

The Combined ALBI-FIB-4 Score for Prognostic Stratification in Hepatocellular Carcinoma: A Single Center Retrospective Study

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Background: Hepatocellular carcinoma (HCC) is influenced not only by tumor burden but also by liver function and the extent of fibrosis. Although the albumin-bilirubin (ALBI) score and the fibrosis-4 (FIB-4) index are validated independent predictors, their combined prognostic impact has been insufficiently examined.

Methods: We retrospectively analyzed 307 patients with HCC diagnosed between 2002 and 2025. ALBI and FIB-4 scores were calculated at baseline, and a composite score was generated using the β -coefficients obtained from a multivariable Cox regression model, allowing each component to contribute proportionally to its prognostic weight (combined score = $0.503 \times \text{ALBI} + 0.0576 \times \text{FIB-4}$). Patients were stratified using the median cutoff value (-0.95). Outcomes included overall survival (OS), event-free survival (EFS) for those undergoing locoregional therapies, and progression-free survival (PFS) for patients treated with systemic therapy.

Results: Median OS was 12.1 months. Patients with combined scores ≤ -0.95 had superior OS (18.3 vs 6.8 months, $p < 0.001$), and the score remained an independent predictor of OS (HR 2.01, 95% CI 1.48–2.72, $p = 0.001$). In the locoregional therapy group, lower scores predicted improved EFS (16.4 vs 5.8 months; HR:1.86; 95% CI:1.17–2.96; $p=0.009$). Among systemic therapy patients, the combined score independently predicted PFS (HR 1.70, 95% CI 1.21–2.41, $p = 0.021$).

Conclusion: The combined ALBI-FIB-4 score is an accessible and reproducible prognostic marker across therapeutic settings in HCC. By integrating measures of hepatic reserve and fibrosis, it provides additional prognostic granularity beyond tumor-centric staging systems. These findings highlight its potential utility in personalized risk stratification and warrant validation in prospective, multi-ethnic cohorts.

Keywords: hepatocellular carcinoma, albumin-bilirubin, ALBI score, fibrosis-4, FIB-4 index, combined ALBI-FIB-4 score

Introduction

Hepatocellular carcinoma (HCC) is a primary malignancy of the liver that most commonly develops in the setting of chronic liver disease, particularly cirrhosis due to chronic hepatitis B or C infection, alcohol-related liver disease, or metabolic dysfunction-associated fatty liver disease (MAFLD).¹ Globally, HCC represents the sixth most frequently diagnosed cancer and is the third leading cause of cancer related death. HCC demonstrates substantial geographic and ethnic variability, with the highest incidence observed in East Asia and subSaharan Africa, while rates continue to rise in Western populations due to the growing burden of metabolic dysfunction associated fatty liver disease.² The Barcelona Clinic Liver Cancer (BCLC) staging system is the most commonly used classification to guide prognosis and treatment strategies in HCC, incorporating tumor burden, liver function, and performance status into a unified clinical framework.³



Currently, HCC is managed through a variety of therapeutic approaches, including surgical resection, local ablative techniques, transarterial chemoembolization (TACE), transarterial radioembolization (TARE), radiotherapy, immunotherapy, targeted agents, and systemic chemotherapy. The selection of treatment modality is primarily determined by the stage of disease and underlying liver function.^{4,5} Despite therapeutic advances, the prognosis for patients with advanced hepatocellular carcinoma remains poor, with median overall survival typically ranging from 6 to 12 months.⁶

The two most critical prognostic determinants in HCC are liver functional reserve and tumor burden. Liver function is most commonly assessed using the Child Pugh score and the Model for End Stage Liver Disease (MELD) score, both of which are widely employed in clinical practice to guide treatment decisions and estimate prognosis.^{7,8}

The albumin bilirubin (ALBI) score, proposed by Johnson et al in 2015, is calculated exclusively from serum albumin and bilirubin levels and has been shown to offer a more objective and precise evaluation of liver function in patients with HCC.⁹ Over the past decade, several noninvasive fibrosis markers based on routine laboratory parameters have been developed as alternatives to liver biopsy for assessing the severity of chronic liver disease. Among these, the Fibrosis-4 (FIB-4) index is one of the most extensively studied tools; it incorporates age, aspartate aminotransferase (AST), alanine aminotransferase (ALT), and platelet count, and has demonstrated reasonable accuracy in evaluating liver fibrosis and predicting hepatic decompensation.¹⁰

Beyond its role in assessing fibrosis severity, the FIB-4 index has emerged as an important predictor of clinical outcomes in patients with chronic liver disease and HCC. FIB-4 index correlate with the degree of portal hypertension and reflect hepatic reserve capacity, both of which are critical determinants of prognosis independent of tumor burden.¹¹ Furthermore, elevated FIB-4 index has been associated with increased risk of hepatic decompensation in HCC patients, reflecting both the burden of underlying cirrhosis and the vulnerability of residual liver function.¹⁰ Therefore, incorporating FIB-4 into a composite prognostic model captures not only fibrosis burden but also the functional status of the liver and the patient's reserve capacity to tolerate treatment-related toxicities and disease progression.

Given the pivotal roles of both liver function and tumor burden in determining prognosis in HCC, there is increasing interest in the development of reliable, noninvasive composite scoring systems to support risk stratification and guide treatment decisions. In this context, the present study aimed to evaluate the prognostic significance of the combined ALBI-FIB-4 score in a cohort of HCC patients treated at our institution. Specifically, we sought to determine whether this composite score could predict overall survival in the entire patient population, event free survival in those with localized disease, and progression free survival among patients receiving systemic therapy.

Materials and Methods

Patients and Study Design

This study included a retrospective analysis of patients diagnosed with HCC and followed at Ankara Bilkent City Hospital. All patients were ≥ 18 years of age at the time of diagnosis, and the diagnosis of HCC was confirmed histopathologically. Clinicopathological characteristics, along with hematological and biochemical data, were retrieved from the institutional electronic medical records and reviewed retrospectively. Patients with incomplete or missing baseline laboratory data required for calculating ALBI and FIB-4 index such as albumin, bilirubin, AST, ALT, and platelet count were excluded from the analysis to ensure accurate score derivation. Additionally, individuals whose diagnosis was established at our center but whose follow up or treatment data were incomplete because care continued at another institution were also excluded to maintain data integrity and consistency. Tumor staging was determined according to the Barcelona Clinic Liver Cancer (BCLC) staging system.

A total of 551 patients diagnosed with hepatocellular carcinoma between 2002 and 2025 were initially screened. After excluding 152 patients with incomplete follow up and 92 patients with missing baseline laboratory data required for ALBI and FIB-4 calculation, 307 patients were included in the final analysis, as summarized in Figure 1.

The ALBI score was calculated using the following formula: $0.66 \times \log_{10}(\text{bilirubin, } \mu\text{mol/L}) - 0.085(\text{albumin, g/L})$. The cut-off values were defined as follows: ≤ -2.60 for ALBI grade 1, -2.60 to -1.39 for grade 2, and > -1.39 for grade 3, where ALBI grade reflects the severity of liver dysfunction based on serum albumin and bilirubin levels.⁹

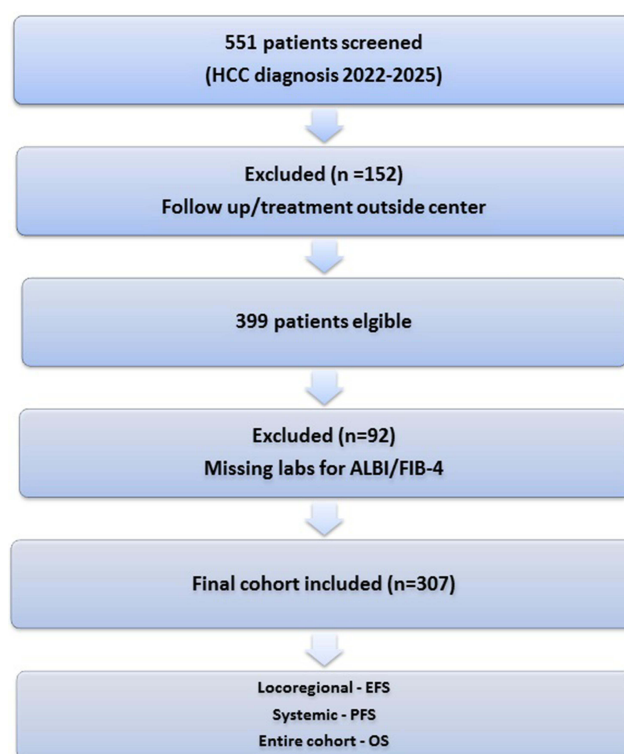


Figure 1 Patient Selection Flow Diagram.

The FIB-4 index was calculated using the following formula: $\text{FIB-4} = (\text{Age [years]} \times \text{AST [U/L]}) / (\text{Platelet count [10}^9/\text{L]} \times \sqrt{\text{ALT [U/L]}})$. For analytical purposes, the FIB-4 index was categorized into three groups based on established cut off values: <1.45 indicating low fibrosis risk, $1.45\text{--}3.25$ indicating intermediate risk, and >3.25 indicating high risk.¹¹

To construct the combined ALBI-FIB-4 score in this study, we first performed separate Cox proportional hazards regression analyses for the ALBI score and the FIB-4 index. The respective regression coefficients (β -values) derived from the multivariable Cox regression model were then incorporated into the final formula. This approach allowed for a weighted combination of the two scores based on their independent prognostic contributions.

The combined score was calculated using the following formula: Combined ALBI-FIB-4 score = $(\beta_1 \times \text{ALBI score}) + (\beta_2 \times \text{FIB-4 index})$.¹²

For the analysis, baseline laboratory parameters obtained at the time of diagnosis were used for all patients. The following threshold values were applied for dichotomization: total bilirubin (1.2 mg/dL), albumin (35 g/L), lactate dehydrogenase [LDH] (280 U/L), alpha-fetoprotein [AFP] (10 ng/mL), AST and ALT (40 U/L each), hemoglobin (10 g/dL), white blood cell count [WBC] ($10,000/\text{mm}^3$), and platelet count ($150,000/\text{mm}^3$).

Overall survival (OS) was defined as the time from initial diagnosis to death from any cause. Event-free survival (EFS) was calculated from the date of local treatment or surgery to the date of recurrence, disease progression or death. Progression-free survival (PFS) was defined as the time from initiation of systemic therapy to either radiological progression or death, whichever occurred first.

Because HCC inherently encompasses a wide spectrum of tumor stages and hepatic functional reserve, our cohort reflects real-world clinical heterogeneity. To minimize confounding related to liver dysfunction, all key liver related prognostic variables specifically Child Pugh score were included as baseline covariates in the multivariate Cox model evaluating the combined ALBI-FIB-4 score. Importantly, the FIB-4 index retains its intrinsic age adjustment within the composite score, as age is a core component of the FIB-4 formula ($\text{Age} \times \text{AST} / [\text{Platelet} \times \sqrt{\text{ALT}}]$). Thus, the prognostic contribution of age is preserved when FIB-4 and ALBI are integrated into a single continuous variable.

Statistical Analyses

All statistical analyses were performed using IBM SPSS Statistics for Windows, Version 22.0 (IBM Corp., Armonk, NY, USA) and R software version 4.4 (R Foundation for Statistical Computing, Vienna, Austria). Continuous variables were expressed as median (minimum–maximum), and categorical variables were presented as frequencies and percentages.

Comparisons between groups were made using the Chi square test or Fisher’s exact test for categorical variables, and the MannWhitney *U*-test for continuous variables, depending on data distribution. Survival analyses, including OS, EFS, and PFS, were conducted using the Kaplan Meier method, with group differences assessed using the log rank test.

Univariate and multivariate Cox proportional hazards regression analyses were performed to identify factors associated with survival outcomes. Variables with a *p* value < 0.05 in univariate analysis were considered statistically significant and included in the multivariate model. In all statistical evaluations, a two sided *p* value < 0.05 was accepted as the threshold for statistical significance.

Results

Patient Characteristics

A total of 307 patients diagnosed with HCC were included in the study. The median age at diagnosis was 63 years (range: 19–89), and the majority were male (75.9%). A history of smoking (current or former) was present in 54.1% of patients, and 50.5% had at least one comorbid condition. Regarding underlying liver disease, hepatitis B virus (HBV) infection was the most common etiology (57.3%), followed by hepatitis C virus (HCV) infection (12.4%), alcohol related cirrhosis (2.9%), non alcoholic steatohepatitis (2.3%), cryptogenic cirrhosis (2.0%), and autoimmune liver disease (2.0%), while 21.2% had no known underlying liver pathology.

Portal vein invasion was observed in 31.9% of patients. According to the BCLC staging system, the majority of patients were diagnosed at an advanced stage: 51.1% were classified as stage C, 27.0% as stage B, 13.0% as stage D, and 8.8% as stage A. Regional lymph node involvement was present in 41.4% of cases. The most frequent sites of extrahepatic metastasis were the lungs (13.4%), bones (4.6%), and adrenal glands (2.6%).

Additionally, ascites and hepatic encephalopathy were documented in 38.1% and 10.7% of patients, respectively. Based on the Child-Pugh classification, 70% of patients had a score of ≤7, indicating preserved liver function in the majority of the cohort. The median ALBI score was –2.01 (range: –3.78 to 0.35). Based on established cut-off values, ALBI grade 1 (≤ –2.60) was observed in 27.4% of patients, grade 2 (–2.60 to –1.39) in 48.2%, and grade 3 (> –1.39) in 24.4%. The median FIB-4 index was 3.1 (range: 0.39–38.7). According to standard cut-off values, 17.6% of patients had low fibrosis risk (<1.45), 33.6% had intermediate risk (1.45–3.25), and 48.9% were classified as high fibrosis risk (>3.25). The demographic and clinical characteristics of the patients are summarized in [Table 1](#).

Table 1 The Demographic and Clinical Characteristics of the Patients

		n	%
Number of Patients		307	100
Median Age (min-max)*		63(19–89)	
Gender	Male	233	75.9
	Female	74	24.1
Smoking History	No	141	45.9
	Yes (former smoker or current smoker)	166	54.1
Comorbidity	No	152	49.5
	Yes	155	50.5

(Continued)

Table 1 (Continued).

		n	%
Underlying Liver Disease	No	65	21.2
	HBV	176	57.3
	HCV	38	12.4
	Alcohol-related cirrhosis	9	2.9
	Non-alcoholic steatohepatitis	7	2.3
	Cryptogenic cirrhosis	6	2
	Autoimmune liver disease	6	2
Portal vein invasion	Yes	98	31.9
	No	201	65.5
	Unknown	8	2.6
Barcelona Clinic Liver Cancer Staging	A	27	8.8
	B	83	27.0
	C	157	51.1
	D	40	13
Encephalopathy	No	274	89.3
	Yes	33	10.7
Child Pugh score	≤ 7	215	70
	> 7	92	30
Median ALBI score (min-max)*		-2.01 (-3.78–0.35)	
ALBI-GRADE	Grade I	84	27.4
	Grade II	148	48.2
	Grade III	75	24.4
Median FIB-4 Index*		3.1 (0.39–38.7)	
FIB-4 Index	< 1.45	54	17.6
	1.45–3.25	103	33.6
	> 3.25	150	48.9

Notes: *Age, ALBI score, and FIB-4 index are presented as median values.

Abbreviations: n, number; %, percent; min, minimum; max, maximum; HBV, Hepatitis B Virus, HCV: Hepatitis C Virus.

Elevated total bilirubin levels (>1.2 mg/dL) and hypoalbuminemia (<35 g/L) were each observed in 49.5% of patients. ALP was elevated (>147 U/L) in 57%, and LDH (>280 U/L) in 42.3% of cases. AFP levels ≥10 ng/mL were detected in 71.7% of patients. Elevated AST and ALT levels (>40 U/L) were present in 67.8% and 62.2%, respectively. Anemia (hemoglobin <10 g/dL) was found in 19.5%, leukocytosis (WBC >10,000/mm³) in 21.2%, and thrombocytopenia (platelet count <150,000/mm³) in 37.1% of the cohort. The laboratory characteristics of the patients are presented in Table 2.

Table 2 Laboratory Values of Patients

		n	%
Total Bilirubin	≤ 1.2	155	50.5
	>1.2	152	49.5
Albumin	<35	155	50.5
	≥ 35	152	49.5
ALP	≤ 147	109	35.5
	> 147	175	57
	Unknown	23	7.5
LDH	≤ 280	137	44.6
	> 280	130	42.3
	Unknown	40	13
AFP	< 10	72	23.5
	≥ 10	220	71.7
	Unknown	15	4.9
AST	≤ 40	99	32.2
	> 40	208	67.8
ALT	≤ 40	116	37.8
	> 40	191	62.2
Hemoglobin	< 10	60	19.5
	≥ 10	247	80.5
WBC	≤10000	242	78.8
	>10,000	65	21.2
Platelet	<150000	114	37.1
	≥150,000	193	62.9

Abbreviations: n, number; %, percent; min, minimum; max, maximum; ALP, Alkaline Phosphatase; LDH, Lactate Dehydrogenase; AFP, Alpha-Fetoprotein; AST, Aspartate Aminotransferase; ALT, Alanine Aminotransferase; WBC, WhiteBlood Cell Count.

Treatment Modalities

Among the entire cohort, 35.5% received systemic therapy as first line treatment, while 15.0% underwent surgery, 16.6% received TACE, 7.5% underwent TARE, and 6.5% were treated with radiofrequency ablation. No first line treatment was administered to 18.9% of patients.

Among patients initially treated with local therapies, disease progression occurred in 71.4%, and 28.6% remained progression-free. Second-line local treatments were most commonly TACE (56.1%), followed by TARE (17.1%), radiofrequency ablation (17.1%), surgery (7.3%), and liver transplantation (2.4%).

In patients who received systemic therapy (either as initial treatment or after local treatment failure), sorafenib was the most frequently administered agent (62.6%), followed by FOLFOX (18.7%), doxorubicin (8.2%), atezolizumab plus bevacizumab (5.3%), and other chemotherapy combinations. In the second-line setting, regorafenib (30.8%), sorafenib (28.2%), and FOLFOX (20.5%) were the most commonly used regimens. The treatment modalities administered to patients are summarized in [Table 3](#).

Table 3 Treatment Modalities of Patients

		n	%
First Line Treatment			
	No	58	18.9
	Surgery	46	15
	TACE	51	16.6
	TARE	23	7.5
	RF Ablation	20	6.5
	Systemic Therapy	109	35.5
Progression After Local Therapy			
	No	40	28.6
	Yes	100	71.4
Second Line Local Treatment			
	TACE	23/41	56.1
	TARE	7/41	17.1
	RF Ablation	7/41	17.1
	Surgery	3/41	7.3
	Liver Transplantation	1/41	2.4
First Line Systemic Therapy *			
	Sorafenib	107 /171	62.6
	FOLFOX	32/171	18.7
	Atezolizumab + Bevacizumab	9/171	5.3
	Doxorubicin	14/171	8.2
	Capecitabine	3/171	1.8
	Gemcitabine + Oxaliplatin	2/171	1.1
	Doxorubicin + Cisplatin + 5-Fluorouracil	4/171	2.3
Second Line Systemic Therapy			
	Sorafenib	11/39	28.2
	FOLFOX	8/39	20.5
	Regorafenib	12/39	30.8
	Doxorubicin	4/39	10.3
	Capecitabine	2/39	5.1
	Gemcitabine	2/39	5.1

Notes: *Includes patients who received systemic therapy as initial treatment and those who received systemic therapy after recurrence following local therapies.

Abbreviations: n, number; %, percent; TACE, Transarterial Chemoembolization; TARE, Transarterial Radioembolization; RF Ablation, Radiofrequency Ablation.

Survival Analysis

The combined ALBI-FIB-4 score was calculated using the regression coefficients derived from multivariable Cox analysis for the ALBI score (0.503) and the FIB-4 index (0.0576), using the formula: Combined score = $(0.503 \times \text{ALBI}) + (0.0576 \times \text{FIB-4})$. The median value of the combined score in the study cohort was -0.95 . Of the entire cohort, 132 patients (43.0%) had a combined ALBI-FIB-4 score below the median cutoff of -0.95 , whereas 175 patients (57.0%) had a score above this threshold. The distribution of overall survival according to patients' combined ALBI-FIB4 scores is presented in Figure 2.

The median follow up time for the entire cohort was 100.1 months (95% CI: 44.6–155.7). The mOS for all patients was 12.1 months (95% CI: 10.73–13.58).

To contextualize the performance of the combined ALBI-FIB-4 score, we first evaluated ALBI grade and FIB-4 category independently. Both metrics demonstrated significant stratification of overall survival on Kaplan-Meier analyses (log rank $p < 0.001$), confirming that each retains independent prognostic value. Their quantitative discriminatory performance, however, differed: ALBI alone yielded an AUC of 0.71 and a Harrell's C index of 0.655, indicating acceptable yet limited discrimination, whereas FIB-4 alone demonstrated an AUC of 0.578 and a C index of 0.701, reflecting moderate prognostic ability. The primary aim of our study was to integrate liver functional reserve (captured by ALBI) and cumulative fibrosis burden (captured by FIB-4) into a unified composite score rather than treat these parameters as competing covariates.

When stratified by the median value of the combined ALBI-FIB-4 score (-0.95), patients below this threshold had significantly longer OS than those above it (median OS: 18.3 months [95% CI: 13.1–23.6] vs 6.8 months [95% CI: 5.5–8.0], $p < 0.001$) (Figure 3A). To further quantify its discriminatory capacity, we performed ROC analysis and

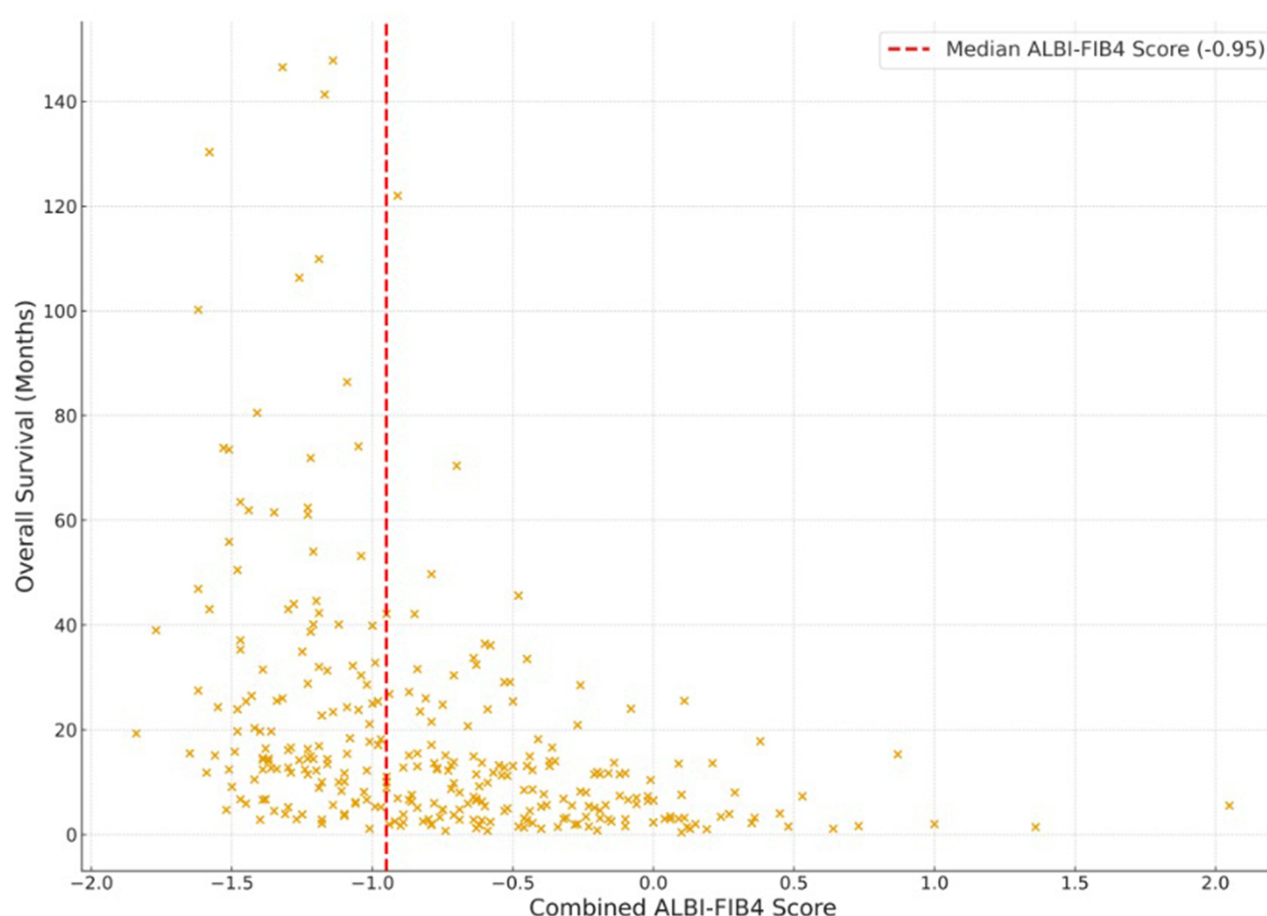


Figure 2 Correlation Between Combined ALBI-FIB-4 Score and Overall Survival.

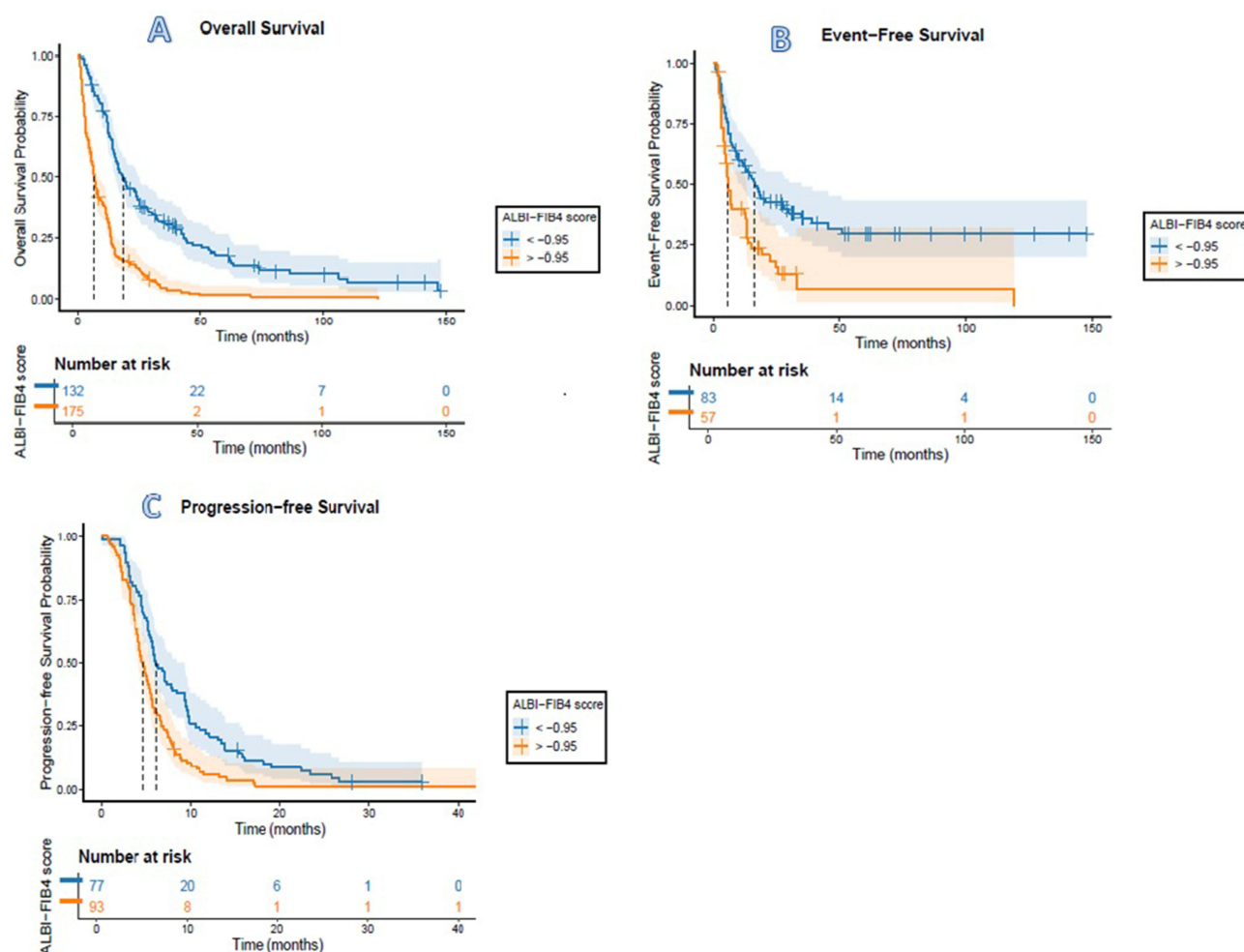


Figure 3 Kaplan Meier curves for (A) Overall Survival, (B) Event Free Survival, and (C) Progression Free Survival.

calculated Harrell's C index for the composite model. The combined ALBI-FIB-4 score achieved an AUC of 0.7932 ($p < 0.001$) and a C-index of 0.681, demonstrating noticeably improved discrimination compared with ALBI or FIB-4 alone. Collectively, these results validate that integrating liver function and fibrosis burden into a single composite measure enhances prognostic precision. The robust concordance between predicted and observed outcomes across 119 mortality events among 274 patients (43.4%) supports the clinical utility of the ALBI-FIB-4 composite score as a reliable and biologically meaningful tool for risk stratification in hepatocellular carcinoma.

In univariate analysis, gender ($p = 0.002$), smoking history ($p = 0.038$), BCLC stage ($p = 0.001$), Child-Pugh score ($p = 0.001$), LDH level ($p = 0.004$), AFP level ($p = 0.001$), and the combined ALBI-FIB-4 score ($p = 0.001$) were significantly associated with OS. In multivariate Cox regression analysis, three variables remained as independent predictors of poorer overall survival: BCLC stage C-D (HR: 2.35; 95% CI: 1.78–3.10; $p = 0.001$), Child-Pugh score >7 (HR: 1.68; 95% CI: 1.24–2.29; $p = 0.002$), and a combined ALBI-FIB-4 score >-0.95 (HR: 2.01; 95% CI: 1.48–2.72; $p = 0.001$). Prognostic factors affecting OS are summarized in Table 4.

Among the 140 patients who received local therapies as first-line treatment, mOS was 25.3 months (95% CI: 22.0–28.7), and the mEFS was 12.4 months (95% CI: 7.8–17.0). When stratified by the median value of the combined ALBI-FIB-4 score (-0.95), patients with scores below -0.95 ($n = 83$) had significantly longer EFS compared to those with scores above -0.95 ($n = 57$). Specifically, the median EFS was 16.4 months (95% CI: 11.1–21.8) in the low-score group versus 5.8 months (95% CI: 4.5–7.2) in the high-score group ($p < 0.001$) (Figure 3B).

Table 4 Univariate and Multivariate Cox Regression Analyses of Overall Survival, Event-Free Survival and Progression-Free Survival

Dependents	Overall Survival		Event-Free Survival		Progression-Free Survival	
	Univariate p value	Multivariate p value HR (95% CI)	Univariate p value	Multivariate p value HR (95% CI)	Univariate p value	Multivariate p value HR (95% CI)
Gender (female vs male)	0.002	0.14 1.24 (0.89–1.71)	0.09		0.354	
Age Groups (≤ 63 vs > 63)	0.585		0.906		0.246	
Comorbidity (no vs yes)	0.08		0.83		0.903	
Smoking (no vs yes)	0.038	0.47 1.05 (0.80–1.37)	0.70		0.155	
Etiology (viral vs nonviral)	0.932		0.89		0.11	
BCLC Staging (A-B vs C-D)	0.001	0.001 2.35 (1.78–3.10)	0.015	0.064 1.50 (0.97–2.32)	0.18	
Child-Pugh Score (≤ 7 vs > 7)	0.001	0.002 1.68 (1.24–2.29)	0.001	0.34 1.34 (0.73–2.46)	0.012	
ALP (normal vs elevated)	0.21		0.095		0.19	
LDH (normal vs elevated)	0.004	0.89 1.08 (0.93–1.41)	0.212		0.65	
AFP (normal vs elevated)	0.001	0.053 1.44 (0.82–1.77)	0.111		0.99	
Hemoglobin (< 10 vs ≥ 10)	0.057		0.763		0.39	
WBC (≤ 10000 vs > 10000)	0.11		0.87		0.63	
ALBI - FIB-4 combined score (< -0.95 vs > -0.95)	0.002	0.001 2.01 (1.48–2.72)	0.001	0.009 1.86 (1.17–2.96)	0.001	0.021 1.70 (1.21–2.41)

Notes: Bold values indicate statistically significant variables ($p < 0.05$). Variables that were significant in univariate analysis were included in the multivariate model.

In univariate analysis, BCLC stage ($p = 0.015$), Child–Pugh score ($p = 0.001$), ALP level ($p = 0.095$), and the combined ALBI-FIB-4 score ($p = 0.001$) were associated with EFS. However, in multivariate analysis, only the combined ALBI-FIB-4 score remained an independent predictor of EFS. Patients with a combined score > -0.95 had significantly shorter EFS compared to those with a score ≤ -0.95 (HR: 1.86; 95% CI: 1.17–2.96; $p = 0.009$). Prognostic factors for event-free survival (EFS) in patients who received local treatment are presented in [Table 4](#).

PFS was analyzed in a total of 171 patients who either received systemic therapy as initial treatment or following recurrence after local therapies. The median PFS for the entire group was 5.3 months (95% CI: 4.87–5.90). When stratified by the combined ALBI-FIB-4 score, patients with scores below -0.95 had a significantly longer PFS compared to those with scores above -0.95 . The median PFS was 6.14 months (95% CI: 4.85–7.43) in the low-score group versus 4.76 months (95% CI: 4.09–5.43) in the high-score group ($p = 0.001$) ([Figure 3C](#)).

In univariate analysis, only Child–Pugh score ($p = 0.012$) and the combined ALBI-FIB-4 score ($p = 0.001$) were significantly associated with PFS. In the multivariate Cox regression model, the combined ALBI-FIB-4 score remained the only independent predictor of PFS. Patients with a combined score > -0.95 had significantly shorter PFS compared to those with a score ≤ -0.95 (HR: 1.70; 95% CI: 1.21–2.41; $p = 0.021$). The prognostic factors associated with PFS in patients who received systemic therapy are presented in [Table 4](#).

Discussion

This study demonstrates that the combined ALBI-FIB-4 score serves as a robust prognostic marker across different therapeutic contexts in HCC. Patients with higher composite scores consistently experienced worse survival outcomes, confirming the relevance of integrating measures of liver function and fibrosis alongside tumor burden. Importantly, the

prognostic strength of this score was observed not only in overall survival for the entire cohort but also in event free survival among those treated with locoregional therapies and progression free survival among patients receiving systemic treatment.

Conventional prognostic systems for hepatocellular carcinoma, such as the BCLC staging and the AJCC TNM classification, primarily emphasize tumor burden and patient performance status while relying on broad categorizations of liver function, most notably the Child Pugh classification. However, the Child Pugh score has recognized limitations due to its subjective components. In contrast, the ALBI score was developed as an objective tool and has demonstrated superior prognostic discrimination. In a recent cohort of patients with advanced HCC, ALBI grade more accurately predicted survival than Child Pugh classification (Harrell's C index 0.65 vs 0.62, $p = 0.008$), and it further stratified outcomes even among patients classified as Child Pugh A. The present analysis supports the notion that combining ALBI with the FIB-4 index can enhance prognostic precision. In support of this, Tian et al reported that the ALBI-FIB4 composite score achieved greater predictive accuracy for post-hepatectomy liver failure than Child Pugh, MELD, or either individual score (AUC 0.783 vs lower AUCs for other models). Their study also identified a high-risk group with a 39% incidence of liver failure, compared to approximately 7% in the low risk group, based on a specific ALBI-FIB4 cutoff. These findings highlight the increased sensitivity of the combined score in identifying vulnerable patients, surpassing traditional liver function based scoring systems.¹²

Importantly, several other integrated prognostic systems also underscore the value of incorporating liver specific parameters into risk models. For instance, the Japan Integrated Staging (JIS) system and the ALBI-T score, which combines ALBI grade with tumor stage, have both been utilized to enhance prognostic stratification. In a large Japanese cohort, a novel prognostic model that incorporated FIB-4 alongside tumor stage the so called FIB4-T score achieved survival stratification comparable to that of the JIS and ALBI-T systems.¹³ These comparisons highlight the ability of the ALBI-FIB4 score to fill a critical gap in existing frameworks by quantitatively reflecting both hepatic fibrosis and liver function.

The combined ALBI-FIB-4 score offers several practical applications in the management of hepatocellular carcinoma. Among surgical candidates, it can serve as a valuable tool for preoperative risk stratification. Patients with elevated ALBI-FIB-4 scores are likely to have limited hepatic reserve and advanced fibrosis, placing them at increased risk for postoperative complications. In fact, one study reported that individuals in the high risk category experienced post-hepatectomy liver failure in nearly 40% of cases, along with higher early mortality rates, whereas the incidence of liver failure in the low-risk group was below 7%.¹⁴ Beyond surgical decision-making, the score may also be clinically useful when selecting systemic therapy, as baseline hepatic reserve and fibrosis burden strongly influence treatment tolerance particularly with immunotherapy and tyrosine kinase inhibitor-based regimens. This information may assist clinicians in selecting appropriate candidates for resection or systemic treatment, recommending limited or staged procedures, and implementing more intensive perioperative or on treatment monitoring and supportive measures for those at higher risk.

The integration of ALBI and FIB-4 offers a more comprehensive assessment of host-related factors in hepatocellular carcinoma. The combined ALBI-FIB4 score reflects both the current hepatic functional status and the cumulative burden of liver injury and fibrosis. Biologically, this is of critical importance in HCC, as the majority of patients have underlying chronic liver disease, which not only contributes to tumor development but also acts as a competing determinant of survival, independent of tumor burden. Our study, along with previous reports, demonstrates that the ALBI-FIB4 score remains an independent prognostic factor even after adjusting for tumor size, number, and vascular invasion. This suggests that the condition of the non-tumorous liver and its surrounding microenvironment plays a key role in determining both the likelihood of tumor recurrence (eg, through field effects) and the patient's capacity to tolerate disease progression or treatment-related toxicities. Supporting this concept, Liao et al observed a significant association between higher ALBI-FIB4 scores and increased peri-tumoral inflammatory activity in liver tissue, as assessed by histologic inflammation scores. Chronic hepatic inflammation and fibrosis are known to drive genetic alterations and pro-growth signaling, which facilitate the emergence of new tumor foci and create a permissive microenvironment for recurrence.¹⁵

Taken together, these findings situate the ALBI–FIB-4 score within a broader movement toward prognostic models that integrate tumor burden with host-dependent determinants of outcome in HCC. Recent advances in systemic therapy including immune checkpoint inhibitors, anti-VEGF combinations, and next-generation TKIs have underscored the crucial role of baseline liver function and fibrosis in shaping both therapeutic efficacy and toxicity profiles.^{3,6} As treatment algorithms become increasingly nuanced, prognostic tools that quantify hepatic vulnerability and structural liver injury offer advantages over tumor centric systems by identifying patient subgroups who may derive differential benefit from locoregional versus systemic approaches. In this regard, our results reinforce the growing emphasis on incorporating liver biology into clinical decision-making, consistent with contemporary shifts in HCC management.

Moreover, integrating ALBI and FIB-4 into a single composite measure may provide a practical means of refining treatment selection in real-world settings, where heterogeneity in hepatic reserve often complicates therapeutic planning. By capturing both functional impairment and the cumulative burden of fibrosis, the ALBI–FIB-4 score may facilitate more accurate prognostic counseling, enhance patient stratification for clinical trials, and help identify candidates at elevated risk for early progression or treatment intolerance domains not fully addressed by existing scores such as Child Pugh or BCLC.^{7,13} These considerations highlight the potential utility of the composite score not only as a prognostic tool but also as a foundation for future multi-dimensional risk models that incorporate biomarkers, radiomics, and dynamic liver function assessments.

One of the main limitations of our study is its retrospective and single-center design, which may introduce selection bias and limit the generalizability of the findings. Additionally, our cohort had a high prevalence of chronic viral hepatitis, and it remains uncertain whether the ALBI–FIB-4 score would demonstrate similar prognostic performance in populations with different etiologic backgrounds, such as NASH dominant cohorts. Although an optimal cut off for risk stratification was defined, this threshold may not be universally applicable. Therefore, external validation of both the cut off and the prognostic utility of the combined score in independent, prospective, and ideally multicenter cohorts is necessary.

Conclusion

The combined ALBI-FIB-4 score effectively integrates liver functional status and fibrosis burden into a unified prognostic tool for hepatocellular carcinoma. In our cohort, elevated ALBI-FIB-4 scores independently predicted worse survival outcomes across multiple therapeutic modalities and tumor stages, demonstrating superior discriminatory ability. This objective, quantitative measure offers substantial clinical applicability for risk stratification and patient counseling in HCC management. However, external validation in prospective, multicenter cohorts with diverse etiologies is imperative before widespread clinical implementation can be recommended. Future research should focus on integrating this score with emerging biomarkers to further refine prognostic accuracy in personalized HCC care.

Data Sharing Statement

The data that support the findings of this study are not publicly available due to privacy reasons but are available from the corresponding author (Doğan Bayram) upon reasonable request.

Ethics Approval and Consent to Participate

This study was approved by the Ankara City Hospital Clinical Research Ethics Committee (Date: December 27, 2023 / Approval No: E1-23-4053). The requirement for informed consent was waived by the ethics committee due to the retrospective design of the study and the use of anonymized patient data. The study was conducted in accordance with the principles of the Declaration of Helsinki.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Methodology, D.B., F.T.K and B.C.; Software, D.B. and E.C.E.; Validation, S.N.Ö.Ç.; Formal analysis, D.B., F.T.K. and M.A.N.Ş.; Resources, S.A.E, G.U., and D.U.; Data curation, S.T., S.S. and P.P.; Writing—original draft, D.B.; Supervision, F.T.K, B.C. All authors have read and agreed to the published version of the manuscript.

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