 (9.0-26.1)	24/30	65.9 (45.7-80.0)	33.2 (16.2-51.3)	23.7 (9.3-41.9)	17.8 (5.3-36.3)	5.9 (0.4-23.0)
			SACT	5.7 (1.6-9.9)	19/20	20.0 (6.2-39.3)	15.0 (3.7-33.5)	N/A	N/A	N/A
		C	Any	3.2 (2.3-4.1)	75/77	11.7(5.7-19.9)	7.4 (2.9-14.8)	N/A	N/A	N/A
			TKI mono	2.9 (2.2-4.1)	37/37	8.1 (2.1-19.6)	2.7 (0.2-12.1)	N/A	N/A	N/A
			Any NST‡	3.3 (2.1-4.8)	27/28	14.3 (4.5-29.5)	14.3 (4.5-29.5)	N/A	N/A	N/A
			IO+antiEGF	3.9 (0.7-11.2)	10/11	18.2 (2.9-44.2)	9.1(0.5-33.3)	N/A	N/A	N/A
	from 1L SACT	C	Any	3.9 (2.9-4.9)	52/69	25.2 (15.0-36.8)	15.5 (7.0-26.9)	7.7 (0.9-24.5)	N/A	N/A
			TKI mono	3.8 (2.3-4.9)	43/53	22.7 (12.0-35.5)	13.0(5.1-24.7)	6.5 (0.8-21.6)	N/A	N/A
			IO+antiEGF	4.2 (2.8-N/A)	8/15	37.6 (12.8-62.7)	37.6 (12.8-62.7)	N/A	N/A	N/A
PFS	from cur.Tx	0/A	Any	17.9 (13.1-23.0)	69/86	63.3 (52.1-72.6)	37.3 (26.9-47.6)	27.5 (18.2-37.7)	18.9(10.7-28.9)	15.5 (8.0-25.2)
			Abl	13.1 (6.2-21.6)	30/34	50.7 (32.4-66.4)	27.0(12.9-43.3)	15.8 (5.3-31.3)	7.9 (1.4-21.8)	3.9 (0.3-16.6)
			LTX / LR R0	40.4 (19.7-67.9)	19/32	78.1 (59.5-88.9)	55.3 (36.5-70.7)	51.6 (32.9-67.5)	36.2 (18.0-54.7)	36.2 (18.0-54.7)

Figure 4 rw-PFS: (A) KM curves from initial HCC diagnosis, overall and per BCLC stage; (B) KM-estimated time and rates of rw-PFS from initial HCC diagnosis, from start of first treatment and from start of 1L SACT, overall, per BCLC stage and per treatment

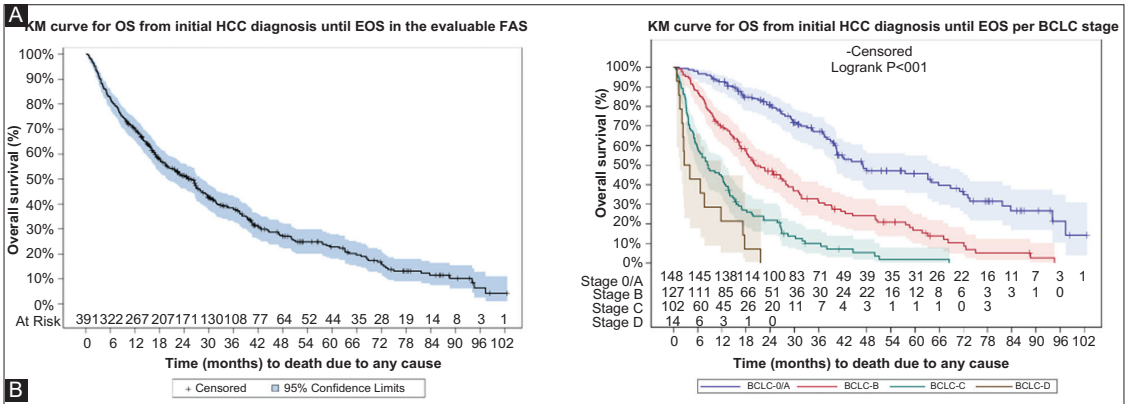
†Eleven (11) patients receiving only 1 Tx for whom it was unknown whether they experienced PD, or with unknown date of PD, and unknown date of death were completely excluded from the analysis. Out of 360 events, 257 were PD, 188 radiologic, 32 both radiologic and clinical, 14 clinical, 1 laboratory (AFP elevation) and 22 unknown; 79 were deaths; and for 24 events the date of disease progression/recurrence was unknown, therefore proxies were used (i.e. date of initiation of subsequent treatment modality)

‡LR/Ablation/TACE/TARE

1L, first line; Abl, ablation; BCLC, Barcelona Clinic Liver Cancer; CI, confidence interval; cur., curative; EOS, end of surveillance; HCC, hepatocellular carcinoma; IO, immunotherapy; KM, Kaplan–Meier; LR, liver resection; LTX, liver transplant; N/A, not available; n_{events}, number of events; $n_{obs.}$, number of observations; NST, non-systemic treatment; PD, progressed disease; rw-PFS, real world progression-free survival; RFS, recurrence-free survival; SACT, systemic anticancer treatment; TACE, transarterial chemoembolization; TARE, transarterial radioembolization; TKI, tyrosine kinase inhibitors; Tx, treatment; VEGF, vascular endothelial growth factor

KM-estimated rates of rw-PFS and rw-OS at 1-5 years are shown in Fig. 4B and Fig. 5B-C, respectively, displaying decreasing rates with advancing stage.

The association of factors of interest with rw-OS in BCLC-C as estimated from HCC diagnosis and from treatment initiation was examined using univariable (Supplementary Figs. 5 and 6) and multivariate (Fig. 5D) regression analyses. Multivariate analysis determined the following factors as predictors of shorter rw-OS: HBV etiology, ECOG PS ≥1, and no receipt of HCC-specific treatment or no receipt of NST as first treatment (Fig. 5D).



B

			KM-estimated time (months)		KM-estimated rates, % (95% CI)				
			Median (95% CI)	$n_{events}/n_{obs.}$	1-year	2-year	3-year	4-year	5-year
from HCC diagnosis		Any stage	25.6 (19.7-28.4)	287/391	69.8 (65.0-74.1)	51.4 (46.2-56.3)	38.1 (33.0-43.2)	27.1 (22.2-32.1)	22.8 (18.1-27.9)
		BCLC-O/A	47.0 (40.2-65.9)	76/148	92.5 (86.9-95.8)	80.8 (73.2-86.4)	67.1 (58.2-74.6)	47.1 (37.3-56.2)	45.6 (35.8-54.9)
		BCLC-B	20.4 (16.8-27.8)	102/127	69.2 (60.4-76.5)	46.9 (37.8-55.5)	31.7 (23.2-40.6)	24.2 (16.4-32.8)	16.7 (9.9-25.0)
		BCLC-C	8.5 (5.8-12.7)	95/102	44.1 (34.3-53.4)	21.8 (14.3-30.4)	10.0 (4.9-17.3)	5.4 (1.7-12.2)	1.8 (0.2-8.0)
		BCLC-D	3.4 (1.6-11.8)	14/14	21.4 (5.2-44.8)	N/A	N/A		
from FIRST Tx	0/A	Any	45.7 (36.8-62.1)	67/134	89.2 (82.5-93.5)	75.7 (67.1-82.4)	61.7 (51.9-70.1)	47.9 (37.5-57.6)	41.2 (30.5-51.5)
		Abl/LR/LTX	62.1 (39.7-73.0)	39/86	95.2 (87.8-98.2)	83.6 (73.5-90.2)	71.7 (59.8-80.6)	57.2 (44.1-68.3)	50.2 (36.6-62.4)
		TACE	33.1 (23.0-53.8)	23/43	80.8 (65.3-39.9)	63.8 (46.3-76.9)	49.7 (31.9-65.3)	34.5 (16.6-53.3)	25.9 (8.8-47.2)
	B	Any	21.8 (14.6-29.6)	83/108	69.7 (60.0-77.5)	49.0 (38.9-58.4)	35.2 (25.5-45.0)	27.4 (18.4-37.1)	18.3 (10.5-27.7)
		TACE	18.2 (12.6-26.1)	47/60	66.0 (52.3-76.5)	42.1 (29.0-54.5)	24.3 (13.5-36.9)	19.9 (10.1-32.1)	15.9 (6.6-28.8)
		Abl/LR	49.5 (26.1-59.4)	20/30	93.2 (75.5-98.3)	78.1 (57.5-89.6)	64.6 (42.5-80.0)	54.6 (32.5-72.2)	29.8 (12.5-49.5)
		SACT	10.6 (5.1-15.9)	16/18	44.4 (21.6-55.1)	25.4 (8.2-47.2)	25.4 (8.2-47.2)	8.5 (0.6-30.4)	8.5 (0.6-30.4)
	C	Any	7.9 (5.0-11.2)	72/78	35.7 (25.3-46.3)	20.6 (12.3-30.4)	9.1 (3.6-17.6)	2.4 (0.2-10.3)	N/A
		TKI mono	5.4 (3.0-8.3)	38/38	28.9 (15.7-43.6)	10.5 (3.3-22.5)	5.3 (1.0-15.5)	2.6 (0.2-11.8)	N/A
		Any NST‡	13.0 (7.1-27.4)	23/28	53.3 (33.5-59.7)	41.0 (22.5-58.7)	16.4 (4.6-34.7)	N/A	N/A
		IO+antiEGF	9.1 (0.7-11.2)	10/11	18.2 (2.9-44.2)	9.1 (0.5-33.3)	N/A	N/A	N/A
from 1L SACT	C	Any	6.9 (4.7-9.4)	64/69	30.8 (20.3-11.9)	16.9 (9.1-26.9)	6.2 (1.8-14.6)	4.2 (0.8-12.0)	N/A
		TKI mono	6.9 (4.1-11.4)	51/53	34.0 (21.7-46.6)	18.9 (9.7-30.3)	6.8 (1.9-16.1)	4.5 (0.9-13.2)	N/A
		IO+antiEGF	9.1 (1.2-11.2)	12/15	19.4 (3.7-44.3)	9.7 (0.6-34.0)	N/A	N/A	N/A

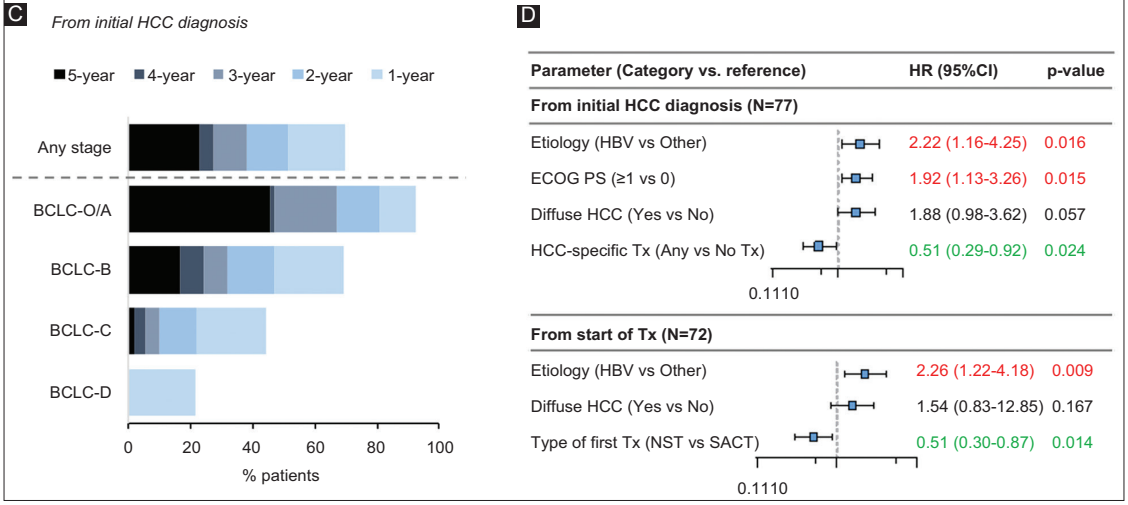


Figure 5 OS: (A) KM curves from initial HCC diagnosis, overall and per BCLC stage; (B) KM-estimated time and rates of OS from initial HCC diagnosis, from start of first treatment and from start of 1L SACT, overall, per BCLC stage and per treatment; (C) KM-estimated rates of OS from initial HCC diagnosis, overall and per BCLC stage; (D) multivariate models for the association of factors of interest with OS among patients with BCLC Stage C‡

†LR/Ablation/TACE/TARE

‡The following variables were included in the initial step of the stepwise procedure for both models: Age, Sex, Etiology, ECOG PS, Child-Pugh class, Portal vein invasion, Extrahepatic spread, Tumor burden, Diffuse HCC, Receipt of HCC-specific Tx (upper model)/Type of first Tx (lower model). The final multivariate model was selected based on minimization of the Akaike information criterion (AIC)

1L, first line; Abl, ablation; BCLC, Barcelona Clinic Liver Cancer; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; EOS, end of surveillance; HCC, hepatocellular carcinoma; HR, hazard ratio; IO, immunotherapy; KM, Kaplan–Meier; LR, liver resection; LTX, liver transplant; N/A, not available; n_{events}, number of events; $n_{obs.}$, number of observations; NST, non-systemic treatment; OS, overall survival; PS, performance status; SACT, systemic anticancer treatment; TACE, transarterial chemoembolization; TARE, transarterial radioembolization; TKI, tyrosine kinase inhibitors; Tx, treatment; VEGF, vascular endothelial growth factor

Discussion

The OPAL study provides valuable insight into the real-world profile, treatments and outcomes in patients diagnosed with HCC in Greece between January 2014 and December 2021, a period that largely preceded the availability of IO options [9,12-18]. The information presented herein represents leading specialized centers in the treatment of HCC across the country; thus, it will be valuable for healthcare policy decision making, in view of the paucity of local population-based studies over the last decade [4].

Our study supports HCC etiology trends previously described for Europe, and for Greece specifically [4-6]. Compared with prior data of 2012-2019 in Greece [4], HBV frequency was lower (33% vs. 44%), HCV frequency was similar (28% vs. 23%), while non-viral risk factors (>40% vs. 33%) were more frequent in OPAL. In spite of global awareness of the major contributors to HCC [3], HCC was newly diagnosed at an advanced/terminal stage in 29% of OPAL patients. Although information on adherence to HCC surveillance was not retrieved, the more frequent diagnosis of HCC at an early/intermediate BCLC stage (0/A/B) in patients with HBV (82%) compared to other causes (65%, excluding any HBV cases) implies that HCC surveillance is beneficial, as chronic HBV patients are usually followed more closely because of their need for long-term therapy. On the other hand, alcohol-related liver disease may be associated with poor adherence to any recommendation, and MASLD with both poor characterization of patients at HCC risk and inferior efficacy of current HCC surveillance methods. These observations highlight the continued need for better HCC surveillance programs to detect HCC early [22].

The OPAL Greek cohort demonstrated that 65% of early-stage HCC received curative-intent treatments, half of advanced-stage patients were treated with SACT only, explaining the low rw-OS, while intermediate-stage patients had the most variable treatment patterns, which is quite reasonable given the heterogeneity of this BCLC subgroup. TACE was the most frequent initial treatment for iHCC (49%). These observations were in line with European guidelines [7,8]. In an analysis of >1400 participants of the ongoing real-world TARGET-HCC study, enrolling patients with a wide range of disease severities from multiple sites in the US and Europe, 40% and 15% of BCLC-0/A and BCLC-B patients received initial treatment with a curative-intent option, which is lower than the OPAL 58% and 24%, respectively [23]. Consistently, a smaller proportion of BCLC-0/A and BCLC-B patients received TACE as initial treatment in OPAL compared with TARGET-HCC (31% and 49% vs. 56% and 77%, respectively). Initial treatment was SACT in a similar proportion of BCLC-C patients between the 2 studies: 50% in OPAL and 46% in TARGET-HCC [23]. As patients in TARGET-HCC are being followed longitudinally, treatment sequences will become available in the future, which will potentially allow more comprehensive comparisons. Although rates of curative intent treatment in OPAL appear favorable compared with the literature, still a large proportion of early-stage HCC patients were not offered this option. Further investigation into the reasoning behind treatment choices is warranted.

With upcoming therapies also expected in the early disease setting [18-21], it is imperative to identify potential applicability at a local level to inform healthcare decisions. For example, 15% and 22% of BCLC-0/A/B patients received SACT after TACE and curative-intent therapies, respectively, implying that significant proportions of HCC patients may relapse/progress and need further treatment, benefiting from new regimens of concomitant or adjuvant systemic therapy [18-21]. Similarly, the OPAL findings showed that HCC disease often recurs in early-stage patients receiving curative therapies, with 5-year recurrence-free survival of 15.5%. Overall, 5-year survival rates remained poor, and sharply decreased with advancing stage, from 46% in patients with very early/early stage to 17% for intermediate and 2% for advanced stage HCC, highlighting the high unmet need across all stages of HCC, especially for patients who are ineligible for curative options. This is further supported by our multivariate analysis showing that NST as first treatment for BCLC-C was associated with better survival time. Interestingly, HBV etiology was identified as an independent factor associated with poorer rw-OS in BCLC-C.

Most SACT comprised TKI monotherapy, reflecting the limited availability of IO-based regimens before 2020, when first EMA approval was granted [9]. BCLC-C patients exhibited a median rw-OS of 7.9 months from treatment initiation, in alignment with the range of 5.5-13.6 months reported for TKI-treated advanced HCC patients in other real-world cohorts in [24] Europe [25-29], as well as the 7.4 months reported for sorafenib-treated advanced HCC patients in clinical trials conducted in Europe [30]. However, clinical outcomes for BCLC-C patients in OPAL appear worse than the 13.2-13.8 months reported for the TKI SOC arm of recent clinical trials in advanced/unresectable HCC, possibly because of the inclusion of a C B population in the context of a real-world study [15,16,31,32]. In a subgroup analysis concerning specifically the 158 unresected BCLC-B/C patients, aiming to better align with the above patient population and with newer approved indications [13,15,17,32], we found that median rw-OS was 11.9 months. This indicates not only that aHCC represents a significant proportion of HCC patients in Greece (39%), but also that these patients have particularly poor outcomes and would welcome newly approved and improved therapies.

To minimize selection bias, a consecutive enrolment method was employed. The planned sample size was met, ensuring a small error margin. An acceptable error margin was generated in the BCLC-A/B/C subpopulations, with maximum error margins ≤10%. However, the small number of BCLC-0 and BCLC-D patients should be considered when interpreting outcomes in these subpopulations. Conservative imputation and censoring methods may have adversely affected time-to-event estimates towards the direction of underestimation. As this was a non-interventional study, no particular criteria were enforced for defining recurrence/progression. Lastly, all participating hospital institutions were public-academic clinics, thus, the results may not capture medical practice paradigms followed in private or non-academic sites.

In conclusion, these findings come to fill the gap of limited real-world evidence on patient, disease, and treatment characteristics, as well as poor clinical outcomes, in this heavily burdened patient population in Greece. As new and upcoming IO-based regimens become readily implemented in clinical practice for HCC management, evidence generated herein will serve as a basis for evaluating the impact of the shifting treatment landscape on long-term outcomes.

Acknowledgment

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Summary Box

What is already known:

- The epidemiology of risk factors for hepatocellular carcinoma (HCC) in the Western world has changed
- Resection and liver transplant remain the main curative therapy for early-stage HCC, while locoregional techniques and molecular targeted systemic therapy have been the mainstay of treatment for intermediate and advanced stages, prior to recent advances in immune-oncology agents
- There is a paucity of information on HCC management and associated outcomes in real-world clinical practice in Greece

What the new findings are:

- An even distribution between viral vs. non-viral etiologies was observed in a Greek cohort of 406 patients diagnosed with HCC between 2014 and 2021
- Nearly a third of HCC patients presented with advanced/terminal disease (Barcelona Clinic Liver Cancer [BCLC]-C/D) underscoring the need for better surveillance to achieve earlier diagnosis
- Patterns of HCC therapy showed adequate alignment with European treatment guidelines, while 5-year recurrence-free survival for early-stage patients treated with curative intent was as low as 15.5%
- Clinical outcomes were poor, with 5-year overall survival decreasing sharply from 46% in BCLC-0/A patients to 2% for BCLC-C, highlighting the high unmet need for new treatments across all stages of HCC

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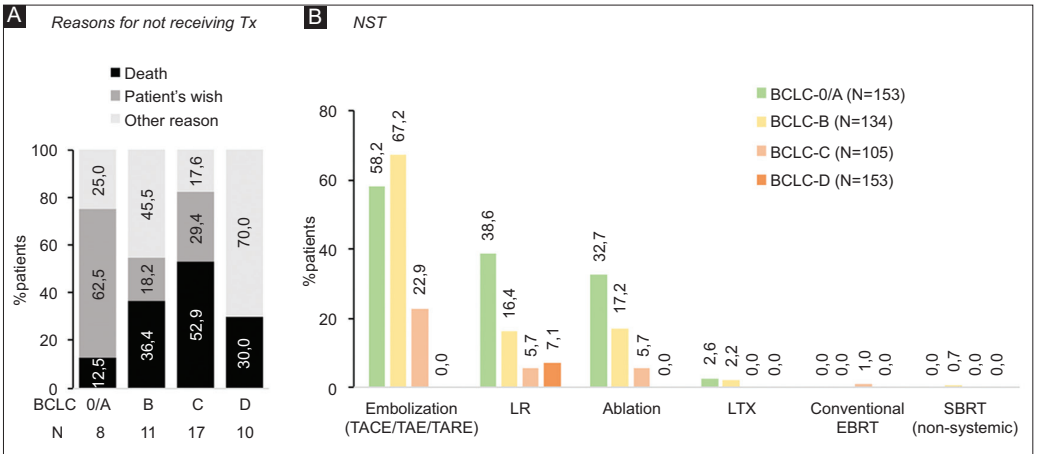
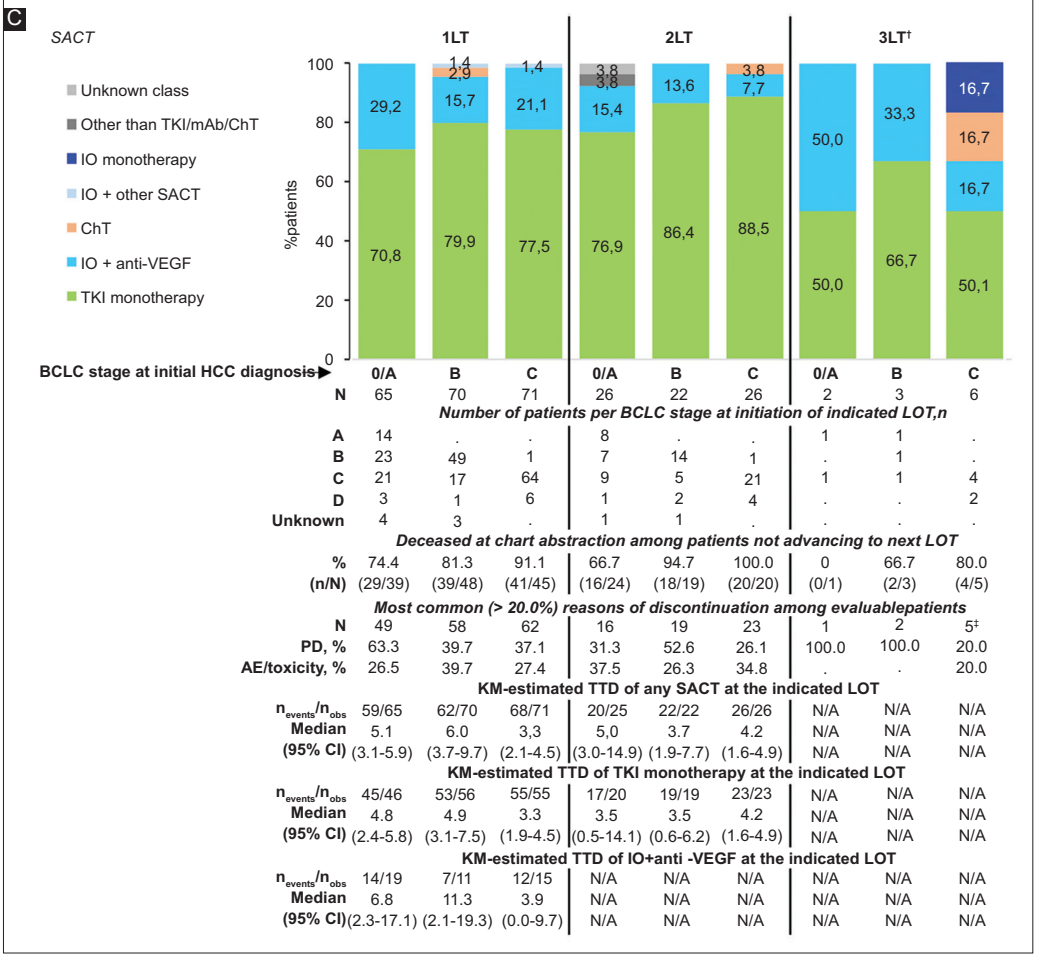
Supplementary material





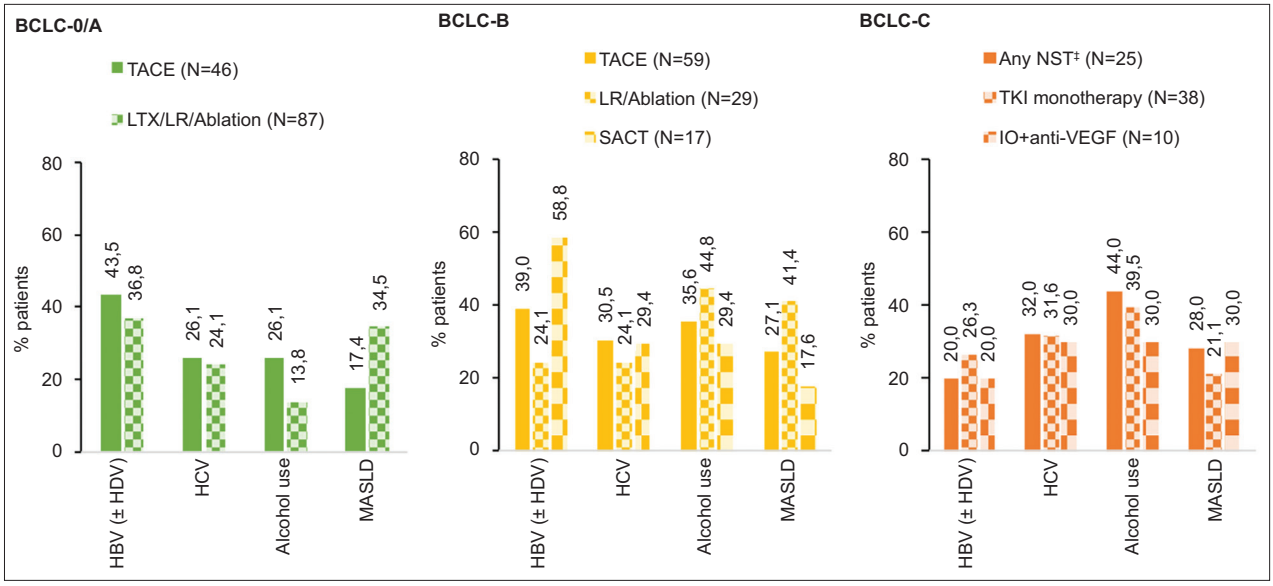
BCLC stage at initial HCC diagnosis	1LT 0/A	1LT B	1LT C	2LT 0/A	2LT B	2LT C	3LT† 0/A	3LT† B	3LT† C
N	65	70	71	26	22	26	2	3	6
Number of patients per BCLC stage at initiation of indicated LOT,n									
A	14	.	.	8	.	.	1	1	.
B	23	49	1	7	14	1	.	1	.
C	21	17	64	9	5	21	1	1	4
D	3	1	6	1	2	4	.	.	2
Unknown	4	3	.	1	1	.	.	.	.
Deceased at chart abstraction among patients not advancing to next LOT									
%	74.4	81.3	91.1	66.7	94.7	100.0	0	66.7	80.0
(n/N)	(29/39)	(39/48)	(41/45)	(16/24)	(18/19)	(20/20)	(0/1)	(2/3)	(4/5)
Most common (> 20.0%) reasons of discontinuation among evaluablepatients									
N	49	58	62	16	19	23	1	2	5‡
PD, %	63.3	39.7	37.1	31.3	52.6	26.1	100.0	100.0	20.0
AE/toxicity, %	26.5	39.7	27.4	37.5	26.3	34.8	.	.	20.0
KM-estimated TTD of any SACT at the indicated LOT									
n_{events}/n_{obs}	59/65	62/70	68/71	20/25	22/22	26/26	N/A	N/A	N/A
Median	5.1	6.0	3,3	5,0	3.7	4.2	N/A	N/A	N/A
(95% CI)	(3.1-5.9)	(3.7-9.7)	(2.1-4.5)	(3.0-14.9)	(1.9-7.7)	(1.6-4.9)	N/A	N/A	N/A
KM-estimated TTD of TKI monotherapy at the indicated LOT									
n_{events}/n_{obs}	45/46	53/56	55/55	17/20	19/19	23/23	N/A	N/A	N/A
Median	4.8	4.9	3.3	3.5	3.5	4.2	N/A	N/A	N/A
(95% CI)	(2.4-5.8)	(3.1-7.5)	(1.9-4.5)	(0.5-14.1)	(0.6-6.2)	(1.6-4.9)	N/A	N/A	N/A
KM-estimated TTD of IO+anti -VEGF at the indicated LOT									
n_{events}/n_{obs}	14/19	7/11	12/15	N/A	N/A	N/A	N/A	N/A	N/A
Median	6.8	11.3	3.9	N/A	N/A	N/A	N/A	N/A	N/A
(95% CI)	(2.3-17.1)	(2.1-19.3)	(0.0-9.7)	N/A	N/A	N/A	N/A	N/A	N/A

Supplementary Figure 1 HCC-specific treatments from initial HCC diagnosis to EOS: (A) reasons for not receiving any treatment, per HCC BCLC stage; (B) type of NST, per HCC BCLC stage; (C) type of SACT among patients receiving the indicated SACT LOT†, per HCC BCLC stage

†A total of 2 patients, 1 with Stage A and 1 with Stage C at initial HCC diagnosis, received 4LT during the study observation period, both with IO-based therapy, both had Stage C at initiation of 4LT, 1 was alive and the other dead at chart abstraction, respectively. No further LOTs were reported in the context of the study

‡PD (n=1), AE/toxicity (n=1), Death without preceding progression (n=1) and Physician's decision (n=2)

1LT/2LT/3LT, first/second/third line treatment; AE, adverse event; BCLC, Barcelona Clinic Liver Cancer; ChT, chemotherapy; CI, confidence interval; EBRT, external beam radiation therapy; EOS, end of surveillance; HCC, hepatocellular carcinoma; IO, immunotherapy; KM, Kaplan–Meier; LR, liver resection; LOT, line of treatment; LTX, liver transplant; N/A, not available; N, number of patients with available data; n, number of patients with variable; n_{events}, number of events; n_{obs}, number of observations; NST, non-systemic treatment; PD, progressed disease; SACT, systemic anticancer treatment; SBRT, stereotactic body radiation therapy; TACE, transarterial chemoembolization; TAE, transarterial embolization; TARE, transarterial radioembolization; TKI, tyrosine kinase inhibitors; TTD, time to treatment discontinuation; Tx, treatment; VEGF, vascular endothelial growth factor

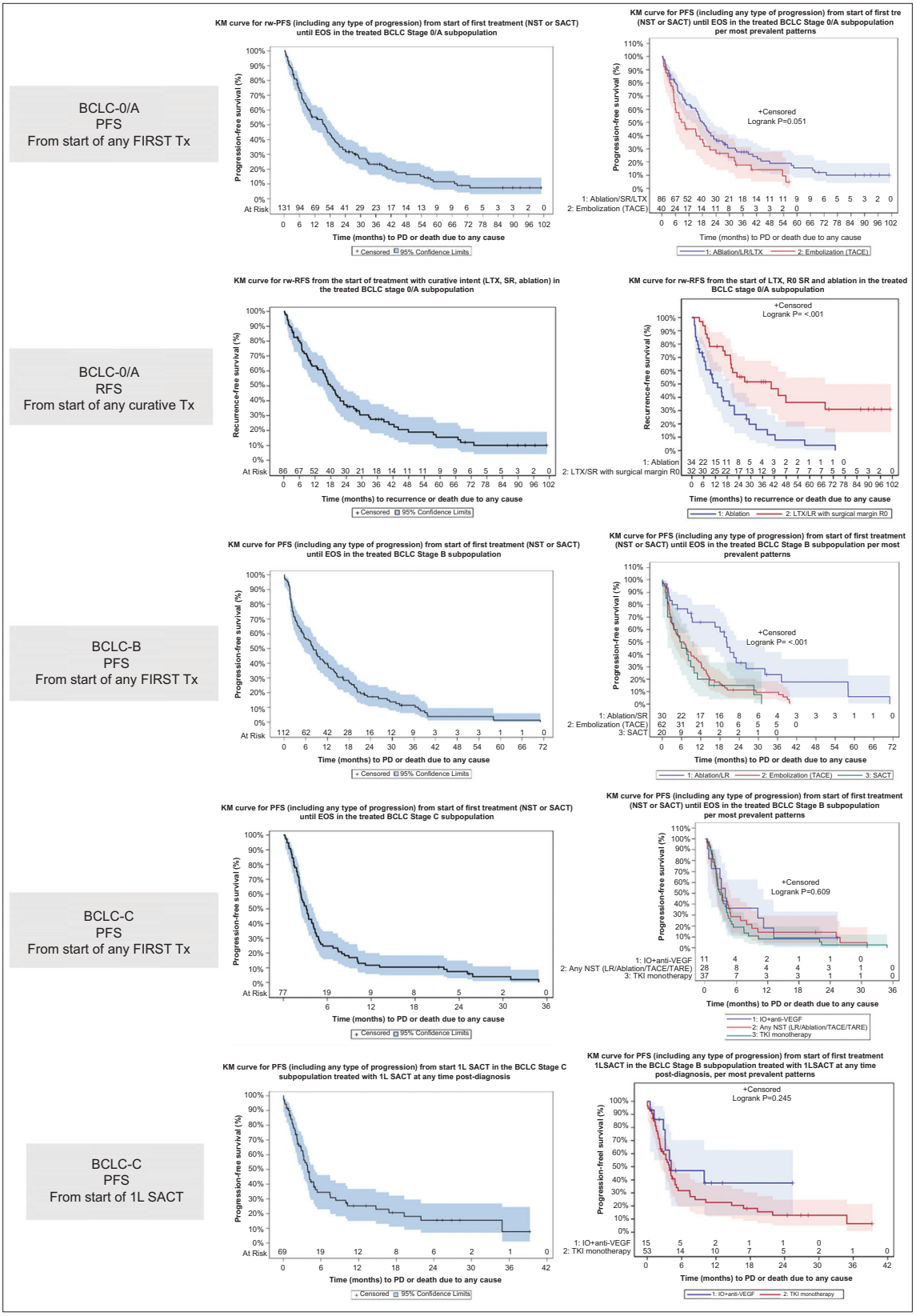


Supplementary Figure 2 Most prevalent† HCC risk factors by most prevalent first treatment (excluding BSC) in each HCC BCLC stage

†Reported at a frequency ≥10% at any subpopulation

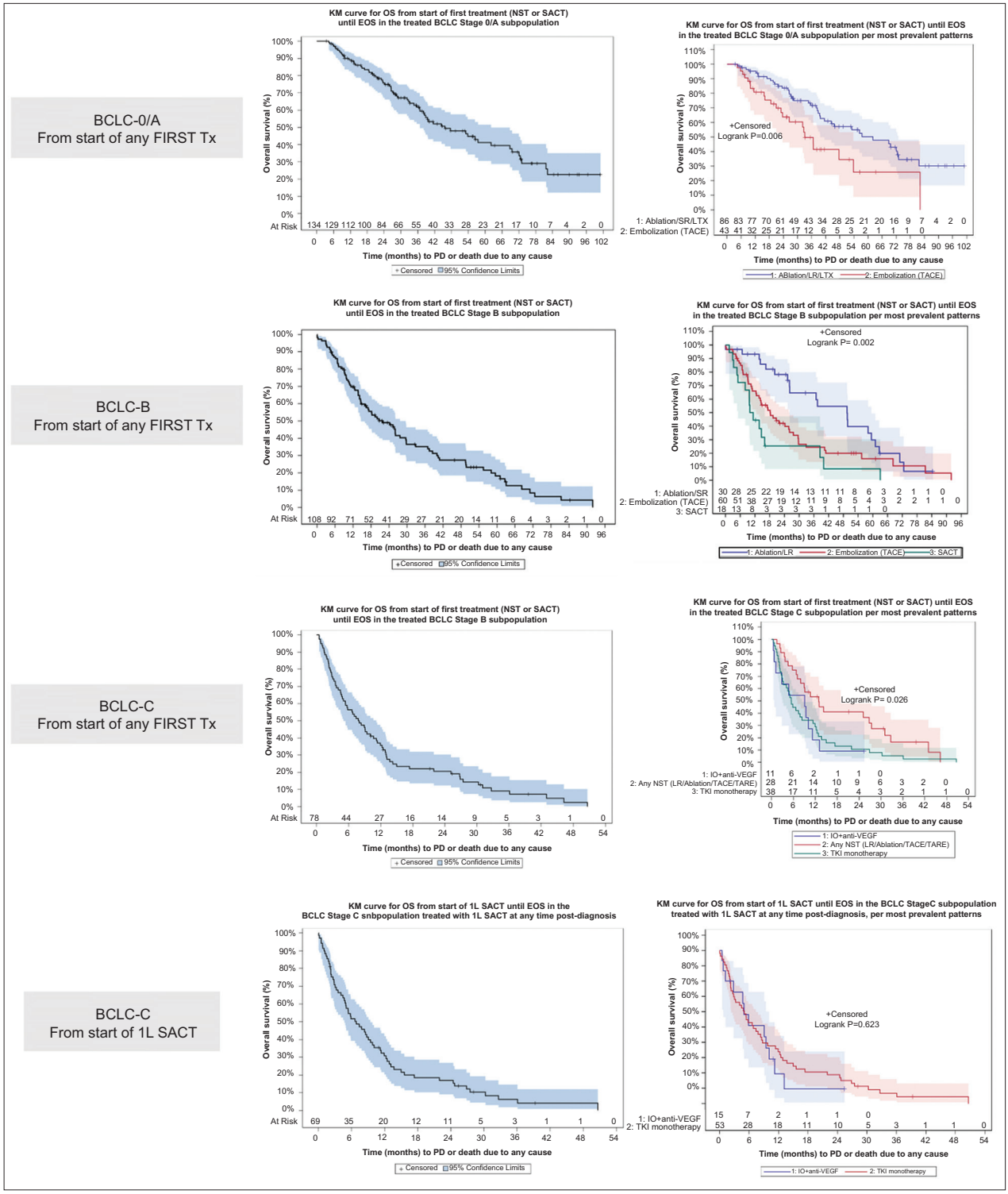
‡LR/Ablation/TACE/TARE

BCLC, Barcelona Clinic Liver Cancer; BSC, best supportive care; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HDV, hepatitis D virus; IO, immunotherapy; LR, liver resection; LTX, liver transplant; N, number of patients with available data; MASLD, metabolic dysfunction-associated steatotic liver disease; NST, non-systemic treatment; SACT, systemic anticancer treatment; TACE, transarterial chemoembolization; TARE, transarterial radioembolization; TKI, tyrosine kinase inhibitors, Tx, treatment; VEGF, vascular endothelial growth factor



Supplementary Figure 3 KM curves for rw-PFS and rw-RFS from start of treatment, per HCC BCLC stage

BCLC, Barcelona Clinic Liver Cancer; EOS, end of surveillance; HCC, hepatocellular carcinoma; IO, immunotherapy; KM, Kaplan–Meier; LR, liver resection; LTX, liver transplant; NST, non-systemic treatment; PD, progressed disease; rw-PFS, real world progression-free survival; rw-RFS, real world recurrence free survival; rw, real-world; SACT, systemic anticancer treatment; TACE, transarterial chemoembolization; TARE, transarterial radioembolization; TKI, tyrosine kinase inhibitors; Tx, treatment; VEGF, vascular endothelial growth factor

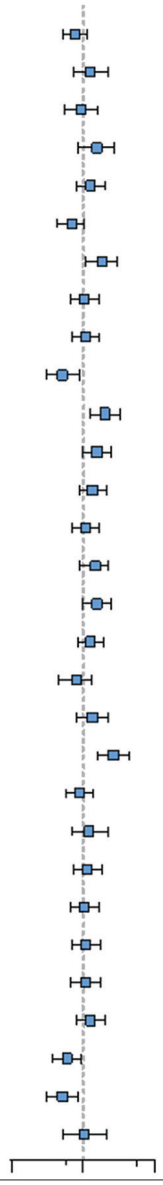


Supplementary Figure 4 KM curves for rw-OS from start of treatment, per HCC BCLC stage

BCLC, Barcelona Clinic Liver Cancer; EOS, end of surveillance; HCC, hepatocellular carcinoma; IO, immunotherapy; KM, Kaplan–Meier; LR, liver resection; LTX, liver transplant; NST, non-systemic treatment; rw-OS, real world overall survival; SACT, systemic anticancer treatment; TACE, transarterial chemoembolization; TARE, transarterial radioembolization; TKI, tyrosine kinase inhibitors; Tx, treatment; VEGF, vascular endothelial growth factor

From start of treatment

Parameter	Category vs. Reference	n_{pt}	n_{events}	HR (95% CI)	p-value
Age at initial diagnosis	≥65 years vs <65 years	57 vs 45	50 vs 45	0.78 (0.52-1.18)	0.235
Sex	Male vs Female	83 vs 19	78 vs 17	1.28 (0.75-2.07)	0.367
Residence	Urban/semiurban vs Rural	85 vs 17	78 vs 17	0.92 (0.54-1.57)	0.768
BMI	≥25 vs <25	35 vs 21	32 vs 18	1.53 (0.85-2.75)	0.153
Ever smoking	Yes vs No	62 vs 33	59 vs 29	1.27 (0.81-1.99)	0.304
	Non-viral vs Viral	47 vs 48	42 vs 48	0.68 (0.44-1.04)	0.072
	HBV Vs Other	**20 vs 75**	**20 vs 70**	**1.81 (1.08-3.02)**	**0.023**
Etiology	HCV Vs Other	28 vs 67	28 vs 62	1.05 (0.67-1.65)	0.832
	Alcohol use vs Other	36 vs 59	33 vs 57	1.08 (0.70-1.67)	0.715
	MASLD vs Other	**23 vs 72**	**20 vs 70**	**0.51 (030-0.87)**	**0.013**
ECOG PS	**≥1 vs 0**	**51 vs33**	**50 vs 27**	**2.03 (1.26-3.28)**	**0.004**
Child-Push	Class B/C vs Class A	41 vs 49	38 vs 45	1.55(1.00-2.39)	0.051
Liver diseasetype	Decompensated cirrhosisvs Other	40 vs 56	38 vs 51	1.35 (0.88-2.06)	0.168
Nodules	>2 vs <2	49 vs 49	48 vs 43	1.07 (0.70-1.63)	0.761
Evidence of vascular invasion	Yes vs No	69 vs 30	65 vs 27	1.44 (0.91-2.28)	0.118
Portal vein invasion	**Yes vs No**	**65 vs 34**	**61 vs 31**	**1.57 (1.01-2.44)**	**0.045**
Main portal vein tumor thrombosis	Yes vs No	41 vs 59	37 vs 56	1.26 (0.83-1.93)	0.278
Extra hepatic spread	Yes vs No	19 vs 82	16 vs 78	0.79 (0.46-1.36)	0.392
Tumor burden	≥50% vs <50% of total liver volume	23 vs 71	22 vs 65	1.33 (0.81-2.17)	0.257
Diffuse HCC	**Yes vs No**	**22 vs 79**	**22 vs 72**	**2.65 (1.59-4.42)**	**<0.001**
Serum AFP	≥400 µg/L vs <400 µg/L	39 vs 52	36 vs 4^	0.90 (0.58-1.39)	0.630
ALBI grade	≥2 vs <1	75 vs 15	69 vs 14	1.23 (0.69-2.20)	0.474
Significant fibros(FIB4 > 3.25)	Yes vs No	63 vs 30	58 vs 28	1.16 (0.72-1.85)	0.545
Clinically significant comorbidity	Yes vs No	66 vs 28	60 vs 27	1.03 (0.65-1.65)	0.894
Diabetes mellitus	Yes vs No	29 vs 73	27 vs 68	1.10 (0.70-1.74)	0.671
HCC-related complication	Yes vs No	68 vs 23	61 vs 23	1.07 (0.65-1.74)	0.797
Esophageal varices	Yes vs No	42 vs 44	38 vs 42	1.28 (0.81-2.02)	0.288
Receipt of HCC-specific Tx	**Any (NST, SACT) vs No Tx**	**78 vs 24**	**72 vs 23**	**0.60 (0.37-0.96)**	**0.035**
Type of first Tx	**NST vs SACT**	**28 vs 50**	**23 vs 49**	**0.51 (0.31-0.85)**	**0.009**
Type of first SACTTx	IO+anti-VEGF vs monotherapy	11 vs 39	10 vs 39	1.02 (0.50-2.07)	0.957



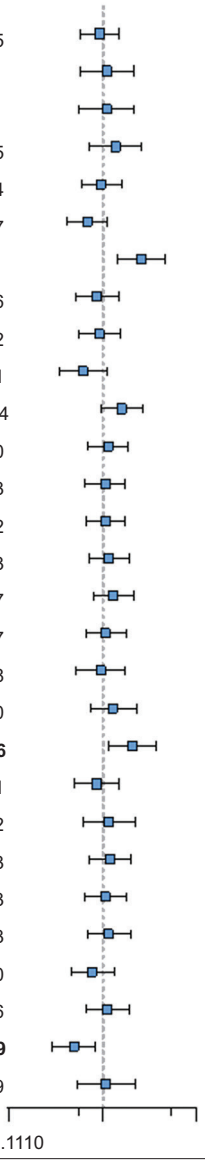
Supplementary Figure 5 Univariable Cox regression models for the association of selected baseline factors with rw-OS from initial diagnosis in the subpopulation with BCLC stage C

Three patients were excluded from the analysis as their date of death was unknown

AFP, alpha fetoprotein; ALBI, albumin-bilirubin; BCLC, Barcelona Clinic Liver Cancer; BMI, body mass index; CI, confidence interval; ECOG, eastern cooperative oncology group; FIB-4, fibrosis-4; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HR, hazard ratio; IO, immunotherapy; n_{events}, number of events; n_{pt}, number of patients with variable; MASLD, metabolic dysfunction-associated steatotic liver disease; NST, non-systemic treatment; rw-OS, real-world overall survival; PS, performance status; SACT, systemic anticancer treatment; TKI, tyrosine kinase inhibitors; Tx, treatment; VEGF, vascular endothelial growth factor

From start of treatment

Parameter	Category vs. Reference	n_{pt}	n_{events}	HR (95% CI)	p-value
Age at initial diagnosis	≥65 years vs <65 years	43 vs 35	37 vs 35	0.92 (0.57-1.47)	0.729
Sex	Male vs Female	66 vs 12	61 vs 11	1.12 (0.57-2.19)	0.750
Residence	Urban/semiurban vs Rural	67 vs 11	61 vs 11	1.10 (0.56-2.16)	0.780
BMI	≥25 vs <25	26 vs 18	23 vs 15	1.37 (0.71-2.64)	0.354
Ever smoking	Yes vs No	48 vs 27	45 vs 24	0.97 (0.59-1.59)	0.891
Etiology	Non-viral vs Viral	35 vs 37	30 vs 37	0.68 (0.42-1.11)	0.121
	HBV Vs Other	**16 vs 56**	**16 vs51**	**2.59 (1.42-4.69)**	**0.002**
	HCV Vs Other	21 vs 51	21 vs 46	0.87 (0.51-1.47)	0.601
	Alcohol use vs Other	28 vs 44	25 vs 42	0.93 (0.56-1.54)	0.784
	MASLD vs Other	19 vs 53	16 vs 51	0.62 (0.35-1.10)	0.103
ECOG PS	≥1 vs 0	38 vs 30	38 vs 24	1.61 (0.96-2.71)	0.072
Child-Push class	Class B/C vs Class A	27 vs 44	25 vs 40	1.14 (0.68-1.89)	0.617
Liver diseasetype	Decompensated cirrhosisvs Other	26 vs 48	25 vs 43	1.06 (0.64-1.75)	0.820
Nodules	≥2 vs <2	39 vs 37	38 vs 32	1.06 (0.65-1.72)	0.818
Evidence of vascular invasion	Yes vs No	54 vs 25	47 vs 23	1.17 (0.71-1.93)	0.542
Portal vein invasion	Yes vs No	47 vs 29	43 vs 27	1.30 (0.80-2.12)	0.285
Main portal vein tumor thrombosis	Yes vs No	28 vs 49	24 vs 47	1.07 (0.65-1.78)	0.781
Extra hepatic spread	Yes vs No	16 vs 62	14 vs 58	0.95 (0.52-1.71)	0.856
Tumor burden	≥50% vs <50% of total liver volume	18 vs 55	17 vs 50	1.30 (0.73-2.29)	0.370
Diffuse HCC	**Yes vs No**	**16 vs 62**	**16 vs 56**	**2.08 (1.16-3.71)**	**0.014**
Serum AFP	≥400 μg/L vs <400 μg/L	25 vs 44	23 vs 41	0.86 (0.50-1.47)	0.579
ALBI grade	≥2 vs <1	57 vs 13	52 vs 12	1.17 (0.62-2.20)	0.633
Significant fibros(BIB-4 > 3.25)	Yes vs No	46 vs 25	42 vs 23	1.18 (0.70-2.00)	0.536
Clinically significant comorbidity	Yes vs No	49 vs 24	44 vs 23	1.07 (0.63-1.80)	0.799
Diabetes mellitus	Yes vs No	21 vs 57	19 vs 53	1.16 (0.68-1.98)	0.575
HCC-related complication	Yes vs No	50 vs 20	44 vs 20	0.78 (0.46-1.33)	0.355
Esophageal varices	Yes vs No	30 vs 38	26 vs 36	1.12 (0.67-1.90)	0.662
Type of first Tx	**NST vs SACT**	**28 vs 50**	**23 vs 49**	**0.50 (0.30-083)**	**0.007**
Type of first SACTTx	IO+anti-VEGF vs monotherapy	11 vs 39	10 vs 39	1.08 (0.53-2.20)	0.824



Supplementary Figure 6 Univariable Cox regression models for the association of selected baseline factors with rw-OS from start of first treatment post-diagnosis in the subpopulation with BCLC stage C treated with HCC-specific treatment (NST, SACT)
Two patients were excluded from the analysis due to unknown date of death
AFP, alpha fetoprotein; ALBI, albumin-bilirubin; BCLC, Barcelona Clinic Liver Cancer; BMI, body mass index; CI, confidence interval; ECOG, eastern cooperative oncology group; FIB-4, fibrosis-4; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HR, hazard ratio; IO, immunotherapy; n_{events}, number of events; n_{pt}, number of patients with variable; MASLD, metabolic dysfunction-associated steatotic liver disease; NST, non-systemic treatment; rw-OS, real-world overall survival; PS, performance status; SACT, systemic anticancer treatment; TKI, tyrosine kinase inhibitors; Tx, treatment; VEGF, vascular endothelial growth factor

Supplementary Table 1 Key patient and disease characteristics, by most prevalent first treatment (excluding BSC) in each HCC BCLC stage

Characteristics	Stage 0/A		Stage B			Stage C		
	TACE (N=47)	LTX/LR/Ablation (N=90)	TACE (N=65)	LR/Ablation (N=32)	SACT (N=21)	Any NST† (N=28)	TKI mono (N=40)	IO + anti-VEGF (N=11)
Sociodemographic characteristics at initial HCC diagnosis								
Age ≥65 years, % (n/N)	63.8 (30/47)	61.1 (55/90)	67.7 (44/65)	59.4 (19/32)	52.4 (11/21)	57.1 (16/28)	45.0 (18/40)	72.7 (8/11)
Male, % (n/N)	87.2 (41/47)	84.4 (76/90)	89.2 (58/65)	81.3 (26/32)	81.0 (17/21)	82.1 (23/28)	90.0 (36/40)	81.8 (9/11)
Disease characteristics at initial HCC diagnosis								
Presence of extrahepatic spread, % (n/N)	0.0 (0/46)	0.0 (0/81)	0.0 (0/63)	0.0 (0/32)	0.0 (0/21)	14.3 (4/28)	25.0 (10/40)	27.3 (3/11)
Evidence of vascular invasion, % (n/N)	0.0 (0/45)	20.9 (18/86)	0.0 (0/63)	13.3 (4/30)	4.8 (1/21)	74.1 (20/27)	64.1 (25/39)	45.5 (5/11)
ECOG PS score, % (n/N)								
PS 0	93.5 (29/31)	96.4 (80/83)	87.9 (51/58)	86.7 (26/30)	66.7 (12/18)	46.2 (12/26)	34.4 (11/32)	60.0 (6/10)
PS 1	6.5 (2/31)	3.6 (3/83)	12.1 (7/58)	10.0 (3/30)	27.8 (5/18)	42.3 (11/26)	56.3 (18/32)	40.0 (4/10)
PS ≥2	.	.	.	3.3 (1/30)	5.6 (1/18)	11.5 (3/26)	9.4 (3/32)	.
CP classification, % (n/N)								
Class A	75.7 (28/37)	82.7 (67/81)	79.3 (46/58)	86.7 (26/30)	63.2 (12/19)	62.5 (15/24)	48.6 (18/37)	90.9 (10/11)
Class B	24.3 (9/37)	16.0 (13/81)	20.7 (12/58)	10.0 (3/30)	36.8 (7/19)	33.3 (8/24)	43.2 (16/37)	9.1 (1/11)
Class C	.	1.2 (1/81)	.	3.3 (1/30)	.	4.2 (1/24)	8.1 (3/37)	.
Tumor burden ≥50% of the total liver volume, % (n/N)	0.0 (0/44)	1.2 (1/86)	13.6 (8/59)	6.3 (2/32)	0.0 (0/17)	19.2 (5/26)	28.9 (11/38)	30.0 (3/10)
ALBI grade, % (n/N)								
Grade 1	48.6 (17/35)	55.2 (37/67)	38.6 (17/44)	55.6 (15/27)	26.3 (5/19)	17.4 (4/23)	18.9 (7/37)	18.2 (2/11)
Grade 2	48.6 (17/35)	37.3 (25/67)	50.0 (22/44)	33.3 (9/27)	57.9 (11/19)	56.5 (13/23)	75.7 (28/37)	81.8 (9/11)
Grade 3	2.9 (1/35)	7.5 (5/67)	11.4 (5/44)	11.1 (3/27)	15.8 (3/19)	26.1 (6/23)	5.4 (2/37)	.
Any known HCC-related complication, % (n/N)‡	42.9 (18/42)	42.2 (27/64)	63.0 (29/46)	38.5 (10/26)	57.9 (11/19)	75.0 (18/24)	71.1 (27/38)	77.8 (7/9)
Esophageal varices	35.7 (15/42)	29.4 (20/68)	50.0 (22/44)	34.6 (9/26)	22.2 (4/18)	40.0 (10/25)	48.6 (17/35)	55.6 (5/9)
Ascites	17.8 (8/45)	11.2 (10/89)	12.5 (8/64)	6.3 (2/32)	28.6 (6/21)	35.7 (10/28)	46.2 (18/39)	18.2 (2/11)
Renal function impairment	0.0 (0/47)	1.1 (1/89)	6.2 (4/65)	0.0 (0/30)	9.5 (2/21)	10.7 (3/28)	10.3 (4/39)	0.0 (0/11)
Any clinically significant comorbidity, % (n/N)‡	70.5 (31/44)	71.4 (60/84)	65.6 (40/61)	86.2 (25/29)	65.0 (13/20)	66.7 (18/27)	58.3 (21/36)	90.9 (10/11)
Arterial hypertension	34.0 (16/47)	41.1 (37/90)	42.2 (27/64)	51.6 (16/31)	50.0 (10/20)	32.1 (9/28)	40.0 (16/40)	90.9 (10/11)
Diabetes mellitus	31.9 (15/47)	26.7 (24/90)	35.9 (23/64)	28.1 (9/32)	23.8 (5/21)	21.4 (6/28)	22.5 (9/40)	45.5 (5/11)
Hyperlipidemia	10.6 (5/47)	14.4 (13/90)	21.9 (14/64)	18.8 (6/32)	9.5 (2/21)	14.3 (4/28)	5.0 (2/40)	9.1 (1/11)
Coronary artery disease	12.8 (6/47)	9.0 (8/89)	10.9 (7/64)	9.7 (3/31)	0.0 (0/21)	11.5 (3/26)	12.8 (5/39)	18.2 (2/11)
Chronic obstructive pulmonary disease	8.5 (4/47)	8.9 (8/90)	9.5 (6/63)	9.7 (3/31)	4.8 (1/21)	7.1 (2/28)	12.5 (5/40)	27.3 (3/11)
Heart failure	4.3 (2/47)	2.2 (2/89)	6.3 (4/64)	12.9 (4/31)	0.0 (0/21)	7.4 (2/27)	7.5 (3/40)	0.0 (0/11)

†LR/Ablation/TACE/TARE; ‡Reported at a frequency ≥10% in any subpopulation

ALBI, albumin-bilirubin; BSC, best supportive care; CP, Child–Pugh; ECOG, Eastern Cooperative Oncology Group; HCC, hepatocellular carcinoma; LR, liver resection; LTX, liver transplant; n, number of patients with variable; N, number of patients with available data; NST, non-systemic treatment; PS, performance status; SACT, systemic anticancer treatment; TACE, transarterial chemoembolization; TARE, transarterial radioembolization; TKI, tyrosine kinase inhibitors