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Prognostic and Predictive factors in patients with advanced hepatocellular carcinoma treated with sorafenib

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ABSTRACT

Background: Hepatocellular carcinoma (HCC) is the most common primary malignancy of the liver and remains a major cause of cancer-related mortality globally. In Egypt, HCC presents a significant public health challenge due to its high incidence, particularly among males. Sorafenib, an orally administered multikinase inhibitor, has become the standard first-line systemic therapy for advanced HCC. However, overall survival rates remain limited, and outcomes vary substantially depending on clinicopathological factors.

Aim: This study aimed to identify clinicopathological prognostic factors that influence survival outcomes in advanced HCC patients treated with sorafenib.

Methods: A prospective, single-center study was conducted at Zagazig University Hospital, enrolling 130 patients with advanced HCC between July 2022 and February 2024. All patients received sorafenib as the initial systemic therapy. Comprehensive baseline demographic, clinical, and laboratory data were collected. Tumor response was evaluated using the modified Response Evaluation Criteria in Solid Tumors (mRECIST). The primary endpoint was overall survival (OS). Univariate and multivariate Cox regression analyses were performed to determine independent prognostic factors for OS.

Results: The median age of patients was 61.5 years, with hepatitis C virus (HCV)-related HCC being the predominant etiology. The median follow-up period was 9.6 months. The observed median OS was 11.53 months (95% CI: 10.51–12.54). Univariate analysis identified several factors significantly associated with overall survival, including ECOG performance status, Child-Pugh class, macrovascular invasion, extrahepatic spread, tumor size, serum albumin, alkaline phosphatase, and alpha-fetoprotein (AFP) levels. Multivariate analysis revealed that poor ECOG performance status, macrovascular invasion, extrahepatic spread, low serum albumin, elevated alkaline phosphatase, and high AFP levels were independent predictors of poor survival.

Conclusion: Baseline clinicopathological characteristics, such as functional status, tumor burden, and key laboratory markers, have a significant impact on survival in advanced HCC patients treated with sorafenib. Incorporating these prognostic factors into routine clinical assessment may improve risk stratification and help guide therapeutic decisions for patients with advanced HCC.

Keywords*: Predictive factors, advanced hepatocellular carcinoma, sorafenib*

Introduction

Hepatocellular carcinoma (HCC) is the most common form of liver cancer, representing 80–90% of primary malignancies in the liver. Despite advancements in therapeutic options, HCC remains a leading cause of high mortality rates both in the United States and globally [1].

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HCC, which is the sixth most common form of cancer and the third leading cause of cancer-related deaths globally, presents a substantial threat to public health [2]. Overall, the 5-year survival rate for patients with HCC is less than 20% [3].

HCC primarily occurs in the context of pre-existing liver cirrhosis [4]. Hepatitis B virus (HBV) is the predominant cause of hepatocellular carcinoma (HCC) worldwide, largely due to its extensive presence in Asia and Africa. Hepatitis C virus (HCV) is another important viral factor that contributes to liver cirrhosis, particularly in Northern Africa and Asia. In recent years, the use of direct-acting antiviral (DAA) therapy has shown great promise in reducing the risk of HCC development [5].

The deployment of surveillance systems for chronic liver disease, cirrhosis, and hepatocellular carcinoma (HCC) allows for the earlier identification of tumors, resulting in curative treatment and an improvement in overall survival rates, as opposed to when patients exhibit advanced symptoms of the disease [6].

In recent years, a significant transformation has occurred in the domain of advanced HCC treatment, principally attributable to the emergence of targeted therapies and immunotherapy [7].

Sorafenib, is an orally active multikinase inhibitor, impedes angiogenesis and tumor proliferation. Specifically, sorafenib hinders the function of targets such as Raf, VEGF receptor, FLT-3, c-Kit, and PDGF receptor. Sorafenib was granted approval by the Food and Drug Administration (FDA) in 2007 for use in treating unresectable HCC [8].

The aim of the present study was to determine the clinicopathological prognostic factors influencing the survival outcome in advanced HCC patients treated with Sorafenib.

Patient and Methods

This single-center prospective study was conducted at Zagazig University Hospital on 130 HCC patients consecutively treated with sorafenib as initial treatment at the time of randomization to the study. The study aimed to determine the clinicopathological prognostic factors influencing the survival outcome in advanced HCC patients treated with sorafenib in a period from July 2022 to February 2024. The entire study patients were diagnosed as advanced hepatocellular carcinoma (HCC) who were not eligible for or had disease progression after surgical or locoregional therapies. None of the patients had received previous systemic therapy and were treated by sorafenib as first line systemic therapy. Eligibility criteria were the same as those of Llovet's pivotal study on sorafenib in HCC [9].

All patients received sorafenib according to the standard schedule (400 mg b.i.d. continuously). Dose reduction was applied as clinically indicated. Follow-up consisted of CT/MRI scan every 8 weeks or as clinically indicated. Tumor response was evaluated by modified Response Evaluation Criteria in Solid Tumors (mRECIST). Treatment with sorafenib was continued until disease progression, unacceptable toxicity, or death.

Statistical Analysis

SPSS (statistical package for social sciences) version 27.0 (IBM© Corp., Armonk, NY, USA) will be used for data management and data analysis. Using the ShapiroWilk and the Kolmogrov-Smirnov tests, numerical data were examined for normality. The aim of this analysis was to examine the association between baseline characteristics and OS in patients with HCC treated with sorafenib. All hematologic blood tests were carried out at baseline the day before the start of the treatment. Association between categorical variables was assessed using Fisher's exact test, when appropriate. OS was defined as the time interval between the time from the start date of treatment to the date of death or last follow-up visit. OS were estimated by the Kaplan-Meier method and curves were compared by the log-rank test. Cox proportional hazard regression analysis will be done to show independent factors found significant on univariate and multivariate survival analysis with calculation of hazard ratio with its 95% confidence interval.

Results

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Between July 2022 and February 2024, 130 HCC patients were treated with sorafenib and were included in our analysis. Most of the studied patients attending the Department of Medical Oncology, Zagazig University, were rural residents, constituting about 61.7%. The median age among studied HCC patients was 60 years (Range, 51-70 years). Fifty-five percent (72/130) of the studied patients were older than 60 years of age (Table 10). Regarding gender distribution, the majority of the studied HCC patients were male (80.8%), while only 19.2% were female.

With respect to comorbid conditions, 33.1% of patients had diabetes mellitus, 26.9% had hypertension, and 18.5% had a history of bilharziasis, indicating a notable presence of metabolic and endemic disease burdens. Additionally, 52.3% of patients were smokers.

As regard to viral hepatitis status, HCV was the predominant etiology, detected in 85.4% of patients, followed by HBV in 3.8%, and dual infection (HBV + HCV) in 1.5%. A minority (9.2%) had non-viral HCC (no evidence of viral hepatitis).

Regarding Clinicopathological Characteristics, The ECOG performance status showed that the majority of patients had preserved functional capacity, with 63.1% having a PS 0 and 36.9% having PS 1. Regarding liver function status, most patients were classified as Child-Pugh A (A5: 72.3%, A6: 27.7%), reflecting preserved hepatic reserve suitable for systemic therapy. The majority (83.8%) had advanced disease (BCLC stage C), while 16.2% were BCLC stage B.

A large proportion of patients (66.9%) had tumor size ≥ 5 cm, with a mean maximum tumor diameter of 6.32 ± 1.85 cm (range: 3.1–13.5 cm), denoting substantial intrahepatic tumor load. Macrovascular invasion was present in 59.2% of patients, while extrahepatic spread was detected in 46.9% of cases. Among the studied patients, 45.4 % had AFP levels ≥ 400 ng/mL, while 54.6 % had AFP levels < 400 ng/mL. The mean AFP level was 4762.3± 9037.1 ng/mL, highlighting a broad range of values (1.8–60181.9 ng/mL), with a median level of 251 ng/mL

At the data cutoff date (October 31, 2024) the median follows up duration was 9.6 months (4.0 to 18.3 months). the median OS of 11.53 months (95% CI: 10.51–12.54) for HCC patients treated with sorafenib.

Basal Characteristics and Clinical Outcome

For basal characteristics, the univariate analysis was done and identified several baseline clinical, pathological, and laboratory variables that significantly influenced overall survival (OS) among the studied HCC patients.

Regarding clinical characteristics in **Table (1)**, variables such as age, gender, residence, viral status, diabetes, hypertension, bilharziasis, and smoking did not demonstrate statistically significant associations with OS ($p > 0.05$). However, certain patterns were observed. A trend toward longer survival was noted among patients aged <60 years, HCV-positive individuals, and those without diabetes, although these did not reach statistical significance.

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Table (1): Identification of prognostic factors for overall survival based on univariate analysis of baseline characteristics of studied patients

Baseline covariate		Overall Survival		Unadjusted HR	
N= 130		Median (months)	95 % CI	HR (95% CI)	P-Value
Age	< 60	12.30	(10.93-13.66)	1 (Reference)	0.104
	≥ 60	11.20	(9.80-12.73)	1.47 (0.925-2.325)	
Gender	Female	11.47	(9.32-13.61)	1 (Reference)	0.961
	Male	11.53	(10.45- 12.6)	1.015 (0.55-1.856)	
Residence	Urban	12.10	(10.585-13.890)	1 (Reference)	0.422
	Rural	11.47	(10.287-12.474)	1.298 (0.868-1.881)	
Viral hepatitis status					
HCV infection	Negative	10.23	(6.814-13.646)	1 (Reference)	0.144
	Positive	12.10	(11.207-13.03)	0.616 (0.321-1.180)	
HBV infection	Negative	12.10	(10.795-13.405)	1 (Reference)	0.102
	Positive	8.13	(5.743-10.517)	2.180 (0.856-5.552)	
Non-Viral	No	11.53	(10.519-12.541)	1 (Reference)	0.478
	Yes	11.47	(7.697-15.243)	1.329 (0.606-2.914)	
Past History					
Diabetic	No	12.30	(10.827-13.773)	1 (Reference)	0.104
	Yes	10.40	(9.863-10.937)	1.420 (0.718- 1.937)	
Hypertensive	No	11.53	(9.760-13.300)	1 (Reference)	0.139
	Yes	13.20	(10.460-15.940)	0.669 (0.393-1.140)	
Bilharziasis	No	13.030	(10.898-15.162)	1 (Reference)	0.140
	Yes	11.530	(11.478- 11.582)	1.180 (0.661- 2899)	
Smoking	No	11.53	(9.149-13.911)	1 (Reference)	0.640
	Yes	11.47	(10.522-12.538)	1.116 (0.704-1.770)	

P-Value<0.05 is statistically significant, HR: Hazard Ratio

Table (2): Identification of prognostic factors for overall survival based on univariate analysis of clinicopathological characteristics of studied patients

Baseline covariate		Overall Survival		Unadjusted HR	
N =130		Median (months)	95 % CI	HR (95% CI)	P-Value
ECOG Performance Status Score	PS 0	13.100	(12.020-14.180)	1 (Reference)	**<0.001**
	PS 1	9.030	(5.215-12.845)	2.733 (1.766-4.871)	
Child-Pugh Score	Child (A5)	13.070	(12.200-13.940)	1 (Reference)	**<0.001**
	Child (A6)	8.370	(3.970-10.440)	2.571 (1.787-4.284)	
BCLC Staging	BCLC (B)	15.100	(13.623-16.577)	1 (Reference)	**<0.001**
	BCLC (C)	11.270	(10.354-12.186)	3.925 (2.230-6.324)	
Number of Lesions	Lesions < 3	13.100	(11.935-14.265)	1 (Reference)	0.156
	Lesions ≥ 3	10.230	(7.938-12.522)	1.498 (0.877-2.228)	
Size of Maximum Tumor diameter(cm)	Tumor < 5	14.030	(13.021-15.039)	1 (Reference)	**<0.001**
	Tumor ≥ 5	10.330	(7.771-12.889)	2.697 (1.925-4.429)	
Macrovascular invasion	Absent	13.630	(12.591-14.669)	1 (Reference)	**<0.001**
	Present	8.370	(5.586-11.154)	3.764 (2.179-5.773)	
Extrahepatic Spread	Absent	13.200	(12.135-14.265)	1 (Reference)	**<0.001**
	Present	10.030	(7.065-12.995)	2.884 (1.351-3.394)	
Previous therapy	No	11.270	(9.740-12.800)	1 (Reference)	

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	Yes	14.030	(13.191-14.869)	0.444 (0.299-0.793)	**<0.001**

P-Value<0.05 is statistically significant, HR: Hazard Ratio

As detailed in **Table (2**), several clinicopathological factors emerged as strong prognostic indicators for OS. Patients with ECOG performance status (1) had significantly shorter survival compared to those with PS 0 (HR = 2.733, $p < 0.001$), as shown in Figure (39). Similarly, those with Child-Pugh class A6 had poorer OS than those with A5 (HR = 2.571, $p < 0.001$), visualized in Figure (1). Advanced disease stage per BCLC classification (stage C) was associated with significantly worse OS than stage B (HR = 3.925, $p < 0.001$), as seen in Figure (2). Tumor characteristics also significantly impacted prognosis. Patients with tumor diameter ≥5 cm had poorer OS (HR = 2.697, $p < 0.001$) (Figure 4), as did those with macrovascular invasion (HR = 3.764, $p < 0.001$) (Figure 5) or extrahepatic spread (HR = 2.884, $p < 0.001$) (Figure 6). Interestingly, patients who received prior local therapy had significantly longer OS (HR = 0.444, $p < 0.001$), indicating a protective effect as shown in Figure (7).

As presented in **Table (3),** several baseline laboratory parameters emerged as significant prognostic indicators of overall survival (OS) in the studied HCC cohort. Patients with hemoglobin levels >11.7 g/dL demonstrated significantly better survival outcomes (HR = 0.458, $p = 0.004$), as illustrated in **Figure (8)**. Similarly, those with platelet counts >157 × 10^9/L showed superior OS (HR = 0.380, $p < 0.001$), as shown in **Figure (9)**. Elevated AST levels >42 U/L were significantly associated with worse OS (HR = 1.818, $p = 0.002$), as depicted in Figure (47). In addition, higher serum albumin levels >3.9 g/dL were predictive of favorable survival (HR = 0.415, $p < 0.001$), as seen in **Figure (10)**, while increased alkaline phosphatase levels >143 IU/L were linked to poorer prognosis (HR = 2.331, $p < 0.001$), as demonstrated in **Figure (11).** Among tumor markers, AFP >251 ng/mL (median level among our patients) stood out as a strong negative prognostic factor (HR = 2.923, $p < 0.001$), as shown in **Figure (12)**, reinforcing its clinical utility as a robust biomarker for survival prediction in HCC.

Table (3): Identification of prognostic factors for Overall Survival based on Univariate analysis of baseline laboratory data and Markers of studied patients

Baseline covariate		**Overall Survival**		**Unadjusted HR**	
N =130		**Median (months)**	**95 % CI**	**HR (95% CI)**	**P-Value**
Median WBCs (10^9 x L)	**≤ 5.7**	12.330	(10.128-14.532)	1 (Reference)	0.440
	>5.7	11.530	(10.295-12.765)	1.198 (0.758-1.894)	
Median Hemoglobin (g/dl)	**≤ 11.7**	11.270	(9.749- 12.791)	1 (Reference)	**0.004**
	> 11.7	13.100	(10.361- 15.839)	0.458 (0.281-0.745)	
Median Platelets count (10^9 x L)	**≤157**	10.030	(6.890- 13.170)	1 (Reference)	**<0.001**
	>157	13.200	(12.588-12.545)	0.380 (0.234-0.617)	
Median ALT (U/L)	**≤ 46**	13.070	(11.782-14.358)	1 (Reference)	0.110
	> 46	11.230	(9.986- 12.474)	1.455 (0.918 -2.306)	
Median AST (U/L)	**≤42**	13.100	(11.844- 14.356)	1 (Reference)	**0.002**
	>42	10.330	(8.839- 11.821)	1.818 (1.118-2.604)	
Median Total Bilirubin (mg/dl)	**≤0.9**	13.070	(11.891-14.249)	1 (Reference)	0.06
	>0.9	11.270	(10.155-12.385)	1.562 (0.984-2.482)	
Median Albumin (g/dl)	**≤3.9**	10.230	(7.411-13.049)	1 (Reference)	**<0.001**
	>3.9	13.630	(12.652-14.608)	0.415 (0.320-0.685)	
Median Alkaline Phosphatase (IU/L)	**≤143**	13.500	(12.417-14.583)	1 (Reference)	**<0.001**
	>143	10.130	(7.013-12.477)	2.331 (1.875 -3.678)	
Median Serum Creatinine (mg/dL)	**≤0.8**	12.300	(10.837-12.763)	1 (Reference)	0.141
	>0.8	11.270	(9.567-12.973)	1.409 (0.892-2.224)	
	>82	11.230	(10.181-11.879)	1.178 (0.683-1.803)	
	≤251	13.330	(12.759-13.901)	1 (Reference)	

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Median Alpha fetoprotein (AFP) Levels (ng/mL)	**>251**	8.130	(3.726-12.534)	2.923 (1.840-4.415)	**<0.001**

P-Value<0.05 is statistically significant, HR: Hazard Ratio

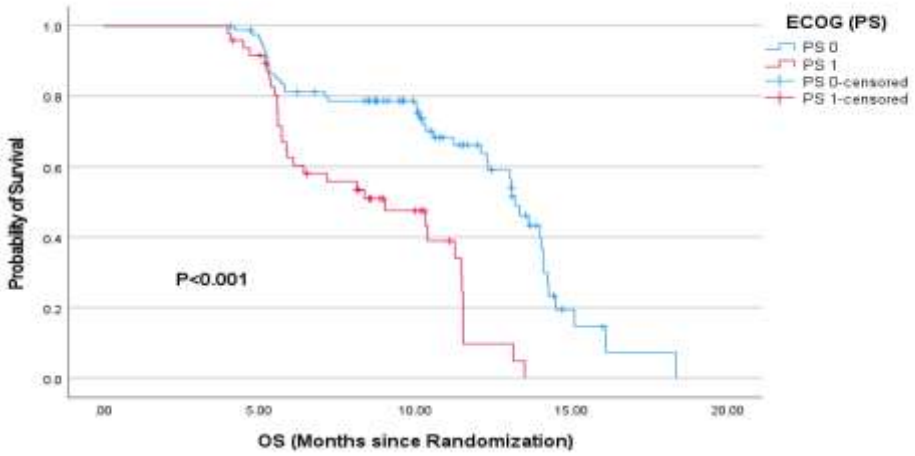

Figure (1): Kaplan–Meier survival curves showing OS according to ECOG (PS) status.

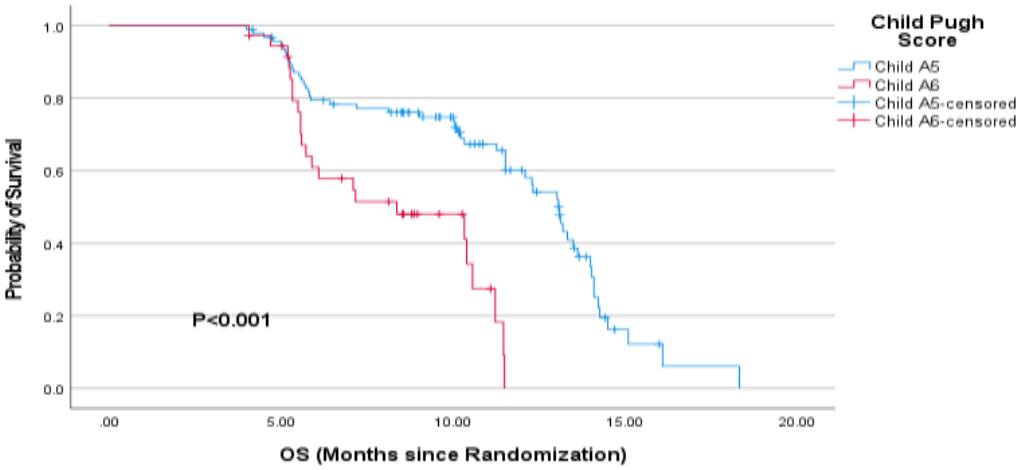

Figure (2): Kaplan–Meier survival curves showing OS according to Child-Pugh Classification.

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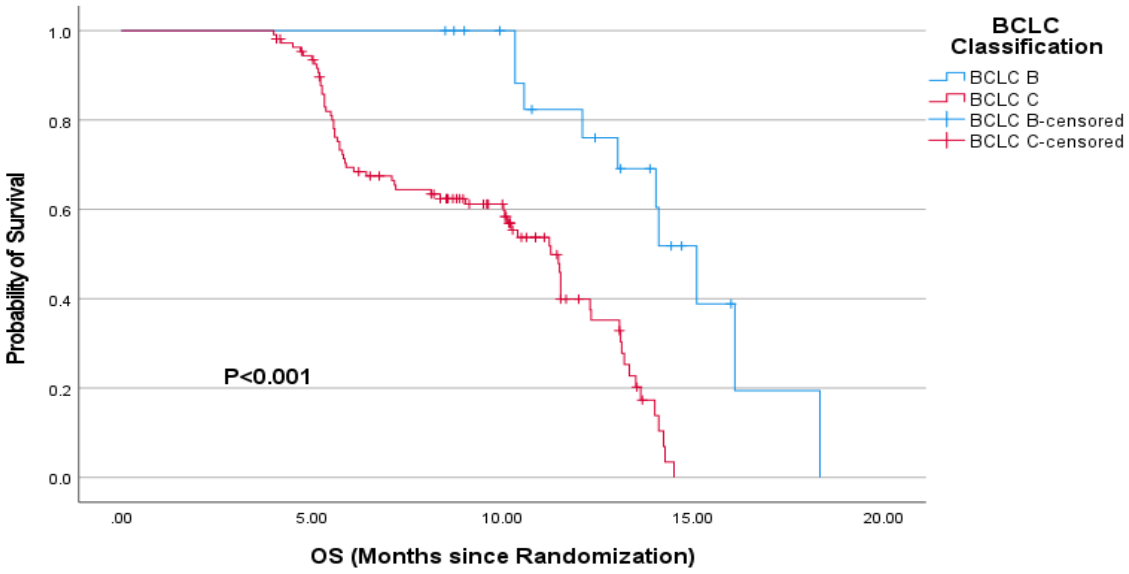

Figure (3): Kaplan–Meier survival curves showing OS according to BCLC staging

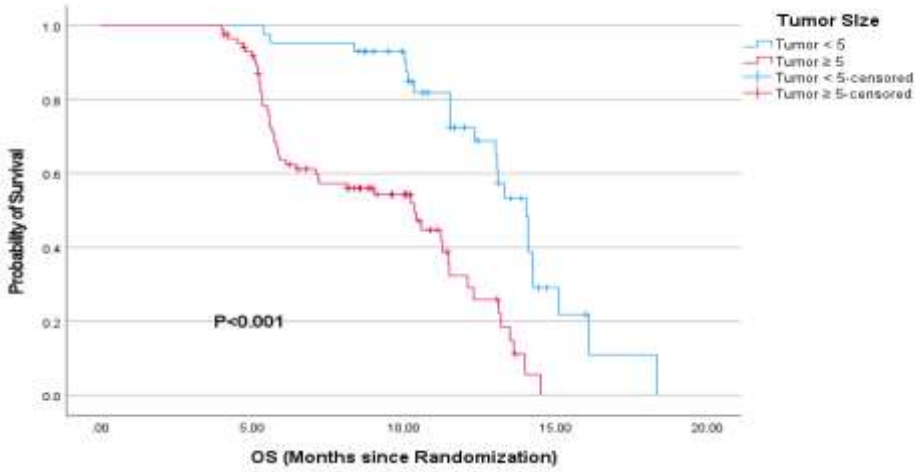

Figure (4): Kaplan–Meier survival curves showing OS according to Tumor Size

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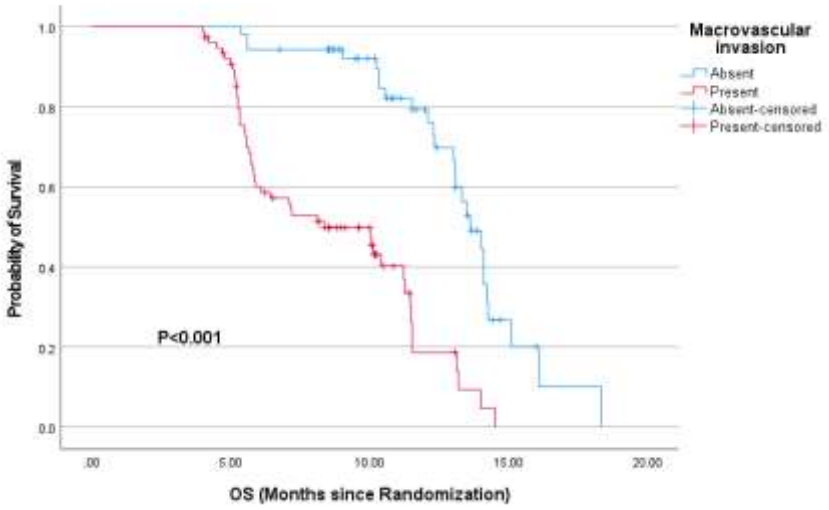

Figure (5): Kaplan–Meier survival curves showing OS according to Macrovascular invasion

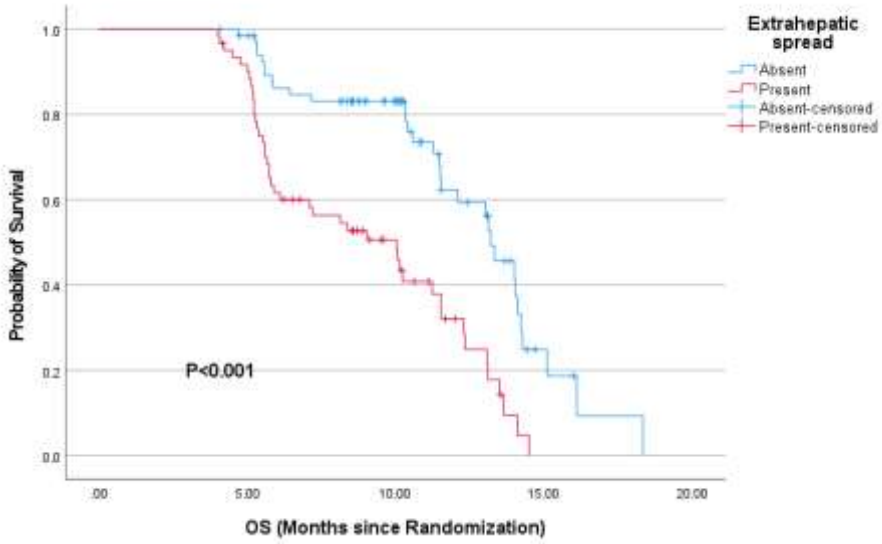

Figure (6): Kaplan–Meier survival curves showing OS according to Extrahepatic Spread

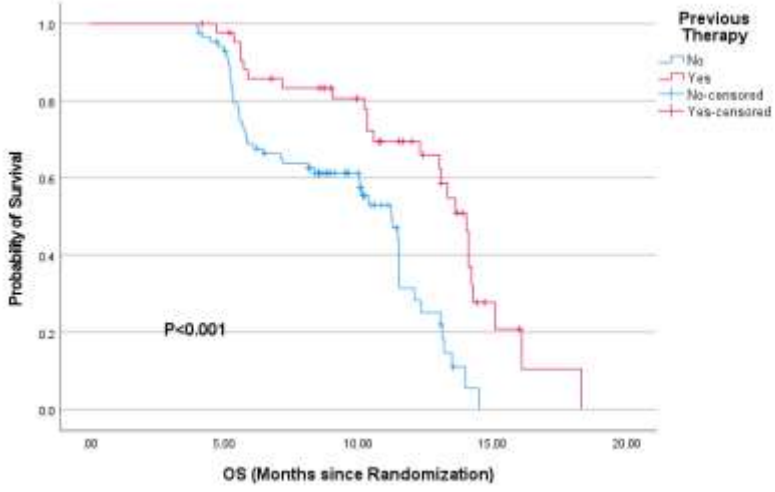

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Figure (7): Kaplan–Meier survival curves showing OS according to Previous Therapy

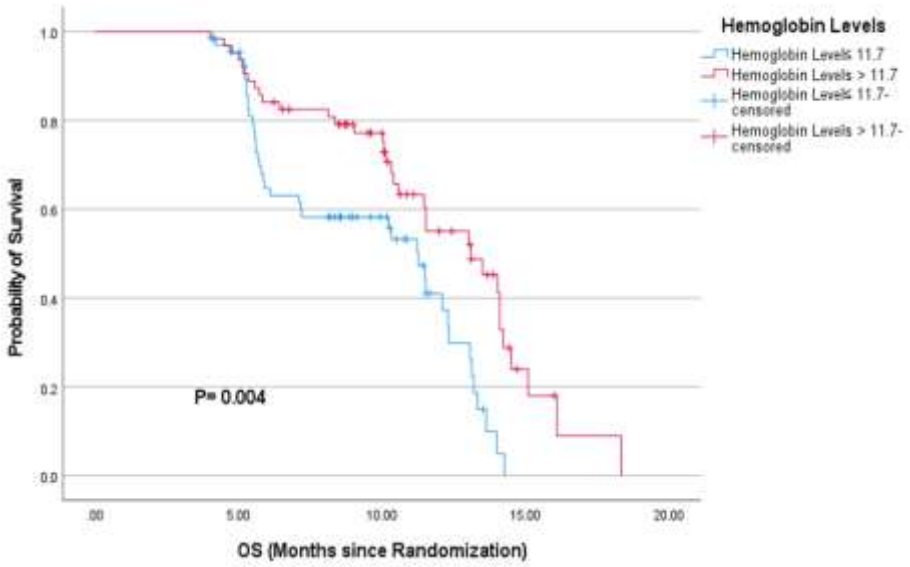

Figure (8): Kaplan–Meier survival curves showing OS according to Baseline hemoglobin Levels

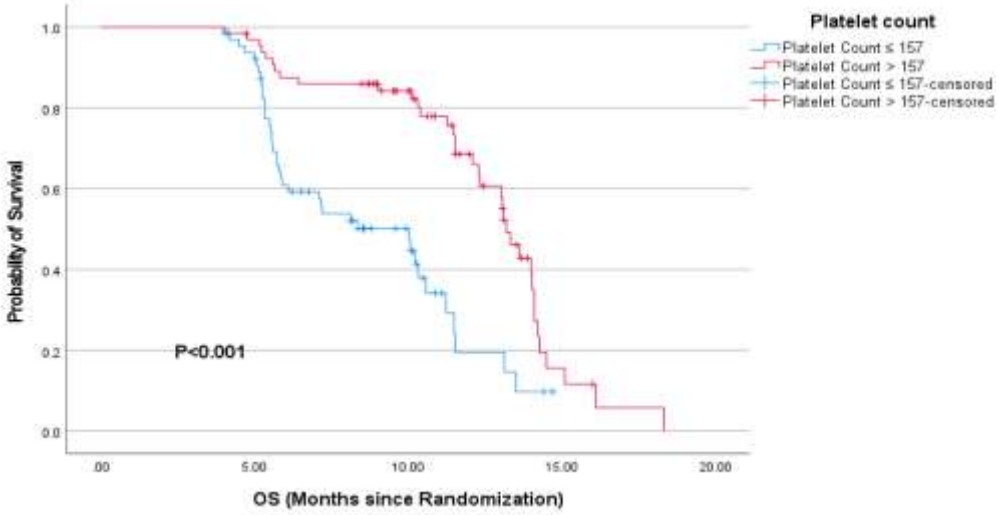

Figure (9): Kaplan–Meier survival curves showing OS according to baseline Platelet Count

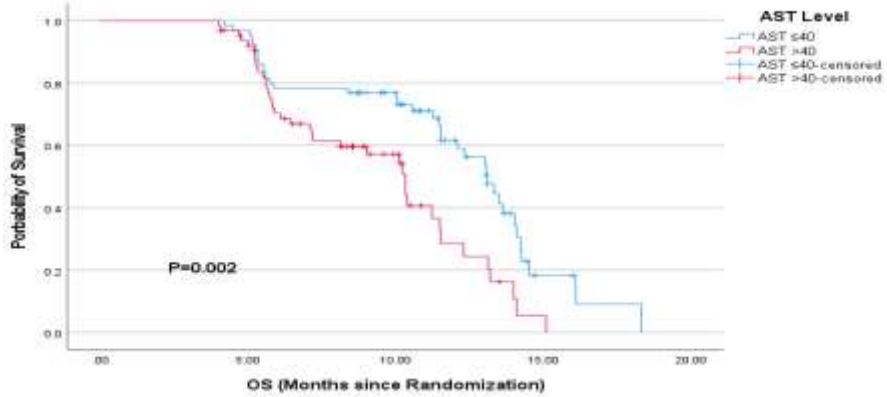

Figure (10): Kaplan–Meier survival curves showing OS according to baseline AST level

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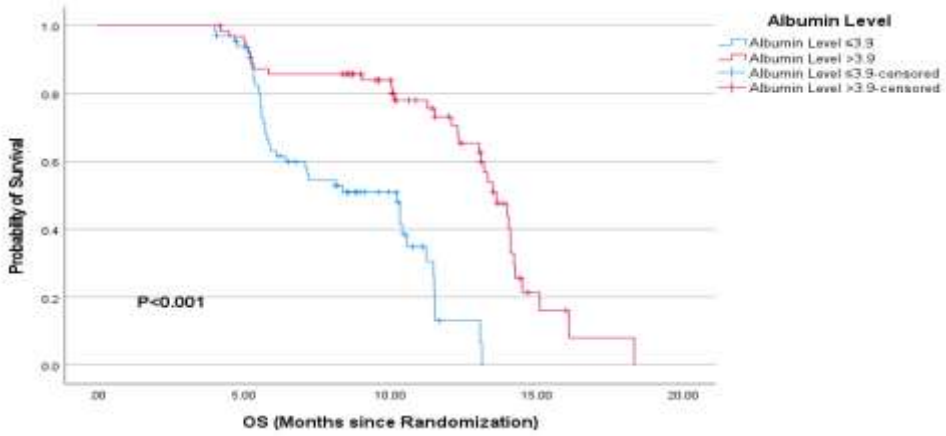

Figure (11): Kaplan–Meier survival curves showing OS according to baseline Albumin level

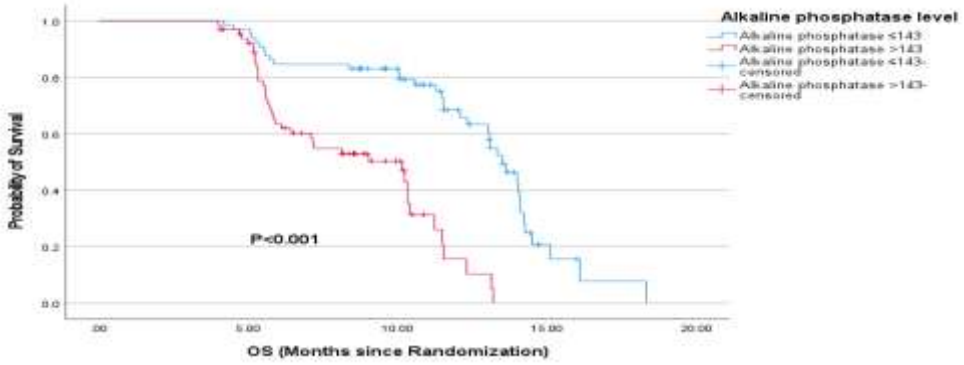

Figure (12): Kaplan–Meier survival curves showing OS according to baseline Alkaline phosphatase level

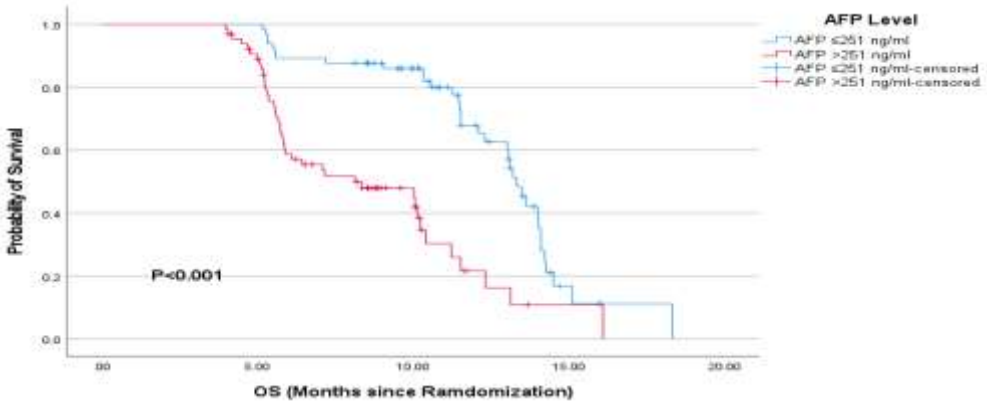

Figure (13): Kaplan–Meier survival curves showing OS according to baseline Alpha Fetoprotein Level

Multivariate analysis

As shown in Table (4), multivariate Cox regression analysis identified several independent prognostic factors significantly associated with overall survival (OS) among the studied HCC patients.

All statistically significant predictors from the univariate analysis of OS were entered into the multivariate model, with the exception of the BCLC stage. This variable was excluded due to its composite nature, as it integrates several prognostic dimensions—namely tumor characteristics (size and number), ECOG performance status, liver function (Child-Pugh class), and the presence of vascular invasion or metastasis. To avoid redundancy and multicollinearity, the individual components of the BCLC system were analyzed separately instead.

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For overall survival (OS), ECOG Performance Status (PS 1 vs. 0) was independently associated with reduced OS (HR = 1.793, 95% CI: 0.987–3.258, p = 0.044), suggesting that even mild functional impairment significantly worsens survival outcomes in HCC. Also, the presence of macrovascular invasion emerged as the most significant adverse prognostic factor (HR = 2.373, 95% CI: 1.544–4.072, p < 0.001), conferring more than twice the risk of mortality. Similarly, extrahepatic spread was independently associated with worse survival (HR = 1.912, 95% CI: 1.326–3.352, p = 0.003). Among laboratory parameters, low serum albumin (≤ median) was significantly associated with poorer OS (HR = 1.531, 95% CI: 1.116–3.017, p = 0.032), likely reflecting impaired liver function or nutritional status. In addition, elevated alkaline phosphatase (> median) predicted worse OS (HR = 1.661, 95% CI: 1.171–2.941, p = 0.013), indicating higher tumor burden. Notably, high serum AFP levels (> median) remained a strong independent predictor of poor prognosis (HR = 1.949, 95% CI: 1.292–3.132, p = 0.006), confirming its role as a surrogate marker for tumor aggressiveness in HCC.

Table (4): Multivariate Cox regression analysis identifying independent Prognostic factors for OS among the studied HCC patients

	Overall Survival (OS)	
Baseline covariate	**Adjusted HR (95% CI)**	***p*-value**
ECOG Performance Status Score (PS 1 vs. 0)	1.793 (0.987- 3.258)	**0.044**
Child-Pugh Score (Child A6 vs. Child A5)	1.563 (0.912 – 2.934)	0.094
Size of Tumor diameter(cm) (Tumor ≥ 5 vs. Tumor <5 cm)	1.399 (0.819 – 2.286)	0.159
Macrovascular invasion (Present vs. Absent)	2.373 (1.544 – 4.072)	**<0.001**
Extrahepatic Spread (Present vs. Absent)	1.912 (1.326 -3.352)	**0.003**
Previous Therapy (No vs. Yes)	1.107 (0.625 – 1.406)	0.323
Hemoglobin (g/dl) Level (≤ median vs. > median)	1.085 (0.562 – 2.736)	0.552
Platelets count (109 x L) (≤ median vs. > median)	1.285 (0.782 -1.975)	0.216
AST (U/L) (>median vs. ≤ median)	1.341 (0.812 – 2.121)	0.115
Albumin (g/dl) (≤ median vs. > median)	1.531 (1.116 – 3.017)	**0.032**
Alkaline Phosphatase (IU/L) (>median vs. ≤ median)	1.661 (1.171 -2.941)	**0.013**
Serum AFP Levels (ng/mL) (>median vs. ≤ median)	1.949 (1.292 -3.132)	**0.006**

Discussion

Hepatocellular carcinoma (HCC) is the predominant form of primary liver cancer and remains a major cause of cancer-related mortality both globally [10] and in Egypt [11]. Among Egyptian cancer patients, HCC represents the most common malignancy in males and ranks second in females [12] with HCV genotype 4 as the most prevalent underlying cause [13,14].

Incidence rates of this disease have risen in several nations over the past few decades. Hepatocellular carcinoma (HCC), which is the primary histological type of liver cancer, is responsible for the majority of liver cancer diagnoses and fatalities.

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While hepatitis B virus (HBV) and hepatitis C virus (HCV) are currently the primary global risk factors for HCC, their significance is expected to decrease in the near future [15,16].

Sorafenib, an orally administered multikinase inhibitor, targets multiple signaling pathways involved in angiogenesis and tumor proliferation, including Raf, VEGF receptors, FLT-3, c-Kit, and PDGF receptors. It received FDA approval in 2007 for the treatment of unresectable HCC. Despite its widespread use, no validated predictive biomarkers have been established to guide sorafenib therapy or identify patients most likely to benefit [17,18].

This prospective study included 130 patients with advanced HCC, who fulfilled the inclusion criteria and were enrolled at the Medical Oncology Department, Faculty of Medicine, Zagazig University, between July 2022 and February 2024. All patients received sorafenib as initial systemic therapy.

The median age of the studied HCC patients was 60 years (range: 51–70 years), with a mean age of 61.5 years, which is consistent with findings from several Egyptian studies [19–21]. Internationally, the age of patients treated with sorafenib for advanced HCC shows notable regional variation. In the pivotal SHARP trial, which evaluated sorafenib in Western populations, the reported median age was 64 years [9]. In contrast, the Asia-Pacific trial, which examined sorafenib efficacy in patients from East and Southeast Asia, documented a significantly younger median age of 51 years [22]. These differences likely reflect regional variations in the underlying etiology of liver disease, with hepatitis B virus (HBV) being more prevalent in Asian populations and hepatitis C virus (HCV) more common in Egypt and Western countries.

In our study, hepatitis C virus (HCV) was the predominant underlying etiology of hepatocellular carcinoma (HCC), identified in 85.4% of patients, followed by hepatitis B virus (HBV) in 3.8%, and dual infection (HBV + HCV) in 1.5%. A minority of patients (9.2%) had non-viral HCC, with no evidence of viral hepatitis. These findings are consistent with several Egyptian studies, which have consistently demonstrated the dominance of HCV as the principal risk factor for HCC in Egypt [23–25], reflecting the country's historically high HCV prevalence. Internationally, the distribution of viral hepatitis etiology differs markedly. In the SHARP trial, conducted primarily in Western populations, HCV accounted for 29% of cases, HBV for 19%, and non-viral causes made up approximately 41% of patients [9]. In contrast, the Asia-Pacific trial, which focused on patients from East and Southeast Asia, showed a clear predominance of HBV infection, present in 73% of patients, while HCV accounted for only 6% [22]. These differences in viral etiology underscore the influence of geographic and epidemiologic factors on HCC pathogenesis, with HBV being more prevalent in Asian countries due to vertical transmission and earlier onset, while HCV-driven HCC remains more common in Egypt and many Western populations, often linked to chronic infection and cirrhosis in older adults.

At the data cutoff date (October 31, 2024), the median follow-up duration was 9.6 months (4.0 to 18.3 months) in our study. The median overall survival (OS) was 11.53 months (95% CI: 10.51–12.54) among hepatocellular carcinoma (HCC) patients treated with sorafenib in our study. These outcomes are among the highest reported for sorafenib-treated HCC patients and are consistent with several Egyptian studies. For instance, Azim et al. [23] reported a median OS of 10.5 months. El Shorbagy et al. [20] documented a median OS of 10 months while Abdel-Rahman et al. [26] and Ramadan et al. [27] reported comparable survival outcomes. On the global level, pivotal trials have demonstrated slightly lower survival outcomes. The SHARP trial reported a median OS of 10.7 months [9]. The Asia-Pacific trial, conducted in a predominantly HBV-infected population, reported lower figures with a median OS of 6.5 months [22]. Moreover, the IMbrave150 trial documented a median OS of 13.4 months in the sorafenib arm [28].

These figures, while impressive, reflect the optimized management conditions and patient selection in high-resource settings. The relatively favorable survival outcomes observed in our study could be attributed to multiple factors. Notably, the very high prevalence of HCV infection (~85%) among our patient cohort likely played a pivotal role. Several studies,

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including subgroup analyses from the SHARP trial and the sunitinib vs. sorafenib phase III study [22,29], have suggested that sorafenib treatment may be more effective in patients with HCV-related HCC compared to those with HBV-related or non-viral etiologies. This may be explained by distinct molecular pathways in HCV-induced hepatocarcinogenesis that confer greater sensitivity to sorafenib's mechanism of action. Additionally, the inclusion of patients with preserved liver function (Child-Pugh A) and good performance status (ECOG 0–1), along with the clinical expertise of Egyptian oncologists in managing sorafenib therapy, likely contributed to maintaining treatment adherence and optimizing outcomes.

In our study, both univariate and multivariate analyses were performed to identify baseline factors influencing survival outcomes in HCC patients treated with sorafenib. A wide range of clinical, pathological, and laboratory variables were found to significantly impact overall survival (OS) in the univariate analysis. However, multivariate Cox regression identified a more refined set of independent predictors. For OS, significant factors included: ECOG performance status, macrovascular invasion, extrahepatic spread, serum albumin, alkaline phosphatase, and alpha-fetoprotein (AFP). These findings emphasize the multifactorial nature of prognosis in advanced HCC and underline the critical importance of tumor burden, liver function, and tumor markers in shaping clinical outcomes under systemic therapy.

In our study, ECOG performance status and Child-Pugh class were significantly associated with overall survival, confirming their prognostic importance in HCC patients receiving sorafenib. Patients with PS 1 and Child-Pugh A6 had significantly worse outcomes, highlighting the impact of baseline functional capacity and hepatic reserve on treatment tolerance and prognosis. Notably, ECOG performance status remained an independent predictor of poor survival in multivariate analysis, underscoring its robust prognostic value beyond other clinical and biochemical variables. These findings are strongly supported by multiple studies conducted in sorafenib-treated cohorts. The GIDEON study reported a stepwise decline in survival across worsening Child-Pugh classes, with median OS of 13.6, 5.2, and 2.6 months for Child A, B, and C, respectively [30] and demonstrated further stratification even within the Child B subgroup. Similarly, Erol et al. [31] found that both ECOG ≥2 and Child-Pugh B were independent predictors of poor survival (HR = 3.94 and 3.23, respectively; $p < 0.001$). In line with these results, Pinter et al. [32] and Rovesti et al. [33] also confirmed that ECOG status and Child-Pugh classification were among the most significant baseline predictors of outcome in sorafenib-treated patients. Collectively, these results reinforce the role of ECOG performance status and Child-Pugh class as critical and validated tools for baseline risk stratification and treatment decision-making in advanced HCC. Their consistent prognostic relevance across both trial-based and real-world data supports their routine incorporation into clinical assessment.

Tumor burden-related factors significantly affected survival outcomes in our study. Specifically, larger tumor size (≥5 cm), macrovascular invasion, and extrahepatic spread were all significantly associated with poorer overall survival (OS) in univariate analysis, with hazard ratios ranging from 2.7 to 3.8 ($p < 0.001$ for all). Notably, macrovascular invasion and extrahepatic spread remained independent predictors of OS in multivariate analysis, underscoring their strong and consistent prognostic impact. These findings are in line with several Egyptian studies, including Azim et al. [23] and Ramadan et al. [27], which also reported that advanced tumor burden—particularly vascular invasion and metastatic spread was strongly associated with reduced survival in sorafenib-treated HCC patients. Our results are further supported by international data. In both the SHARP and Asia-Pacific trials, macrovascular invasion and extrahepatic disease were established as key negative prognostic indicators, with subgroup analyses confirming significantly shorter OS among patients with these features. Likewise, the pooled analysis by Bruix et al. [3] identified macrovascular invasion as one of the most consistent predictors of poor OS in sorafenib-treated populations. In the large prospective INSIGHT study, Marrero et al. [30] similarly found that macrovascular invasion and extrahepatic spread were the only tumor-related factors significantly associated with OS in multivariate analysis. Collectively, these findings confirm that tumor burden,

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particularly vascular invasion and metastatic spread, is a critical determinant of prognosis in advanced HCC and should be a central component of baseline risk stratification for patients undergoing systemic therapy.

In our study, serum albumin >3.9 g/dL was significantly associated with improved overall survival (OS), with a hazard ratio of 0.415 ($p < 0.001$) for OS in univariate analysis and HR = 1.531 ($p = 0.032$) in multivariate analysis. This reinforces the well-established role of albumin as a marker of hepatic synthetic capacity, systemic nutritional reserve, and overall prognosis in advanced HCC. Our findings are strongly supported by the pooled analysis of the SHARP and Asia-Pacific trials conducted by Bruix et al. [3], where low baseline albumin levels were significantly associated with worse survival outcomes. Although albumin did not remain an independent factor in the multivariate model, it was identified as one of the most consistent univariate predictors of poor prognosis among sorafenib-treated patients. Similarly, in real-world data, Marasco et al. [34] incorporated albumin into a validated prognostic nomogram for sorafenib-treated HCC, where hypoalbuminemia independently predicted reduced OS. The GIDEON study also confirmed that albumin <3.5 g/dL was associated with significantly shorter median OS, highlighting its importance across diverse clinical settings. In an Egyptian context, Soliman et al. [21] reported a significantly higher frequency of hypoalbuminemia among patients with poor outcomes, reinforcing its prognostic value in cirrhotic and nutritionally compromised populations.

In our study, elevated serum alkaline phosphatase (ALP) levels >143 IU/L were significantly associated with poorer overall survival (OS) in both univariate and multivariate analyses. In univariate analysis, high ALP was associated with a hazard ratio of 2.331 (95% CI: 1.875–3.678, $p < 0.001$), and this association remained significant in the multivariate model (HR = 1.661, 95% CI: 1.115–2.474, $p = 0.013$). These findings suggest that ALP may reflect underlying tumor aggressiveness, cholestasis, or biliary involvement features commonly associated with more advanced disease. Our results align with the meta-analysis by Sun et al. [35], which demonstrated that elevated pretreatment ALP was consistently associated with poorer OS (pooled HR = 1.15, 95% CI: 1.12–1.19) and shorter recurrence-free survival in HCC patients. Similarly, Bruix et al. [3] in the pooled analysis of SHARP and Asia-Pacific trials also reported worse outcomes in patients with elevated ALP. Together, these findings support the utility of ALP as an accessible and clinically informative prognostic biomarker in HCC, particularly in patients undergoing sorafenib therapy.

In our study, elevated serum alpha-fetoprotein (AFP >200 ng/mL) was significantly associated with poorer overall survival (OS). In univariate analysis, high AFP was associated with a hazard ratio of 2.307 (95% CI: 1.763–3.017, $p < 0.001$) for OS and remained a significant independent predictor in the multivariate model (HR = 1.949, 95% CI: 1.219–3.118, $p = 0.006$). These results highlight AFP as one of the most consistent and clinically relevant tumor markers in advanced HCC. Our findings are strongly supported by previous evidence. In the pooled analysis of the SHARP and Asia-Pacific trials, Bruix et al. [3] identified AFP >200 ng/mL as one of the few baseline variables independently associated with reduced OS in sorafenib-treated patients. Similarly, Azim et al. [23], Rovesti et al. [33] and Erol et al. [31] all found high AFP to be an independent predictor of poorer outcomes in real-world HCC populations, further confirming its prognostic value across different settings. AFP is believed to reflect tumor biology, including tumor burden, vascular invasion, and biologic aggressiveness, and has been widely used in prognostic models. Our results further support the integration of AFP into routine baseline assessment and risk stratification in patients receiving systemic therapy for HCC.

Conclusion

In advanced HCC patients, the prediction of prognosis is extremely complex because survival is affected by both tumor burden and liver function. In our study, we have provided insights into the impact of baseline characteristics on the OS of sorafenib-treated HCC patients in real-life setting, highlighting that hepatic function, patient-centered variables, and HCC etiology, rather than tumor stage, AFP, and immune inflammation indicators, have prognostic value. These findings might have implications in terms of therapeutic decision-making and patient counseling.

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