

Pretreatment Prognostic Nutritional Index Predicts Progression-Free Survival in BCLC Stage C Hepatocellular Carcinoma Treated with Sorafenib

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Background: Systemic inflammation and nutritional status are key determinants of tumor progression in advanced hepatocellular carcinoma (HCC). This study aimed to evaluate the prognostic significance of inflammation and nutrition based indices in patients with BCLC stage C HCC treated with sorafenib.

Methods: This retrospective cohort study included 109 patients with Barcelona Clinic Liver Cancer (BCLC) stage C HCC who received sorafenib as first line systemic therapy. A complete-case approach was used for multivariate Cox regression analysis. Progression-free survival (PFS) was defined according to RECIST version 1.1. Kaplan–Meier survival analysis and Cox proportional hazards regression models were used to assess prognostic factors.

Results: In Kaplan–Meier and univariate Cox analyses, several inflammation- and nutrition-based indices, including NLR, PLR, SII, mGPS, PI, and ALBI grade, were significantly associated with PFS. Although the total cohort included 109 patients, the final multivariate Cox regression model for PNI included 78 complete-case patients. In this model, low prognostic nutritional index (PNI) (HR: 2.36, 95% CI: 1.14–4.87, $p=0.020$) and prior local ablative treatment (HR: 0.45, 95% CI: 0.24–0.83, $p=0.011$) remained independently associated with PFS.

Conclusion: Pretreatment low PNI was independently associated with shorter progression-free survival in patients with BCLC stage C HCC treated with sorafenib. Other inflammation and nutrition-based indices were associated with PFS in univariate analyses but did not retain independent prognostic significance after adjustment. PNI may serve as a simple prognostic marker for risk stratification in real-world settings, although external validation is required.

Keywords: Hepatocellular carcinoma, BCLC stage C, prognosis, progression-free survival, PNI, NLR, PLR, SII, ALBI, mGPS, PI, sorafenib

Introduction

Hepatocellular carcinoma (HCC) is the most common primary malignancy of the liver and represents a major cause of cancer-related mortality worldwide.¹ A substantial proportion of patients are diagnosed at an advanced stage, at which curative treatment options such as surgical resection, liver transplantation, or local ablative therapies are no longer feasible. Consequently, systemic therapy constitutes the mainstay of treatment for patients with advanced disease.^{2,3}

Chronic inflammation and impaired nutritional status are fundamental components of hepatocarcinogenesis and tumor progression. Persistent liver inflammation, most commonly related to viral hepatitis, alcohol-associated liver disease, or metabolic dysfunction-associated steatotic liver disease, promotes genomic instability, immune dysregulation, and a pro-tumorigenic microenvironment.^{4–6}

In recent years, several inflammation- and nutrition-based indices derived from routine laboratory parameters have been developed to quantify systemic inflammatory response and host nutritional status. Among these, the neutrophil-to-lymphocyte

ratio (NLR), platelet-to-lymphocyte ratio (PLR), systemic immune-inflammation index (SII), albumin–bilirubin (ALBI) grade, modified Glasgow Prognostic Score (mGPS), prognostic nutritional index (PNI), and prognostic index (PI) have been widely investigated as potential prognostic markers in patients with HCC. Previous studies have demonstrated associations between these indices and clinical outcomes across different disease stages and treatment settings; however, their relative and independent prognostic value in advanced-stage HCC remains incompletely defined.^{7,8}

Although immunotherapy-based combinations and lenvatinib are currently recommended as preferred first-line systemic therapies for advanced HCC, access to these agents may be limited in real-world clinical practice due to reimbursement policies, regional availability, or patient-related factors. In such settings, sorafenib continues to represent a clinically relevant treatment option, particularly in resource-constrained environments.^{9,10}

PFS was selected as the primary outcome because it directly reflects disease control during sorafenib treatment and is less affected than overall survival by subsequent therapies, heterogeneous post-progression management, and non-cancer-related mortality in a retrospective real-world cohort. Therefore, the aim of the present study was to evaluate the prognostic significance of inflammation and nutrition-based indices in patients with Barcelona Clinic Liver Cancer (BCLC) stage C hepatocellular carcinoma treated with sorafenib, with a specific focus on progression-free survival (PFS).

Materials and Methods

Study Population

This retrospective cohort study included 109 patients diagnosed with hepatocellular carcinoma (HCC) at İnönü University Turgut Özal Medical Center between January 2014 and December 2024. Only patients with Barcelona Clinic Liver Cancer (BCLC) stage C disease and Child–Pugh class A liver function were included. BCLC stage C was defined according to established BCLC criteria, including macrovascular invasion and/or extrahepatic spread in patients who were candidates for systemic therapy.

HCC diagnosis was established based on histopathological findings or characteristic radiological imaging features in accordance with established clinical guidelines. All patients received sorafenib as first-line systemic therapy due to limited access to immunotherapy-based regimens and lenvatinib at the time of treatment initiation. Sorafenib was administered orally at a standard dose of 400 mg twice daily. Dose reductions, treatment interruptions, and supportive management were performed at the discretion of the treating physician according to toxicity, patient tolerance, and routine clinical practice.

Data Collection

Demographic, clinical, and laboratory data were retrospectively collected from electronic medical records. Variables included age, sex, HCC etiology, maximum tumor diameter, presence of vascular invasion, cirrhosis status, and history of prior local ablative treatment.

Inflammation- and nutrition-based indices, including neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), systemic immune-inflammation index (SII), albumin–bilirubin (ALBI) grade, modified Glasgow Prognostic Score (mGPS), prognostic index (PI), and prognostic nutritional index (PNI), were calculated using baseline laboratory values obtained prior to initiation of sorafenib therapy. Definitions and calculation methods of inflammation- and nutrition-based prognostic indices are summarized in Table 1.

Outcome Definition

Progression-free survival (PFS) was defined as the time from initiation of sorafenib treatment to radiologically confirmed disease progression or death from any cause. Tumor response and disease progression were evaluated according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 by experienced radiologists blinded to clinical data.

Statistical Analysis

Categorical variables were summarized as frequencies and percentages, while continuous variables were expressed as mean $\pm$ standard deviation or median (minimum–maximum), depending on distribution. The normality of continuous variables was assessed using the Shapiro–Wilk test.

Table 1 Inflammation-Based Prognostic Scores

PI	Score
Crp $\leq$ 10 mg/L + Wbc $\leq$ 11×10^9 /L	0
Crp $\leq$ 10 mg/L + Wbc $>$ 11×10^9 /L	1
Crp $>$ 10 mg/L + Wbc $\leq$ 11×10^9 /L	1
Crp $>$ 10 mg/L + Wbc $>$ 11×10^9 /L	2
PNI	
Alb (g/L) + $5 \times$ Lym ($\times 10^9$ /L) $\geq$ 45	0
Alb (g/L) + $5 \times$ Lym ($\times 10^9$ /L) $<$ 45	1
mGPS	0
Crp $\leq$ 10 mg/L	1
Crp $>$ 10 mg/L + Alb $\geq$ 35 g/L	
Crp $>$ 10 mg/L + Alb $<$ 35 g/L	2
ALBI	$(\log_{10} \text{bilirubin}(\mu\text{mol/L}) \times 0.66) + (\text{albumin(g/L)} \times 0.085)$
ALBI Grade I	≤ -2.60
ALBI Grade II	> -2.60 to ≤ -1.39
ALBI Grade III	> -1.39
SII	$\text{Plt}(\times 10^9/\text{L}) \times \text{Neu}(\times 10^9/\text{L}) / \text{Lym}(\times 10^9/\text{L})$
NLR	$\text{Neu}(\times 10^9/\text{L}) / \text{Lym}(\times 10^9/\text{L})$
PLR	$\text{Plt}(\times 10^9/\text{L}) / \text{Lym}(\times 10^9/\text{L})$

Note: Bold text indicates the names of the prognostic indices.

Abbreviations: Abbreviations: PI, Prognostic Index; PNI, Prognostic Nutritional Index; mGPS, modified Glasgow Prognostic Score; ALBI, albumin–bilirubin grade; SII, systemic immune-inflammation index; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; CRP, C-reactive protein; WBC, white blood cell; Alb, albumin; Plt, platelet; Neu, neutrophil; Lym, lymphocyte.

Kaplan–Meier survival analysis with Log rank testing was used to compare progression-free survival across predefined groups. Univariate Cox proportional hazards regression analyses were performed to assess the association between individual variables and PFS. Because multiple inflammation- and nutrition-based indices were evaluated, the univariate analyses were considered exploratory.

Multivariate Cox proportional hazards regression models were constructed to identify independent prognostic factors. Each inflammation- or nutrition-based index was evaluated in a separate multivariate Cox regression model adjusted for clinically relevant covariates, including age, maximum tumor diameter (≥ 5 cm), presence of vascular invasion, cirrhosis status, and history of local ablative treatment. A complete-case approach was used for multivariate Cox regression analysis; therefore, only patients with complete data for all covariates included in each model were analyzed.

The number of events and the events per variable (EPV) were calculated to assess the adequacy of the multivariate Cox regression models. Hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated. A two-sided p-value < 0.05 was considered statistically significant. All statistical analyses were performed using IBM SPSS Statistics version 26.0 (IBM Corp., Armonk, NY, USA).

Results

Baseline demographic and clinical characteristics of the study population are presented in Table 2. All patients had Barcelona Clinic Liver Cancer (BCLC) stage C disease and received sorafenib as first-line systemic therapy.

Missing data were observed for maximum tumor diameter and vascular invasion in 10 patients, ALBI grade in 14 patients, mGPS and PI in 12 patients, and PLR/SII in 1 patient. Therefore, multivariate Cox regression analyses were performed using a complete-case approach. Although the total cohort included 109 patients, the final multivariate Cox regression model for PNI included 78 patients with complete data for all covariates and 78 PFS events. The PNI model included six variables, resulting in an events-per-variable value of 13.

Table 2 Baseline Demographic, Clinical, and Laboratory Characteristics of Patients with Hepatocellular Carcinoma

Variables		n	%
GENDER	Male	100	91.7
	Female	9	8.3
AGE	<50	17	15.6
	>50	92	84.4
HCC ETIOLOGY	HBV	71	65.1
	HCV	6	5.5
	CRYPTOGENIC	32	29.4
MAXIMUM TUMOR DIAMETER	<5	30	30.3
	≥5	69	69.7
VASCULAR INVASION	NO	55	55.6
	YES	44	44.4
CIRRHOSIS	NO	25	22.9
	YES	84	77.1
LOCAL ABLATIVE TREATMENT	NO	84	77.1
	YES	25	22.9
FIRST PFS EVENT	PROGRESSION	39	35.8
	DEATH	70	64.2
ALBI GRADE	≤-2.60	11	11.5
	-2.60 – -1.39	65	68.5
	>-1.39	19	20.0
mGPS	0	30	30.9
	1	32	33.0
	2	35	36.1
	3	3	3.1
PI	0	31	32.0
	1	62	63.9
	2	4	4.1
PNI	0	40	36.7
	1	69	63.3
		Average ± SD	Median (Min-Max)
AGE OF DIAGNOSIS		60.89±11.36	60(23–94)
PFS MONTH		6.57±6.08	4.46(0.33–27.73)
NLR		4.33±3.52	3.21(1.13–19.75)
SII		986.81±1540.86	570.5(85–12,879)
PLR		176.95±157.64	134(43–1358)

Note: Bold text indicates variable names and category headings.

Abbreviations: SD, standard deviation; Min, minimum; Max, maximum; PI, Prognostic Index; PNI, Prognostic Nutritional Index; mGPS, modified Glasgow Prognostic Score; ALBI, albumin–bilirubin grade; SII, systemic immune-inflammation index; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio.

Kaplan–Meier survival analyses demonstrated significant differences in PFS according to several inflammation- and nutrition-based indices. Several inflammation- and nutrition-based indices, including NLR, PLR, SII, mGPS, PI, PNI, and ALBI grade, were significantly associated with PFS in Kaplan–Meier and/or univariate Cox analyses. Kaplan–Meier curves for mGPS, PI, PNI, and ALBI grade are shown in [Figures 1–4](#). In addition, the presence of cirrhosis and the absence of prior local ablative treatment were associated with inferior PFS in Kaplan–Meier analyses ([Table 3](#)).

Univariate Cox proportional hazards regression analyses yielded results consistent with the Kaplan–Meier findings. Higher levels of inflammation-based indices and poorer nutritional status were associated with an increased risk of

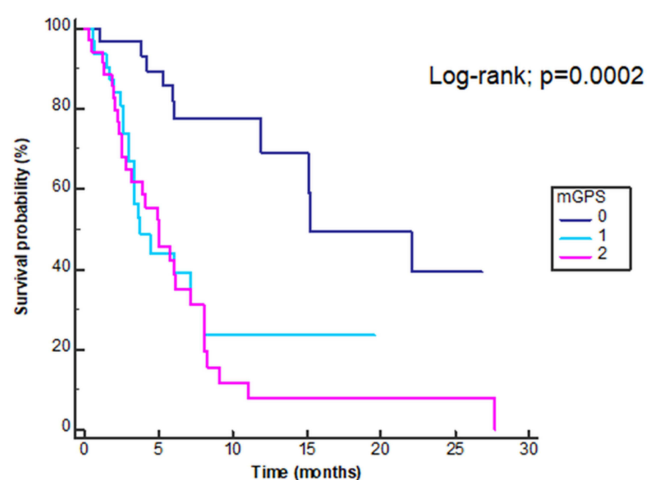


Figure 1 Kaplan–Meier curves for progression-free survival (PFS) stratified by the Modified Glasgow Prognostic Score (mGPS). Patients with an mGPS of 0 demonstrated longer PFS compared with those with mGPS scores of 1 and 2. Detailed survival data are provided in Table 3.

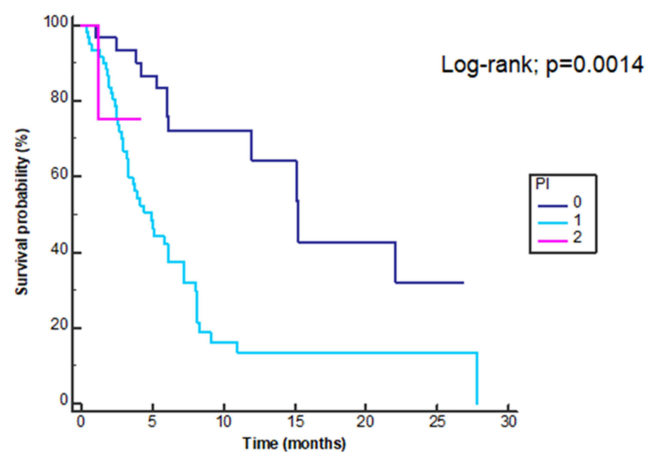


Figure 2 Kaplan–Meier curves for progression-free survival (PFS) stratified by the prognostic index (PI). Patients with a PI of zero demonstrated significantly longer PFS compared with those in the PI one and two groups. Detailed survival data are provided in Table 3.

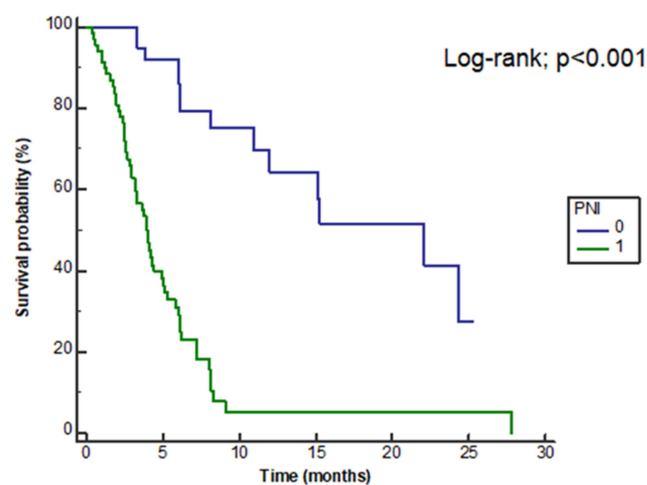


Figure 3 Kaplan–Meier curves for progression-free survival (PFS) stratified by the prognostic nutritional index (PNI). Patients with a PNI of 0 demonstrated significantly longer PFS compared with those with a PNI of 1. Detailed survival data are provided in Table 3.

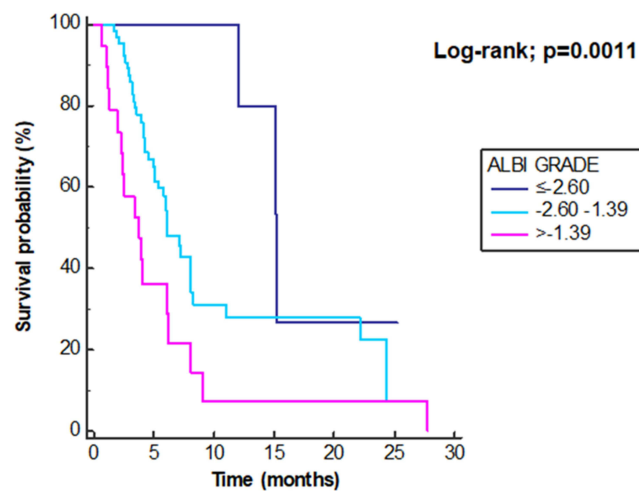


Figure 4 Kaplan–Meier curves for progression free survival (PFS) according to albumin bilirubin (ALBI) grade. Worsening ALBI grade was associated with shorter progression-free survival. Detailed survival data are provided in Table 3.

disease progression. Cirrhosis and history of local ablative treatment also demonstrated statistically significant associations with PFS in univariate Cox models (Table 3).

Multivariate Cox proportional hazards regression analyses were performed to identify independent prognostic factors for PFS (Table 3). After adjustment for clinically relevant tumor-related factors and liver function parameters, low PNI and history of local ablative treatment remained independently associated with PFS. The associations observed for other inflammation- and nutrition-based indices were attenuated and did not retain statistical significance after multivariable adjustment.

Table 3 Univariate and Multivariate Cox Regression Analyses for Progression-Free Survival

Variable	Univariate HR (95% CI)	p value	Multivariate HR (95% CI)	p value
Age (per year)	0.994 (0.975–1.013)	0.540	0.996 (0.967–1.025)	0.782
Maximum tumor diameter ≥5 cm	1.211 (0.782–1.875)	0.391	1.261 (0.598–2.655)	0.542
Vascular invasion (yes vs no)	1.181 (0.791–1.762)	0.416	1.073 (0.605–1.905)	0.809
Cirrhosis (yes vs no)	0.632 (0.401–0.997)	0.048	1.189 (0.560–2.527)	0.652
Local ablative treatment (yes vs no)	0.589 (0.372–0.931)	0.024	0.451 (0.245–0.830)	0.011
HCC etiology (non viral vs viral)	1.386 (0.913–2.105)	0.125	1.377 (0.702–2.701)	0.352
Neutrophil lymphocyte ratio (NLR) (per 1 unit)	1.054 (1.000–1.111)	0.051	1.097 (0.963–1.250)	0.163
Platelet lymphocyte ratio (PLR) (per 100-unit)	1.129 (1.019–1.250)	0.020	1.068 (0.782–1.458)	0.679
SII (per 1000-unit)	1.132 (1.019–1.258)	0.021	0.965 (0.681–1.367)	0.841
ALBI grade (II vs I)	1.791 (0.939–3.416)	0.077	0.921 (0.373–2.271)	0.857
ALBI grade (III vs I)	2.545 (1.189–5.448)	0.016	0.692 (0.189–2.532)	0.578
mGPS (1 vs 0)	2.428 (1.453–4.059)	<0.001	1.619 (0.654–4.003)	0.297
mGPS (2 vs 0)	1.876 (1.139–3.087)	0.013	1.470 (0.484–4.465)	0.496
PNI (low vs normal)	2.550 (1.686–3.856)	<0.001	2.362 (1.143–4.879)	0.020
PI (1 vs 0)	1.861 (1.202–2.883)	0.005	0.783 (0.295–2.078)	0.623
PI (2 vs 0)	4.445 (1.512–13.074)	0.007	1.951 (0.275–13.832)	0.504

Notes: Univariate analyses were performed using the maximum available number of patients for each variable. Multivariate Cox regression analyses were performed using complete-case data. Each inflammation or nutrition-based index was evaluated in a separate multivariate Cox regression model adjusted for age, maximum tumor diameter ≥5 cm, presence of vascular invasion, cirrhosis, and history of local ablative treatment. SII was entered per 1000-unit increase, PLR per 100-unit increase, and NLR per 1-unit increase. Bold values indicate statistical significance at $p < 0.05$. The final multivariate Cox regression model for PNI included 78 complete-case patients.

Abbreviations: HR, hazard ratio; CI, confidence interval; PFS, progression-free survival; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; SII, systemic immune-inflammation index; ALBI, albumin–bilirubin grade; mGPS, modified Glasgow Prognostic Score; PNI, Prognostic Nutritional Index; PI, Prognostic Index.



Discussion

In this retrospective cohort study, we evaluated the prognostic significance of inflammation- and nutrition-based indices in patients with BCLC stage C hepatocellular carcinoma treated with sorafenib. By using a hierarchical analytical approach, associations observed in Kaplan Meier and univariate Cox analyses were further examined in multivariate Cox regression models to determine independent prognostic factors for PFS.

Several inflammation and nutrition based indices, including NLR, PLR, SII, mGPS, PI, and ALBI grade, were significantly associated with PFS in univariate analyses. These findings are consistent with previous reports demonstrating the prognostic relevance of systemic inflammation and nutritional status across different stages and treatment settings in hepatocellular carcinoma. However, after adjustment for clinically relevant tumor related and liver function variables, the prognostic impact of most inflammation based indices was attenuated, suggesting overlapping biological information captured by these composite markers.^{11–15}

Notably, low PNI remained independently associated with shorter PFS in multivariate analysis. PNI is a composite index reflecting both nutritional and immunological status and may capture host-related factors that are not fully represented by conventional tumor burden or liver function parameters. Advanced hepatocellular carcinoma is frequently accompanied by cancer-related cachexia, sarcopenia, and chronic cytokine-mediated catabolism. Elevated levels of proinflammatory cytokines such as interleukin-6 and tumor necrosis factor- α reduce albumin synthesis and lymphocyte counts, thereby compromising both nutritional status and antitumor immune responses. Impaired nutritional and immune status may reduce tolerance to systemic therapy and accelerate disease progression. Collectively, these findings suggest that PNI functions as a composite biomarker of biological resilience and support its role as a clinically meaningful prognostic marker in patients with advanced hepatocellular carcinoma.^{16–25}

In addition, a history of local ablative treatment remained independently associated with improved PFS after multivariable adjustment. Prior locoregional therapy may identify a subgroup of patients with lower effective tumor burden or more favorable tumor biology, even within an advanced stage population. Furthermore, locoregional tumor control may contribute to delayed disease progression when combined with systemic therapy. These findings align with previous studies suggesting a benefit of multimodal treatment strategies in selected patients with advanced hepatocellular carcinoma.^{26,27}

HCC develops in a chronically inflamed hepatic environment characterized by persistent cytokine activation, angiogenesis, immune dysregulation, and progressive parenchymal damage. In our cohort, viral hepatitis represented the predominant etiology, consistent with global epidemiologic data. Chronic inflammation contributes to tumor progression through genomic instability, immune escape, and enhanced metastatic potential.^{28–30}

The presence of cirrhosis was associated with inferior PFS in univariate analyses but did not retain independent significance in multivariate models. This finding likely reflects the close interaction between cirrhosis and other liver function related variables included in the multivariate analysis, rather than a lack of clinical relevance of cirrhosis itself.^{31,32}

Although immunotherapy based combinations and lenvatinib are currently recommended as preferred first line systemic therapies for advanced HCC, access to these agents may be limited in real world clinical practice due to reimbursement policies, regional availability, or patient-related factors. In such settings, sorafenib remains a relevant treatment option, and evaluating prognostic markers in patients treated with sorafenib continues to have clinical importance.^{33,34}

Several limitations of this study should be acknowledged. First, the retrospective and single-center design may limit the generalizability of the findings and may introduce selection bias. Second, the relatively small sample size and missing data for some variables necessitated the use of a complete-case approach in multivariate analyses, which may have reduced statistical power and introduced potential bias if the missing data were not completely random. Third, multiple inflammation- and nutrition-based indices were evaluated, and the univariate analyses should therefore be interpreted as exploratory. Although each index was assessed in a separate multivariate model adjusted for clinically relevant covariates, the possibility of type I error due to multiple testing cannot be fully excluded.

Fourth, prior local ablative treatment was independently associated with improved PFS; however, this finding should be interpreted with caution. Patients who had previously received local ablative treatment may represent a subgroup with a more favorable tumor biology, lower initial tumor burden, or earlier disease detection before progression to BCLC stage C. Therefore, potential lead-time bias and selection bias related to prior local therapy cannot be excluded. Finally, this study did not include an

external validation cohort. Independent validation in larger, multicenter cohorts is required before PNI can be incorporated into routine clinical decision-making as a prognostic marker in patients with advanced HCC treated with sorafenib.

Conclusion

In patients with BCLC stage C hepatocellular carcinoma treated with sorafenib, pretreatment low PNI was independently associated with shorter progression-free survival after adjustment for clinically relevant covariates. Other inflammation and nutrition-based indices were associated with PFS in univariate analyses but did not retain independent prognostic significance after multivariable adjustment. These findings suggest that PNI may serve as a simple and readily available prognostic marker for risk stratification in real-world clinical practice. However, external validation in larger, multicenter cohorts is required before routine clinical implementation.

Use of Artificial Intelligence Tools

The authors used artificial intelligence based language editing tools solely to improve the clarity and readability of the manuscript. No AI tools were used for data analysis, data interpretation, or generation of scientific conclusions. All authors take full responsibility for the accuracy and integrity of the content.

Abbreviations

HCC, Hepatocellular Carcinoma; HBV, Hepatitis B; HCV, Hepatitis C; BCLC, Barcelona Clinic Liver Cancer; VEGFR, Vascular Endothelial Growth Factor Receptor; PDGFR, Platelet Derived Growth Factor Receptor; PI, Prognostic Index; PNI, Prognostic Nutritional Index; mGPS, Modified Glasgow Prognostic Score; ALBI, Albumin Bilirubin Index; NLR, Neutrophil Lymphocyte Ratio; PLR, Platelet Lymphocyte Ratio; HR, Hazard ratio; ICI, Immune Checkpoint Inhibitor; GITRL, Glucocorticoid induced TNF related ligand; NK, Natural Killer; Alb, Albumin; IL, Interleukin; TNF, Tumor Necrosis Factor; CRP, C-Reactive Protein; OS, Overall Survival; WBC, White blood cells; NSCLC, Non-small cell lung cancer.

Data Sharing Statement

The data associated with present study are available from the corresponding author upon reasonable request.

Ethics Approval

This retrospective study was performed in accordance with the principles of the Declaration of Helsinki. The study protocol was approved by the İnönü University Clinical Research Ethics Committee (Approval No: 2025/7300; Date: 25 March 2025). All patient data were anonymized before analysis, and confidentiality was strictly maintained throughout the study in accordance with institutional regulations.

Consent to Participate

Due to the retrospective design of the study, the requirement for informed consent was waived by the İnönü University Clinical Research Ethics Committee.

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.

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Disclosure

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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