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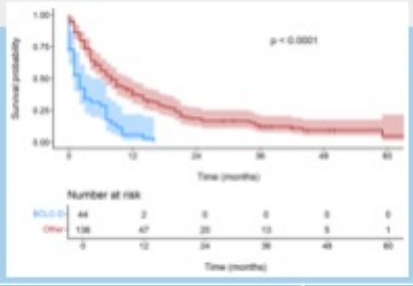
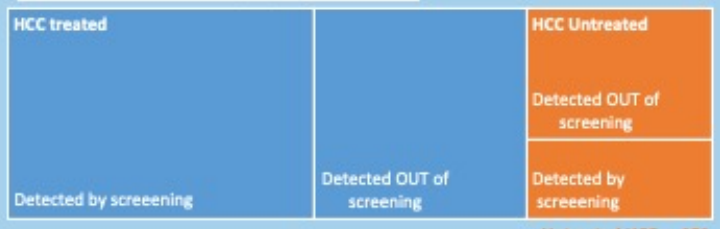
CHARACTERISTICS OF UNTREATED HEPATOCELLULAR CARCINOMA PATIENTS: INSIGHTS INTO THE NATURAL HISTORY AND PROGNOSTIC DETERMINANTS.

Restrospective unicenter cohort
n=685 HCC patients

Untreated HCC
n = 181



Untreated BCLC-D patients have a median overall survival of 2 months, compared to 8 months for those untreated due to other causes (comorbidity, frailty, etc.)



n = 299 (43,65%)

n=205 (29,93%)

Untreated HCC n=181
Out of screening n=114 (16,64%)
Detected by screening n=67 (9,78%)

* Overdiagnosis in 37% of untreated HCC patients

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Demographic and survival characteristics of untreated hepatocellular carcinoma patients: insights into the natural history and prognostic determinants

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ABSTRACT

Background: Hepatocellular carcinoma (HCC) patients with advanced symptoms or liver failure are often ineligible for transplantation, leading only to symptom control. Additionally, various factors lead to other HCC stage patients remaining in natural history.

Objective: To describe the demographic of untreated HCC patients and to analyze survival-influencing factors.

Methods: single-center retrospective observational study examining HCC patients diagnosed from 2015 to 2021 who received symptom control as their primary treatment. Baseline characteristics and survival data were collected and analyzed.

Results: Of 685 HCC patients, 26% (n=181) remained in natural history, median age 71 years, 82% male patients, 93% with cirrhosis, 53% with previous decompensation. At a mean follow-up of 9.98 months, the mortality rate was 84%. While 49.8% of patients were BCLC-D stage, other reasons for remaining in natural history included frailty (25.4%) comorbidities (16%), and patient's treatment refusal (8%). Independent survival factors were BCLC stage, previous decompensation and diagnosis within the screening program, with 37% of untreated patients detected through surveillance.

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Conclusions: Liver function, BCLC stage and functional status influence survival in natural HCC history. A significant 37% diagnosed through screening indicates inclusion criteria refinement necessity to avoid overdiagnosis and optimize resources.

Keywords: Overdiagnoses. Frailty. Surveillance. Liver neoplasms.

Key points:

Recent studies on Western populations with untreated hepatocellular carcinoma (HCC) often lack comprehensive data on patient characteristics and reasons for remaining untreated. This article offers insights into a contemporary cohort of untreated HCC patients, primarily with alcohol-related liver disease, amidst the backdrop of available direct-acting antivirals for hepatitis C and emerging systemic therapies, including immunotherapy. It details their clinical features, reasons for the absence of treatment, and survival based on BCLC staging.

Such real-world data, which cannot be gathered from clinical trials, is extremely valuable for informing the prognosis of current patients.

Indeed

1. The BCLC stage and previous decompensation are predictors of higher mortality among patients with untreated HCC.
2. Tumour progression and liver failure are the main causes of death in untreated HCC patients.
3. The presence of frailty and comorbidities inhibits treatment in nearly half of the patients.
4. Nearly 40% of patients with untreated HCC originate from screening programmes, highlighting the need to reallocate resources toward more suitable candidates to decrease cancer mortality.

INTRODUCTION

Hepatocellular carcinoma (HCC) ranks as one of the predominant neoplasms globally and is the third leading cause of cancer-related mortality, trailing only lung and

colorectal cancers (**1**). HCC distribution is remarkably heterogeneous, with its emergence significantly influenced by various factors that precipitate the progression of advanced chronic liver disease. Over 80% of HCC cases arise in cirrhotic livers. The prognosis is primarily contingent upon the therapeutic interventions feasible at diagnosis, delineated by the Barcelona Clinic Liver Cancer (BCLC) stage. Notwithstanding advancements in science and technology and the advent of novel treatments, the prognosis for this tumor type remains grim (**2-5**).

A substantial number of patients experience the natural history of HCC from diagnosis or at a juncture in their clinical course. Current data reveals considerable variability in survival and baseline characteristics among these patients, even when stratified by BCLC stage. Various observational studies have identified potential prognostic variables in untreated HCC patients, including Eastern Cooperative Oncology Group Performance Status (ECOG PS), International Normalized Ratio (INR), and Alpha-Fetoprotein (AFP) levels (**2**); presence of ascites, multinodular disease, and male gender (**3**); Model for End-Stage Liver Disease (MELD) score and AFP levels (**4**).

A comprehensive understanding of the baseline characteristics, prognosis, and survival outcomes of current untreated HCC patients is essential for making informed clinical decisions in routine practice. This real-world evidence, which is often unattainable through clinical trials, would provide critical insights for accurately assessing the prognosis of contemporary patients.

Clinical guidelines (**5**) advocate for the enrollment of high-risk individuals in HCC surveillance programs, employing semiannual ultrasonography to diminish cancer mortality. This strategy facilitates earlier detection, enhancing the chances of administering potentially curative treatments. However, the clinical outcomes attributable to HCC surveillance are suboptimal. Within our clinical setting, a mere 47% of diagnoses arise from screening programs (**6)**, and of these, only 20-40% are at a very early stage (single lesions < 2 cm). Additionally, some patients present with severe comorbidities or frailty at tumor detection, which constrains access to curative treatments, prompts stage migration in therapeutic planning, or even influences the decision to maintain natural history management.

There is a dearth of contemporary literature examining the characteristics and survival outcomes of HCC patients who continue under natural history management. Hence, we aim to conduct this study to delineate these patients' demographics and ascertain survival-associated factors. A secondary objective is to evaluate the proportion of patients remaining in natural history post-diagnosis within the HCC surveillance program, to enhance patient selection and mitigate overdiagnosis and resource misallocation (**7**).

METHODS

Study design

This retrospective cohort study was conducted at a single center, including all patients consecutively diagnosed with HCC from January 27th, 2015, to December 27th, 2021. We selected patients who did not receive specific HCC treatment (natural history cohort), monitoring them from diagnosis to follow-up termination or death until January 31st, 2022.

Liver function and disease etiology were established using standard commercial assays. Cirrhosis diagnosis relied on histological examination or unequivocal clinical and imaging evidence, with severity assessed by Child-Pugh scores. HCC was confirmed via ultrasound-guided biopsy or in accordance with established contrast-enhanced imaging guidelines. Tumor dimensions and stage were evaluated radiologically. Patient functional status was ascertained using Eastern Cooperative Oncology Group (ECOG) performance criteria. We employed the Barcelona Clinic Liver Cancer (BCLC) staging system to classify HCC: very early (BCLC 0), early (BCLC A), intermediate (BCLC B), advanced (BCLC C), and terminal (BCLC D). Survival time, expressed in months, was calculated from the point of HCC diagnosis to the event of death or the last follow-up update.

Ethical considerations

The present study was approved by the Research Ethics Committee of our institution, under the registration number CEImPA-2023.027. It adhered to pertinent guidelines and regulations, ensuring participant data were anonymized prior to statistical

analysis.

Statistical analysis

We characterized the patient cohort utilizing standard measures of central tendency and variability: means and standard deviations or medians and interquartile ranges for quantitative variables, contingent on the data distribution. Categorical variables were expressed as frequencies and percentages. For comparative analyses, the chi-square test or the Fisher's exact test were employed for categorical variables, while the Student's t-test or the Mann-Whitney test were utilized for continuous variables. Survival comparisons were facilitated through the Kaplan-Meier method paired with the log-rank test. Univariable Cox proportional hazards regression models with baseline variables were fitted, and a multivariable model was then fitted with those variables that yielded p-value < 0.05. The results were reported as Hazard Ratio (HR), its 95% confidence interval and p-value. All statistical tests were bidirectional, with a p-value < 0.05 denoting statistical significance. Statistical procedures were conducted using SPSS software, version 21.0 (SPSS Inc., Chicago, IL, USA) and R (version 4.4.1).

RESULTS

Among the 685 patients diagnosed within the specified timeframe, 181 (26%) fulfilled the inclusion criteria. **Table 1** details the baseline characteristics of treated and untreated HCC patients. The untreated patient cohort was predominantly male (82%, n=149), with a median age of 71. Cirrhosis was diagnosed in 93% (n=168) of patients, with 53% (n=97 experiencing some form of disease decompensation. The mean follow-up duration was 9.98 months, with 20 patients (11%) lost to follow-up.

Median survival by BCLC stage at diagnosis was as follows: 14 months for stage 0/A, 12 months for stage B and 4 months for stage C, as depicted in **Figure 1**. Patients with an ECOG Performance Status (PS) of 0 had a median survival of 13 months, those with ECOG PS-1 had 6 months, and those with ECOG >= 2 had a median survival of merely 2 months. A total of 49.8% of patients did not receive treatment due to decompensated cirrhosis with contraindication for liver transplantation and/or advanced symptoms

(ECOG PS > 2, BCLC-D stage) at diagnosis, resulting in a median survival of 2 months. The remaining 49% also had a median overall survival of 8 months but were untreated due to frailty (24.9%), comorbidities (16%), or patient refusal (8%), as shown in **Figure 2.**

Cox regression multivariate analysis identified three independent predictors of survival: 1) BCLC stage [Hazard Ratio (HR) 2.804, 95% Confidence Interval (CI) (1.628, 4.830)], 2) previous decompensation [HR 1.923, 95% CI (1.130, 3.273)] and 3) diagnosis via screening program [HR 0.583, 95% CI (0.383, 0.887)] as outlined in **Table 2, Figure 3**.

By the study's conclusion, 84% (n=152) of the patients had passed away, primarily due to tumor progression (74.3%, n=75). Tumor progression caused death more frequently in BCLC-D patients (94.4%) and frail individuals (71.1%), whereas non-tumor diseases were the leading cause of death (54.2%) for those with extrahepatic comorbidities.

Addressing the secondary objective, 357 of the 685 patients (53.4%) were diagnosed through a screening program. The reasons for not treating those diagnosed within the screening program but remaining on natural history at diagnosis (n=67, 37% of total untreated patients) included BCLC-D stage (41.8%, n=28), frailty (27%, n=18), comorbidities (22.4%, n=15), patient refusal (7.5%, n=5) and unknown (1.49, n=1).

DISCUSSION

An accurate assessment of the prognostic landscape for patients with untreated HCC is paramount for understanding the natural history of the disease and for evaluating survival rates that reflect everyday clinical practice. This knowledge is essential not only in aiding the correct diagnostic and therapeutic approach, optimizing resources, and facilitating clinical, social, and personal decision-making by the patient, but also in identifying predictive factors crucial for patient counseling.

Observational studies to date have examined various factors influencing the prognosis and survival of untreated HCC patients, presenting a spectrum of outcomes (**Table 3**). The reasons for foregoing treatment are diverse, relating to the presence of comorbidities precluding any therapeutic approach, advanced age, advanced tumor stage, poor residual liver function in patients not candidates for liver transplantation,

and patients' refusal of treatment. More than a quarter of individuals in our cohort remained untreated following HCC diagnosis, primarily due to decompensation of chronic liver disease, such as ascites unsuitable for liver transplantation, or the presence of HCC with symptoms (ECOG PS > 2 at diagnosis, BCLC-D stage), together accounting for 51% of cases. An additional 49% of patients did not receive specific treatment due to frailty, comorbidities that limited prognosis or contraindicated treatment, and patient refusal.

Previous studies like Cabbibo's (2012), which encompassed patients in their natural history between 1999 and 2010 with a predominant HCV etiology and a median survival of 6.8 months, identified an independent association of patient survival with ECOG PS, INR, and AFP (**2**). Giannini (2015) considered the pre-sorafenib Italian multicenter experience, noting a median survival of 9 months and lower survival associated with the presence of ascites, more than three lesions, and male sex (**4**). Khalaf's (2017) research on American veterans primarily afflicted by HCV, with 28% diagnosed through screening, recognized BCLC stage, MELD index, and AFP as independently associated with survival (**3**). Conversely, Kwon's (2023) study from the Korean registry reported that only 15.6% of patients remained in natural history, with a stark contrast in median overall survival between BCLC stages: BCLC-0 and A, 31 months versus BCLC-B and C, with median survivals of 10 and 1 month, respectively, underscoring BCLC stage, AFP, and MELD as baseline factors independently associated with survival (**8**).

Our study aligns with the understanding that BCLC stage and prior decompensation increase mortality risk, while diagnosis through screening programs independently correlates with extended survival, possibly affected by lead-time and selection biases. Remarkably, tumor progression and liver failure cause 75% of deaths among untreated patients, with over half of those precluded from HCC treatment due to comorbidity succumbing to their non-tumor conditions. Our findings emphasize the significance of screening programs in diminishing cancer mortality, with over 37% of untreated patients traced to screening, almost half of whom remained without treatment for reasons unrelated to their liver disease (frailty/comorbidities/patient refusal). This underscores the necessity for meticulous patient evaluation at each disease stage to

enhance screening and prioritize follow-up for those who will benefit from early detection (**7**).

The study's limitations include its nature as a single-center retrospective analysis that only accounts for baseline variables at HCC diagnosis, despite the data being derived from a prospective database serving a population of one million. The assessment of frailty and comorbidities as deterrents to treatment was non-systematic. Frailty, signaling loss of muscle mass, malnutrition, and functional capacity decline, is independently associated with mortality risk on the liver transplant waitlist and with poorer post-transplant outcomes. It also independently influences the likelihood of cancer patients receiving treatment and their survival prospects (**9**).

Liver Frailty Index (**10**), Charlson Comorbidity Index, or other scores **(21-24)** have not been used systematically. Nevertheless, the study's strengths are notable: the decision to maintain patients in their natural history was uniformly made within the multidisciplinary liver cancer committee, composed of expert members with extensive experience in this pathology. Additionally, with a single-payer system and the National Health Insurance Service covering the entire population, treatment rates could be higher than in other countries. No published series so far have defined frailty and comorbidity as compelling reasons (49% of our patients) for not receiving treatment. Furthermore, this is the first series where the primary etiology is alcohol, and it is a contemporary series in which direct-acting antivirals for hepatitis C and various systemic treatments for advanced hepatocellular carcinoma were already available, adding to its value. Recently, several antiangiogenic-free immunotherapy combinations have been introduced, potentially offering treatment options for patients with severe cardiovascular disease who were previously excluded from systemic therapy, which could alter their survival (**11-12**).

In conclusion, our study finds that 1) more than a quarter of patients remain without treatment after the diagnosis of HCC due to liver failure, contraindicating liver transplantation or other treatments, and the presence of extrahepatic comorbidities, and 2) that earlier BCLC stage and the absence of previous decompensation of cirrhosis are linked to increased survival in natural history.

This highlights the critical importance of proficient management and follow-up of chronic liver disease. It is vitally important to remain proactive in evaluating the inclusion and/or continuation of patients in the screening program to avoid unnecessary tests and focus resources on detecting those individuals for whom an early diagnosis implies the possibility of receiving curative treatment and improving survival.

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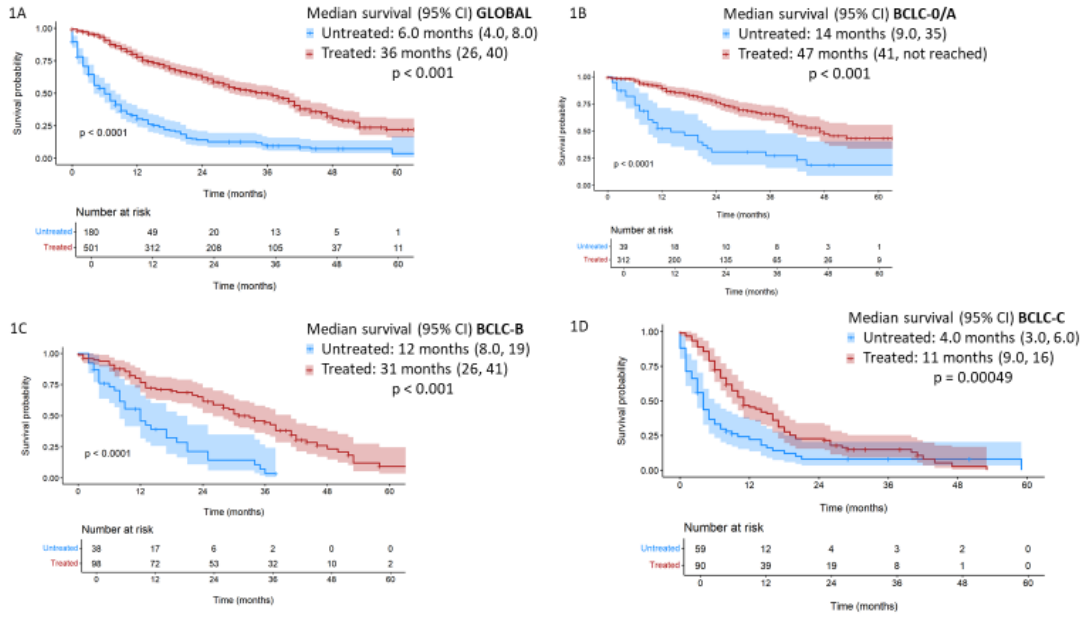

Figure 1: Kaplan-Meier graphs showing the overall survival (OS) of patients with HCC. Fig 1A: untreated vs treated patients [median OS 6 months, 95% CI 4.0, 8.0 vs median OS 36 months, 95% CI 26, 40]. Fig 1B: untreated vs treated BCLC 0-A patients [median OS 14 months, 95% CI 9.0, 35 vs median OS 47 months, 95% CI 41.0, not reached]. Fig 1C: untreated vs treated BCLC B patients [median OS 12 months, 95% CI 8.0, 19 vs median OS 31 months, 95% CI 26, 41]. Fig 1D: untreated vs treated BCLC C patients [median OS 4 months, 95% CI 3.0, 6.0 vs median OS 11 months, 95% CI 9.0-16.0].

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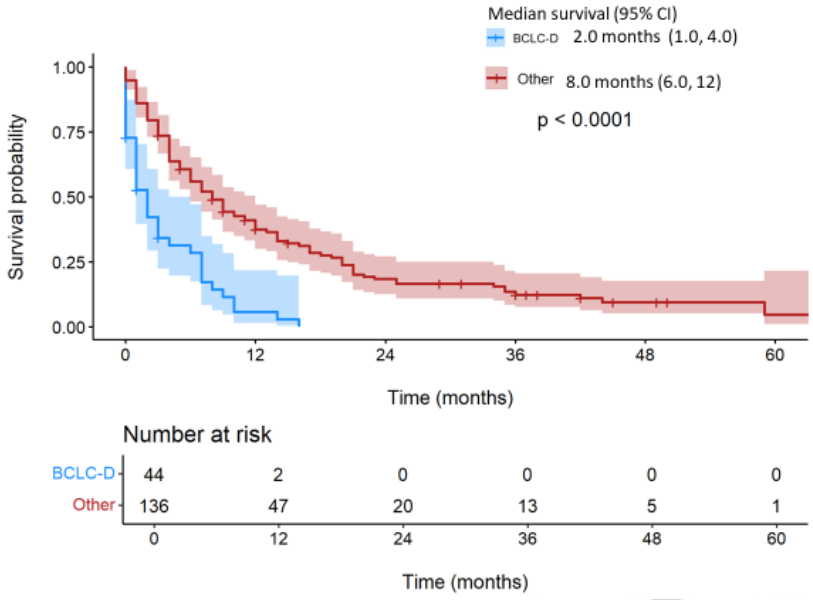

Figure 2: Kaplan-Meier graph comparing the survival of untreated patients due to BCLC-D status versus other causes: 2 months (95% CI 0.985-3.015) versus 8 months (95% CI 5.677-10.323), p<0.001.

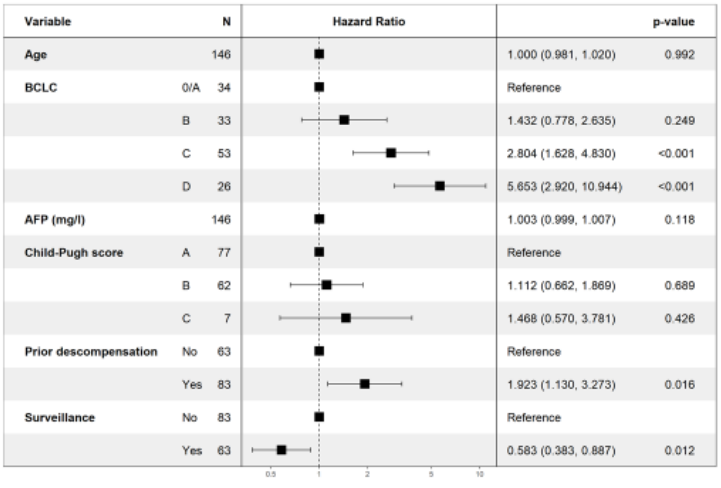

Figure 3: Multivariate analysis represented on a forest plot based on ratios.

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Table 1: Baseline characteristics of the cohort with treated and untreated HCC patients.

	Global	**Untreated**	**Treated**	**p-value**
n	685	181	501	
Age, years, median [IQR]	66 [59, 74]	71 [63, 79]	65 [58, 72]	< 0.001
Males, n (%)	586 (85.5)	149 (82.3)	435 (86.8)	0.139
Liver cirrhosis, n (%)	636 (92.8)	168 (92.8)	465 (92.8)	0.999
Etiology, n (%)				0.795
Alcohol	330 (51.9)	93 (55.4)	237 (51)	
Viral	232(36.5)	57 (33.9)	172 (37)	
MASLD	39 (6.1)	9 (5.4)	26 (5.6)	
Others	35 (5.5)	9 (5.4)	26 (5.6)	
Prior decompensation, n (%)	254 (37.1)	97 (53.6)	157 (31.3)	< 0.001
Child-Pugh class A score, n (%)	482 (76.9)	86 (51.2)	393 (86.2)	< 0.001
AFP >= 200 ng/mL, n (%)	112 (17.3)	50 (31.6)	62 (12.8)	< 0.001
ECOG PS, n(%)				< 0.001
PS 0	540 (79.3)	87 (48.1)	450 (90.5)	
PS 1	78 (11.5)	36 (19.9)	42 (8.5)	
PS 2	48 (7.0)	43 (23.8)	5 (1.0)	
PS 3	12 (1.8)	12 (6.6)	0 (0.0)	
PS 4	3 (0.4)	3 (1.7)	0 (0.0)	
BCLC stage at diagnosis, n (%)				< 0.001
BCLC stage 0	48 (7)	1 (0.6)	45 (9.0)	
BCLC stage A	306 (44.7)	38 (21)	267 (53.3)	
BCLC stage B	136 (19.9)	38 (21)	98 (19.6)	
Vascular invasion, n (%)	151 (22)	70 (38.7)	81 (16.2)	< 0.001
Extrahepatic spread, n (%)	52 (7.6)	30 (16.6)	22 (4.4)	< 0.001

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Table 2: Univariate and multivariate analysis of factors related to survival in the untreated HCC patients.

	Univariate		**Multivariate**	
	HR (95% CI)	p-value	HR (95% CI)	p-value
Age	0.982 (0.970, 0.996)	0.007		
Male	1.414 (0.925, 2.162)	0.109		
Cirrhosis	1.007 (0.558, 1.818)	0.981		
Prior decompensation	1.424 (1.029, 1.970)	0.033	1.923 (1.130, 3.273)	0.016
Child-Pugh score > A	1.793 (1.261, 2.549)	0.001		
Albumin	0.953 (0.929, 0.977)	< 0.001		
INR	1.016 (1.000, 1.032)	0.046		
Platelets	1.000 (1.000, 1.000)	0.352		
Bilirubin	1.020 (0.973, 1.068)	0.410		
Surveillance	0.587 (0.418, 0.823)	0.002	0.583 (0.383, 0.887)	0.012
AFP 200	2.315 (1.609, 3.331)	< 0.001		
ECOG-PS >0	2.124 (1.375, 3.281)	< 0.001		
BCLC > B	2.604 (1.635, 4.146)	< 0.001	2.804 (1.628, 4.830)	< 0.001
Vascular invasion	1.981 (1.420, 2.765)	< 0.001		
Extrahepatic disease	2.037 (1.336, 3.106)	< 0.001		
Reason for non-treatment: BCLC-D vs others	3.147 (2.136, 4.637)	< 0.001		

HR: hazard ratio; CI: confidence interval; INR: international normalized ratio; ECOG: Eastern Cooperative Oncology Group Performance Status; AFP: alpha-fetoprotein; BCLC: Barcelona Clinic Liver Cancer

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Table 3: Summary of studies published on the untreated HCC population.

Author, year [REF]	Source of patients	Period of Study	Untreated HCC: n (% of total HCC)	Untreated HCC: n (% from surveillance)	Overall survival, months: median (95% CI)	Overall survival by BCLC stage, months, median	Causes of death n (%)
Pawarode A, 1998 [13]	Retrospective unicenter study in Bangkok	1989 - 1996	157 (NR)	NR	8.7 weeks	NR	GI bleeding (34.1) Cancer related (31.8) Hepatic failure (25)
Villa E, 2000 [14]	Retrospective unicenter study in Modena	1993 -997	96 (NR)	NR	22 (17.8 – 26.1)	NR	Liver failure 29 (48.6) Tumor progression 20 (29.4) GI bleeding 7 (10.3) Undefined 12
Shah SA, 2011 [15]	SEER-Medicare database*	1991 - 2005	6135 (70.3)	NR	NR	NR	NR
Cabibbo G, 2012 [2]	Retrospective unicenter study in Palermo	1999 - 2010	320 (38.8)	NR	6.8 (5.8 – 7.7)	BCLC A: 33 BCLC B: 17.4 BCLC C: 6.9 BCLC D: 1.8	NR
Tan D, 2013 [16]	Meta-analysis **	1989-2013	NR (47.2)	NR	NR	NR	NR
Shaya FT, 2014 [17]	SEER database in USA	2000 - 2007	6583 (59.6)	NR	NR	NR	NR
Giannini EG, 2015 [3]	ITALICA database in Italy	1988 - 2008	600 (NR)	NR	9 (7.9-10.2)	BCLC 0: 38 BCLC A: 25 BCLC B: 10	HCC progression 279 (46.5) Liver failure 97 (16.2) GI bleeding 25 (4.2)

						BCLC C: 7 BCLC D: 6	Infection 4 (0.7) Various 17 (2.8) Unknown 68 (11.3)
Zeeneldin AA, 2015 [18]	Retrospective unicenter study in Cairo	1999 - 2007	288 (NR)	NR	2.3 (1.9 – 2.6)	NR	NR
Serper M, 2017 [19]	US Department of Veteran Affairs	2008 - 2010	957 (24)	NR	NR	NR	NR
Khalaf N, 2017 [4]	Department of Veterans Affairs in US	2004 - 2011	518 (34.5)	144 (27.8)	3.6 (IQR 1.4-9.1)	BCLC 0/A: 13.4 BCLC B: 9.5 BCLC C: 3.4 BCLC D: 1.6	NR
Kim YA, 2021 [20]	KNCI + Korean NHIS + Korean ATC database	2008 -2013	17572 (27.6)	NR	NR	NR	Liver cancer (88.9)
Kwon MJ, 2023 [8]	Korean Primary Liver Cancer Registry	2008 -2014	1045 (15.6)	NR	3	BCLC 0/A: 31 BCLC B: 10 BCLC C: 1 BCLC D: 1	
González-Sánchez H, 2024	Retrospective unicenter study in Oviedo	2015 - 2021	181 (26)	67 (37)	6 (4.2 – 7.8)	BCLC-0/A: 14 BCLC-B: 12 BCLC-C: 4 BCLC-D: 2	Tumor progression 75 (74.3)

NR: non reported; CI: confidence interval; GI: gastrointestinal; IQR interquartile range; Korea National Cancer Incidence (KNCI) database; Korean National Health Insurance Service (NHIS)

database; Korean Drug and Anatomical Therapeutic Chemical (ATC) Codes.

* SEER-Medicare only included HCC patients ≥ 65 years of age.

** There were 16 studies, comprising a total of 24,237 patients, that assessed the receipt of any treatment — including both curative and non-curative treatments — among patients with HCC. Treatment rates varied from 28% to 85% across the studies, with a pooled treatment rate of 52.8% (95% CI 52.2–53.4%).