

# The Role of Easy-to-use Non-invasive Scores in the Assessment of Hepatocellular Carcinoma Prognosis – Data from the Romanian Hepatocellular Carcinoma Registry

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## ABSTRACT

**Background & Aims:** Hepatocellular carcinoma (HCC) is currently the third leading cause of cancer-related mortality, a figure that is on the rise. The shared hallmark of different etiologies, progression, and HCC survival is chronic inflammation, making it a significant field of interest for prognostic and therapeutic strategies. We aimed to evaluate the prognostic accuracy of several inflammation-based scores in HCC.

**Methods:** A consecutive series of patients at their first HCC diagnosis were enrolled during a 5-year timespan in a prospectively maintained multicentric database. Demographic, clinical, biological, and imagistic data were collected. Representative inflammation-based prognostic scores, including the platelet-to-lymphocyte ratio (PLR), neutrophil-to-lymphocyte ratio (NLR), systemic immune inflammation index (SII), prognostic nutritional index (PNI), albumin-to-bilirubin index (ALBI), platelet-albumin-bilirubin-index (PALBI), AST-to-lymphocyte ratio (ALRI), AST/ALT, AST-to-platelet ratio (APRI) were assessed for prediction of overall survival (OS) in a scenario-based setting, using Kaplan-Meier curves, univariate and multivariate analyses.

**Results:** A total of 467 patients from five tertiary-care hospitals were enrolled in this study. The median age was 64.94 years, and the most frequent etiology of the liver disease was hepatitis C (50%). During a median of 14.85 (35) months of follow-up, the cumulative mortality was 84.8%. In the univariate analysis, PNI (HR=2.414; p=0.021), ALBI grade (HR=2.023; p<0.001), and PALBI grade (HR=2.022; p<0.001) demonstrated the highest prognostic accuracies for OS in HCC, regardless of the clinical scenario. Moreover, PLR (HR=1.635; p=0.002), ALRI (HR=1.555; p<0.001), NLR (HR=1.461; p=0.007), AST/ALT (HR=1.420; p=0.012), and APRI (HR=1.356; p=0.009) were also significant prognostic factors for OS. The multivariate analysis showed that only ALBI grade (HR=1.974; p<0.001), SII (HR=1.487; p=0.009), and PLR (HR=1.647; p=0.014) were independently associated with OS.

**Conclusions:** Inflammation-based scores allow for an accurate prediction of survival in HCC. Their ability to predict the response to treatment and complications merits further investigation.

**Key words:** hepatocellular carcinoma – prognosis – biomarkers – non-invasive – inflammation scores – survival.

**Abbreviations:** ALBI: albumin-to-bilirubin index; ALRI: AST-to-lymphocyte ratio; APRI: AST-to-platelet ratio; BCLC: Barcelona Clinic Liver Cancer; ECOG: Eastern Cooperative Oncology Group; HCC: hepatocellular carcinoma; HR: hazard ratio; MASLD: metabolic dysfunction-associated steatotic liver disease; MELD: Model for End-Stage Liver Disease; NLR: neutrophil-to-lymphocyte ratio; OS: overall survival; PALBI: platelet-albumin-bilirubin-index; PLR: platelet-to-lymphocyte ratio; PNI: prognostic nutritional index; SII: systemic immune inflammation index; TACE: transarterial chemoembolization.

## INTRODUCTION

Hepatocellular carcinoma (HCC) is one of the most common and lethal malignancies worldwide, being among the top five causes of cancer death in 90 countries according to the

GLOBOCAN 2020 database. A predicted 1.3 million people could die from liver cancer in 2040 (56.4% more than in 2020) [1].

It primarily arises in the context of chronic liver diseases such as hepatitis B, hepatitis C, and metabolic or ethanolic steatohepatitis. A key pathological feature shared by these conditions is chronic inflammation, which not only contributes to liver damage and fibrosis but also plays a pivotal role in

carcinogenesis. Recent studies have highlighted that the inflammatory microenvironment in the liver is critical in the progression from cirrhosis to HCC, making inflammation a major area of interest for prognostic and therapeutic strategies.

Inflammation-based prognostic scores, such as the neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and systemic immune-inflammation index (SII) have been increasingly used to assess prognosis in HCC patients [2-4]. These biomarkers reflect the host's immune response and the tumor-associated inflammatory milieu, offering insight into both the biological aggressiveness of the tumor and the patient's systemic inflammatory status. Additionally, inflammatory scores are valuable in predicting treatment responses, such as the efficacy of immune checkpoint inhibitors and other novel immunotherapies [5].

Understanding the role of inflammation in HCC and utilizing inflammation-based scores can improve risk stratification and individualized patient management, which is crucial in a cancer as heterogeneous and challenging as HCC. This study aimed to assess the role of different simple and common inflammation scores in the prognosis of HCC.

## METHODS

### Study Population

A consecutive series of patients were included at the time of their first diagnosis of HCC using data from a prospectively maintained multicenter database. Five tertiary care centers of hepatology, which were the largest in Romania in terms of patient volume, responded to the invitation of including patients in the database. The enrollment period spanned from June 2016 to February 2020. Patients diagnosed after March 2020 were excluded to prevent potential biases rising from care modifications imposed by the COVID-19 pandemic. End of follow-up was defined as inquiry of the national insurance registry regarding the survival of the patients at 2nd of April 2023. This study comes as a complement to previously published data from the same registry, which analyzed the demographic and epidemiologic characteristics of the patients with HCC in Romania [6].

Inclusion criteria were as follows: patients over 18 years of age, first diagnosis of HCC (including those referred from secondary care facilities within a six-week period). All patients signed an informed consent. To minimize selection bias, only practicing gastroenterologists enrolled patients, avoiding data skewing toward either early-stage (curative treatment such as surgery) or advanced-stage disease (requiring oncology care). Patients with a prior history of HCC, whether fully treated or with ongoing disease, were excluded from the study. Hepatocellular carcinoma diagnosis was confirmed using either two concordant contrast-enhanced imaging modalities, fulfilling the Li-RADS 5 criteria for cirrhotic patients, or through pathology for non-cirrhotic patients or inconclusive imaging results [7].

### Patients' Characteristics

Demographic, clinical, laboratory, and imaging data were collected from each patient. From the clinical point of view, variables registered were Eastern Cooperative Oncology Group

(ECOG) performance status and any decompensating events [8]. The underlying etiology of liver disease was classified as viral (hepatitis B or C), alcohol-related, metabolic dysfunction-associated steatotic liver disease (MASLD) and other causes (such as autoimmune hepatitis, cholestatic liver disease, hemochromatosis, Wilson's disease). Liver disease severity was assessed using the Child-Pugh score and the Model for End-Stage Liver Disease (MELD) score. HCC staging followed the latest version of the Barcelona Clinic Liver Cancer (BCLC) classification available at the time of enrollment [9]. Imaging data focused on tumor burden (number and size of HCC nodules) and the presence of vascular invasion.

For the calculation of the inflammatory scores, we used the variables included in the blood count, the level of C-reactive protein, aspartate aminotransferase (AST), alanine aminotransferase (ALT), and albumin, as it was suggested by previous articles that tested the role of inflammatory markers in digestive cancers and HCC also:

$$\text{PLR} = \text{P (absolute platelet count)/L (lymphocyte count)} \quad [10]$$

$$\text{NLR} = \text{N (absolute neutrophil count)/L (absolute lymphocyte count)} \quad [11]$$

$$\text{ALBI} = \log_{10} \text{Bilirubin } (\mu\text{mol/L}) \times 0.66 + \text{albumin (g/L)} \times -0.085. \text{ ALBI score } \leq -2.60 \text{ was defined as grade 1, } > -2.60 \text{ but } \leq -1.39 \text{ as grade 2, and } > -1.39 \text{ as grade 3} \quad [12]$$

$$\text{PALBI} = 2.02 \times \log_{10} \text{TBIL } (\mu\text{mol/L}) - 0.37 \times (\log_{10} \text{TBIL})^2 - 0.04 \times \text{ALB (g/L)} - 3.48 \times \log_{10} \text{PLT } (10^9/\text{L}) + 1.01 \times (\log_{10} \text{PLT}). \text{ PALBI grade was defined as: grade 1: } \leq -2.53; \text{ grade 2: } -2.09 \text{ to } -2.53; \text{ grade 3: } > -2.09 \quad [12].$$

$$\text{SII (Systemic Immune-inflammation Index)} = \text{Platelet count } (\times 10^9/\text{L}) \times \text{neutrophil count } (\times 10^9/\text{L}) / \text{lymphocyte count } (\times 10^9/\text{L}) \quad [13]$$

$$\text{PNI (Prognostic Nutritional Index)} = \text{Albumin (g/L)} + 5 \times \text{lymphocyte count } (\times 10^9/\text{L}) \quad [14]$$

$$\text{ALRI} = \text{AST value/lymphocyte count} \times 10^9/\text{U} \quad [15]$$

$$\text{APRI (ASAT to Platelet ratio)} = \text{ASAT value IU/l} / \text{ASAT (upper normal limit IU/lL)/platelet count } (10^9/\text{l}) \quad [16]$$

The assessment of inflammatory scores was made using the optimal cut-off values recommended in the original articles on this topic (4 for NLR, 150 for PLR, 330 for SII, 45 for PNI, 1 for AST/ALT, 34 for ALRI and 0.5 for APRI respectively) [13, 14, 17-21]. The ALBI and PALBI scores were classified as it follows: an ALBI score of -2.60 or lower was classified as grade 1, between -2.60 to -1.39 was classified as grade 2, and a score of -1.39 or higher was classified as grade 3; a PALBI score of -2.53 or lower was classified as grade 1, between -2.53 and -2.09 was classified as grade 2, and a score of -2.09 or higher was classified as grade 3.

### Statistical Analysis

The statistical analysis was conducted under the supervision of a certified biomedical statistician, using the Statistical Product and Service Solution (SPSS®) software version 28.0 (IBM®, Armonk, New York, USA). Data normality was evaluated using the Shapiro-Wilk test. Normally distributed variables were reported as mean  $\pm$  standard deviation (SD), while non-normally distributed variables were expressed as

median and interquartile range (IQR). Comparisons of means were performed using the Student's t-test, and medians were compared using the Mann-Whitney U test. Depending on the sample size, categorical variables were analyzed using either Fischer's exact test or the Chi-squared test. Univariate analysis was used to associate the inflammation scores with survival. Variables significantly associated with survival in univariate analysis were included in multivariate analysis. Kaplan Meyer survival curves were used to compare the survival depending on the inflammatory scores. Statistical significance was set at  $p < 0.05$ .

### Ethical Considerations

The study protocol was approved by all five Institutional Review Boards. Given the prospective observational nature of the study, written informed consent was obtained for anonymized personal data use, according to the European Union General Data Protection Regulation (GDPR).

## RESULTS

A total of 467 patients with a median age of 64.94 years from five tertiary-care hospitals in Romania were included. The cohort consisted of 327 men and 140 women, viral hepatitis C being the most frequent etiology of the liver disease (50%). Regarding the severity staging, according to BCLC classification, most of the patients were included in A class (164 patients, 34.3%), with an even distribution of the patients in the other classes, except for the 0 class, which was the worst represented (34 patients, 7.1%). Of the whole study group, 31.8% had a history of decompensated liver disease and 38.2% had ascites at the time of the evaluation. After a median follow up of 14.85 months, there were only 58 (15.6%) patients still alive, with a median survival time of 10.38 months from the diagnosis. The baseline characteristics of the population are found in Table I.

The assessment of inflammatory scores was made using the optimal cut-off values recommended in the original articles on this topic, as mentioned in the method chapter. The biological features of the patients included in the study group and the distribution of the patients depending on the cut-offs of the inflammatory scores are shown in Table II.

### Univariate and Multivariate Analysis of Variables Associated with Survival

We performed a univariate analysis of the association of inflammatory scores with overall survival (OS). The results of the univariate Cox regression analysis showed that the high values of NLR (HR=1.461;  $p=0.007$ ), PLR (HR=1.635;  $p=0.002$ ), ALBI grade (HR=2.023;  $p<0.001$ ), PALBI grade (HR=2.022;  $p<0.001$ ), PNI (HR=2.414;  $p=0.021$ ), ASAT/ALAT (HR=1.420;  $p=0.012$ ), ALRI (HR=1.555;  $p<0.001$ ) and APRI (HR=1.356;  $p=0.009$ ) were found to be significant prognostic factors for OS (Table III).

The variables associated with OS in univariate analysis were further evaluated in the multivariate analysis. The results showed that only the high value of ALBI grade (HR=1.974;  $p<0.001$ ), SII (HR=1.487;  $p=0.009$ ) and PLR (HR=1.647;  $p=0.014$ ) were independently associated with OS (Table IV).

**Table I.** Baseline characteristics of the studied population

Category	Number (percentage)/ Median (IQR)*
Gender - male/female, n (%)	327 (70)/140 (30)
Age (years)	64.94 (10.99)
Etiology of liver disease, n (%)	
Viral hepatitis C	232 (50)
Viral hepatitis B	110 (23.7)
Alcohol related liver disease	88 (19)
Metabolic associated fatty liver disease	10 (2.2)
Other	24 (5.2)
Child Pugh class, n (%)	
A	230 (52.6)
B	121 (27.7)
C	86 (19.7)
MELD score*	11 (8)
BCLC stage, n (%)	
0	34 (7.1)
A	164 (34.3)
B	93 (19.4)
C	68 (14.2)
D	118 (24.7)
Ascites	
Present	176 (38.2)
Absent	285 (61.8)
Status of studied event at the end of follow-up, n (%)	
Alive	58 (15.6)
Dead	313 (84.4)
Survival at 14.85 months depending on BCLC	
Stage 0	
Alive	12 (60)
Dead	8 (40)
A	
Alive	28 (21.9)
Dead	100 (78.1)
B	
Alive	12 (16.9)
Dead	59 (83.1)
C	
Alive	1 (1.7)
Dead	57 (98.3)
D	
Alive	3 (3.9)
Dead	74 (96.1)
Survival time in months*	10.38 (26)
Median follow-up time*	14.85 (35)

Normally distributed variables were expressed as mean  $\pm$  standard deviation; non-normally distributed variables were expressed as median and inter-quartile range; MELD: model for end-stage liver disease; IQR: inter-quartile range; BCLC: Barcelona Clinic Liver Cancer stage; \* data expressed as median and IQR.

ALBI score proved to have the best HR, showing that patients included in the group of high ALBI level will have a risk of death of 2 folds higher compared to those in the lower ALBI groups.

**Table II.** Characteristics of the studied variables

Studied variable	Median (IQR)
AST (UI/L)	69 (72)
ALT (UI/L)	53 (52)
Total bilirubin (mg/dl)	1.4 (1)
Direct bilirubin (mg/dl)	0.64 (1)
AP (mg/dl)	147 (167)
GGT (mg/dl)	85 (142)
Urea (mg/dl)	36 (21)
Albumin (g/dl)	3.4 (1)
Neutrophils (*10 <sup>3</sup> /uL)	3.51 (3)
Lymphocytes (*10 <sup>3</sup> /uL)	1.47 (1)
Platelets (*10 <sup>3</sup> /uL)	117 (106)
Alfa fetoprotein	30.2 (297)
CRP (mg/dl)	3.05 (9)
INR	1.28 (0.35)
NLR	2.51(1.9)
NLR (n,%)	
>4	89 (20.8)
<4	338 (79.2)
PLR	80.2 (68.1)
PLR, n (%)	
<150	70 (15.2)
	390 (84.8)
ALBI score	-1.91 (1.14)
ALBI grade, n (%)	
1	78 (16.8)
2	251 (54)
3	136 (29.2)
PALBI score	-4.3 (1.35)
PALBI grade, n (%)	
1	443 (95.9)
2	11 (2.4)
3	8 (1.7)
SII	274.99 (347.17)
SII, n (%)	
>330	180 (42.2)
<330	247 (57.8)
PNI	33 (10.85)
PNI (n,%)	
>45	20 (4.2)
<45	455 (95.8)
ASAT/ALAT	1.31 (0.9)
ASAT/ALAT, n (%)	
>1	341 (74.0)
<1	120 (26.0)
ALRI	47.7 (60.25)
ALRI, n (%)	
>34	299 (65.0)
<34	161 (35.0)
APRI	0.621 (0.79)
APRI, n (%)	
>0.5	268 (57.9)
<0.5	195 (42.1)

Non-normally distributed variables were expressed as median and inter-quartile range; AST: aspartate transaminase; ALT: alanine transaminase; AP: alkaline phosphatase; GGT: gamma-glutamyl transferase; CRP: C-reactive protein; INR: international normalized ratio; NLR: neutrophils to lymphocyte ratio; PLR: platelets to lymphocyte ratio; ALBI: albumin-bilirubin grade; PALBI: platelets-albumin-bilirubin grade; SII: systemic immune inflammation index; ALRI: aminotransferase to lymphocyte ratio index; APRI: aminotransferase to lymphocyte ratio index.

**Table III.** Univariate analysis of inflammation scores for overall survival of HCC patients

Variable	Univariate analysis		
	HR	95% CI	p
NLR>4	1.461	1.108-1,928	<b>0.007</b>
PLR>150	1.635	1.200-2,228	<b>0.002</b>
ALBI GRADE	2,023	1.688-2.424	<b>&lt;0.001</b>
PALBI GRADE	2,022	1.416-2,886	<b>&lt;0.001</b>
SII>330	1.223	0.965-1.548	<b>0.05</b>
PNI<45	2.414	1.140-5.111	<b>0.021</b>
ASAT/ALAT>1	1.420	1.080-1.866	<b>0.012</b>
ALRI>34	1.555	1.225-1.975	<b>&lt;0.001</b>
APRI>0.5	1.356	1.079-1.705	<b>0.009</b>

For abbreviations see Table II

**Table IV.** Multivariate analysis of inflammation scores for overall survival of HCC patients

Variable	Multivariate analysis		
	HR	95% CI	p
NLR>4	0.952	0.685-1.323	0.769
PLR>150	1.647	1.105-2.454	<b>0.014</b>
Highest ALBI grade	1.974	1.583-2,462	<b>&lt;0.001</b>
Highest PALBI grade	1.612	0,998-2,603	<b>0.05</b>
SII>330	1.487	1.104-2,002	<b>0.009</b>
PNI<45	0,923	0,413-2,061	0.845
ASAT/ALAT>1	1.129	0,831-1,533	0.438
ALRI>34	1,115	0,780-1,594	0.551
APRI>0.5	1,390	0,976-1,980	0.068

For abbreviations see Table II

Subsequently, we combined the scores that yielded the highest statistical significance in our analysis, in order to obtain a higher prognostic accuracy, but only the combination of ALBI and PLR showed a slightly increased HR in the multivariate analysis (HR=2.105, p=0.019).

A subgroup analysis was then performed according to BCLC stage. We included BCLC stage 0 and A in the same group (early-stage HCC) given the fact that for these patients the curative treatment is recommended as the primary therapeutic modality. In the univariate analysis the scores that were found to be significant prognostic factor for OS were ALBI for BCLC stages 0, A and C, and PALBI for BCLC stages B and C. Moreover, SII and PLR showed a good prognostic accuracy in BCLC stage D (Table V). In the multivariate analysis, both ALBI and PALBI maintained their statistical significance (Table VI).

### Survival Analysis

Finally we analyzed the influence of these variables on OS using the Kaplan Mayer curve. The median survival time was significantly lower in patients with a NLR>4 (133 vs 414; p=0.028) (Fig. 1) and a PLR>150 (166 vs 369; p=0.044) (Fig. 2) compared with those who had lower levels of these variables. PLR>150 was also associated with OS in the subgroup D of BCLC, p=0.002.

**Table V.** Subgroup univariate analysis according to BCLC stage

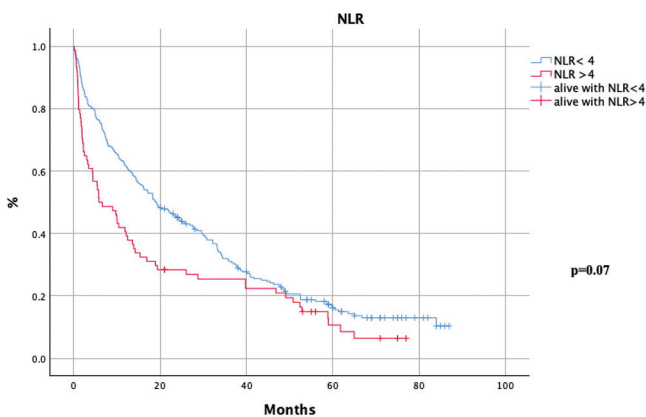
	Univariate analysis							
	BCLC 0 and A		BCLC B		BCLC C		BCLC D	
	HR	p	HR	p	HR	p	HR	p
NLR>4	1.043	0.888	0.973	0.940	0.793	0.456	1.394	0.223
PLR>150	1.167	0.643	0.833	0.672	1.098	0.777	2.385	<b>0.003</b>
HIGHEST ALBI GRADE	1.636	<b>0.002</b>	1.162	0.542	1.615	<b>0.047</b>	1.665	0.07
HIGHEST PALBI GRADE	1.706	0.455	3.149	<b>0.004</b>	2.368	<b>0.015</b>	1.040	0.891
SII>330	0.802	0.302	0.927	0.789	1.127	0.683	2.049	<b>0.008</b>
PNI<45	3.035	0.059	0.526	0.284	1.467	0.706		*
ASAT/ALAT>1	1.504	0.064	0.983	0.957	1.524	0.202	0.527	0.057
ALRI>34	1.444	0.065	1.586	0.093	1.003	0.993	0.924	0.798
APRI>0.5	1.280	0.205	1.238	0.423	0.870	0.617	0.750	0.325

\*small sample size

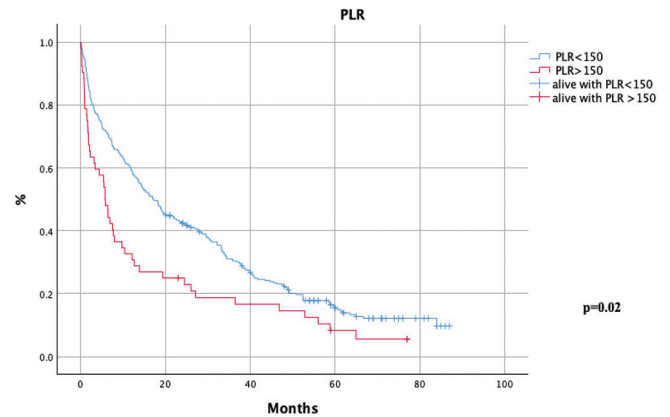
**Table VI.** Subgroup multivariate analysis according to BCLC stage

	Multivariate analysis							
	BCLC 0 and A		BCLC B		BCLC C		BCLC D	
	HR	p	HR	p	HR	p	HR	p
NLR>4	1.037	0.915	0.717	0.437	0.716	0.339	0.704	0.329
PLR>150	1.111	0.801	0.716	0.532	1.037	0.928	1.860	0.125
Highest ALBI grade	1.508	<b>0.036</b>	1.194	0.609	1.973	<b>0.043</b>	1.328	0.374
Highest PALBI grade	1.311	0.710	2.352	0.129	2.292	<b>0.040</b>	1.047	0.926
SII>330	1.095	0.736	1.131	0.721	1.934	0.109	1.920	0.114
PNI<45	1.926	0.290	0.256	0.069	0.450	0.528		*
ASAT/ALAT>1	1.234	0.385	1.132	0.745	1.943	0.107	0.493	0.085
ALRI>34	1.148	0.630	2.466	<b>0.043</b>	1.115	0.805	0.741	0.569
APRI>0.5	1.130	0.686	0.845	0.692	0.602	0.239	1.188	0.712

\*small sample size. For the rest of abbreviations see Table II.



**Fig. 1.** Association of NLR (cut-off 4) with survival time.



**Fig. 2.** Association of PLR (cut-off 150) with survival time.

When comparing ALBI grade 1 and 2 patients, there was no significant difference in survival time ( $p=0.257$ ), but this was not the case with ALBI grade 3 patients, who had a lower OS when compared to the first two grades (70 vs 786/440,  $p<0.001$ ) (Fig. 3). ALBI 3 also identified patients with lower survival time in each of the BCLC subgroups: in 0+A ( $p=0.001$ ), in class B ( $p=0.04$ ) and in class C ( $p=0.03$ ) (Fig.

4 a,b,c). Similarly, HCC patients with PALBI grade III had significant lower survival compared to grade I ( $p<0.001$ ), as represented in Fig. 5. SII was not confirmed as being associated with OS. Lower PNI was associated with lower survival time, as seen in Fig. 6. Biological scores involving AST as a marker of severe liver fibrosis were also prognostic for the survival time, as seen in Figs. 7 a,b,c.

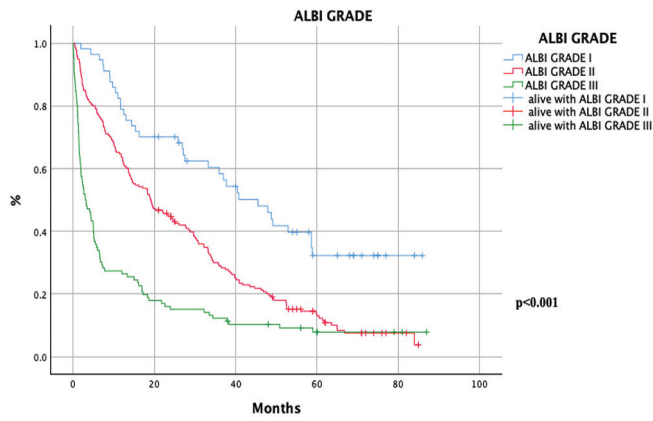


Fig. 3. ALBI grades associated with survival time.

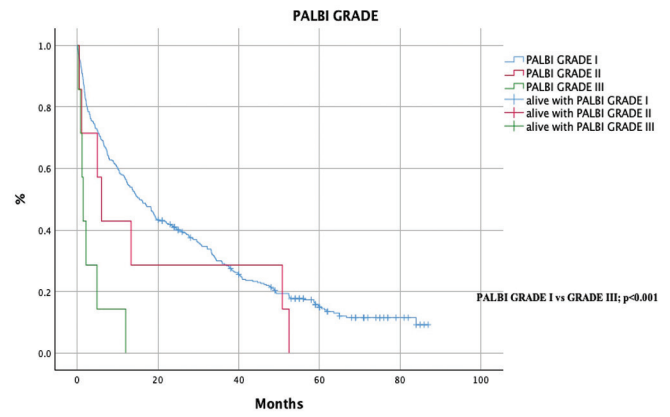


Fig. 5. Higher PALBI score associated with lower survival.

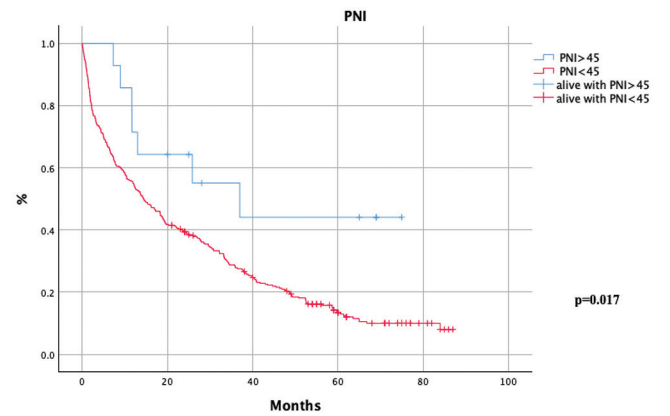
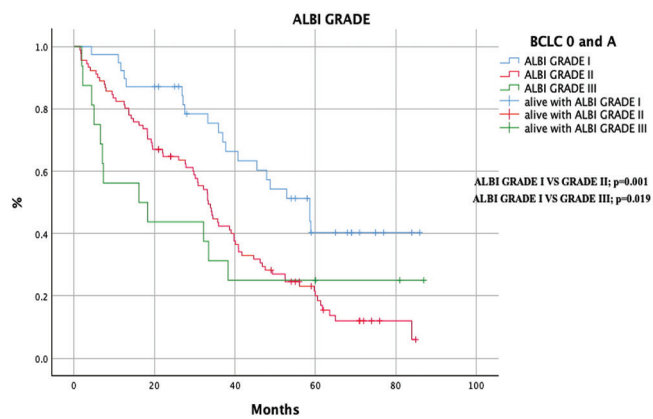


Fig. 6. Lower PNI associated with lower survival time.

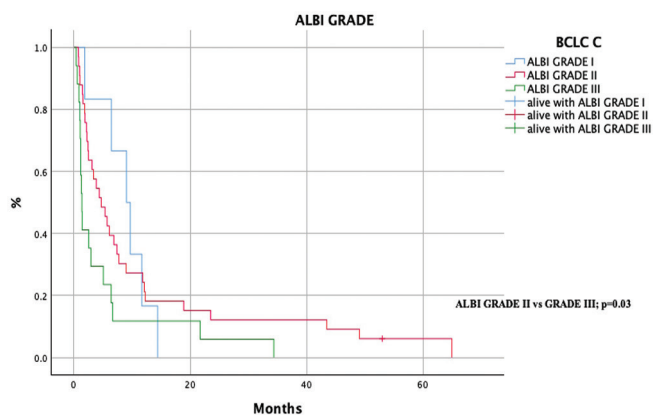
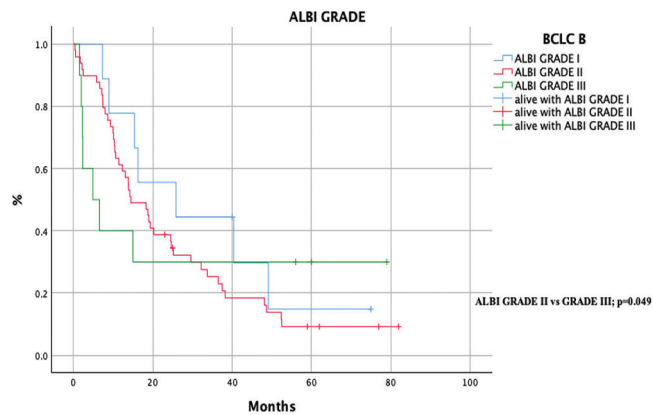


Fig. 4 a,b,c. Prognostic importance of ALBI grades in BCLC 0+A (1a), in BCLC B (1b), BCLC C (1c).

## DISCUSSIONS

Hepatocellular carcinoma is strongly linked to chronic inflammation, particularly when it develops on the background of chronic hepatitis or cirrhosis. In recent years, inflammation-based prognostic markers, including NLR, PLR, SII, PNI, and ALBI, have garnered attention as valuable tools in predicting clinical outcomes in HCC. These markers are not only easily accessible from routine blood tests, but also provide critical insights into the tumor microenvironment, immune responses, and systemic inflammation.

The NLR reflects the balance between systemic inflammation and immune surveillance. Elevated NLR levels have been consistently associated with poor prognosis in HCC patients [22]. Neutrophils are known to contribute to cancer progression by promoting angiogenesis, tumor growth, and metastasis, while lymphocytes play a key role in anti-tumor immunity. A high NLR indicates a relative increase in neutrophils and a decrease in lymphocytes, which suggests an impaired immune response against the tumor. Several studies have demonstrated that patients with higher NLR levels are more likely to exhibit aggressive tumor characteristics, advanced disease stages, and reduced overall survival rates [23-25]. These findings underscore the potential utility of NLR as a non-invasive biomarker to stratify risk and guide therapeutic decisions in HCC patients. Our data also suggested that a NLR higher than 4 was associated with a poor OS in univariate analysis, but it did not maintain its significance in multivariate analysis.

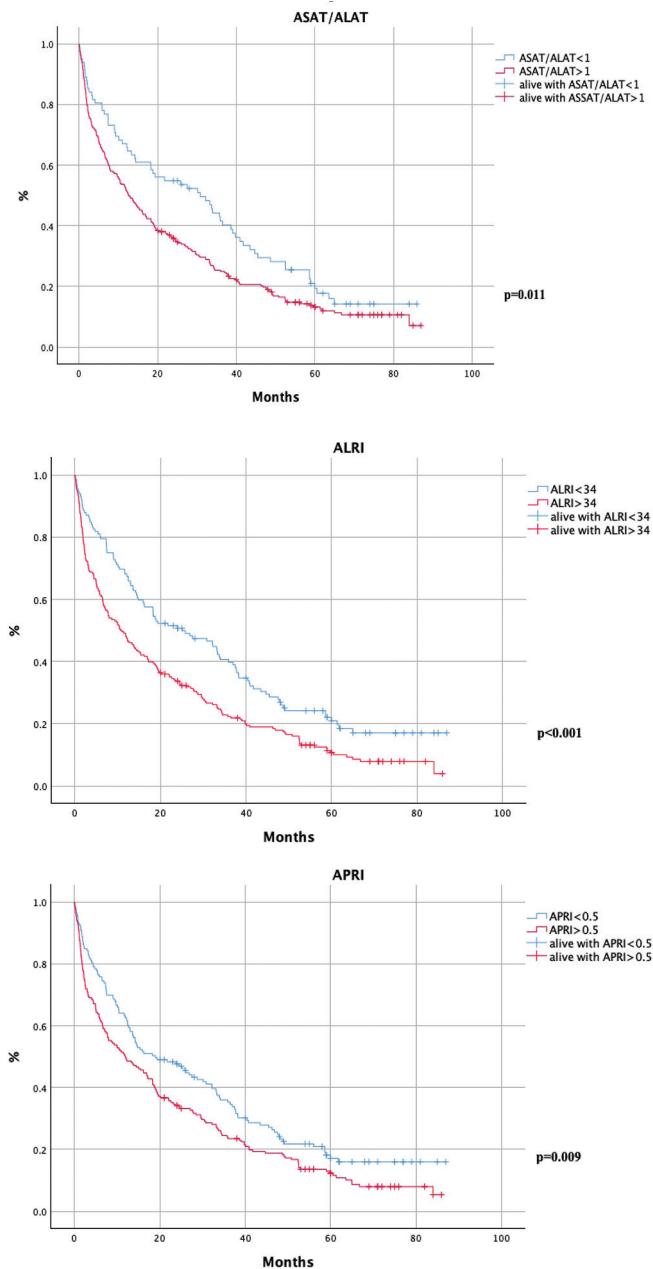


Fig. 7 a,b,c. Higher values of AST/ALT (a), ALRI (b) and APRI (c) associated with lower survival time.

Similarly, the PLR higher than 150 performed well in predicting OS in univariate analysis in our study. PLR has emerged as another indicator of the systemic inflammatory response. Elevated PLR levels have been associated with poor prognosis in HCC [22]. Platelets, through their interactions with tumor cells, can facilitate cancer cell dissemination and metastasis. Like NLR, a high PLR is thought to reflect increased systemic inflammation and reduced anti-tumor immunity, correlating with more advanced disease and worse outcomes [18]. Although PLR is less studied than NLR, available evidence supports its role as a prognostic marker, particularly in patients undergoing surgical resection or locoregional therapies such as transarterial chemoembolization (TACE) [26].

A better relevance was shown by SII which proved to be associated with OS in multivariate analysis at a value higher

than 330. The SII index, which incorporates neutrophils, lymphocytes, and platelets, has gained prominence as a composite biomarker that captures the complex interactions between inflammation and immune function. Elevated SII levels are indicative of both increased inflammatory responses and reduced immune surveillance, making it a strong predictor of poor outcomes in HCC [27]. Research suggests that SII can predict survival more accurately than NLR and PLR in certain patient populations, particularly those undergoing systemic therapies such as sorafenib or immunotherapy [28]. Its robust prognostic ability may be due to its comprehensive nature, integrating both inflammatory and immune components into a single index.

The PNI, which is based on serum albumin levels and total lymphocyte count, reflects both the nutritional and immune status of patients. A low PNI indicates poor nutritional status and compromised immune function, both of which are associated with worse outcomes in HCC [29]. Malnutrition and sarcopenia are common in HCC patients, especially those with cirrhosis, and these conditions can negatively impact treatment tolerance and survival. PNI has been shown to predict postoperative complications, disease recurrence, and overall survival in HCC patients undergoing oncological treatment, liver resection or liver transplantation [14, 30].

As such, it is a valuable tool for preoperative risk assessment and postoperative management [31].

In our study, PNI did not perform well in predicting OS, but this might be because of the very low number of the subjects in the group higher than 45 (4.5%).

The ALBI grade is a relatively novel marker that provides an objective assessment of liver function by combining serum albumin and bilirubin levels. Unlike traditional liver function scores such as the Child-Pugh classification, ALBI is entirely laboratory-based and avoids subjective criteria. In regards to our data, ALBI performed excellently in predicting OS, in univariate and multivariate analysis as well. Results of many other studies have proven that ALBI is an effective predictor of prognosis in HCC, particularly in patients undergoing resection or transarterial therapies [32]. Studies have shown that patients with lower ALBI grades have better survival outcomes, highlighting the importance of preserving liver function in the management of HCC [33].

Aspartate aminotransferase and ALT levels are commonly used liver function markers and have significant prognostic value in hepatocellular carcinoma (HCC) patients. Elevated levels of these enzymes often indicate liver inflammation or damage, and their ratios or absolute levels can correlate with tumor progression, liver function, and overall prognosis. Higher AST levels have been independently associated with worse OS and recurrence-free survival in patients undergoing surgical resection or liver transplantation for HCC [34].

Alanine aminotransferase levels correlate with the degree of liver fibrosis or cirrhosis, and patients with elevated AST are more likely to have advanced liver disease, which limits treatment options and increases the risk of complications. While ALT is more specific to liver cells, it is typically used to assess hepatocellular damage. Elevated ALT often signals acute or chronic liver damage, but isolated ALT levels are not always a strong prognostic indicator of survival outcomes in HCC

compared to AST. However, in combination with AST and other biomarkers, ALT can be useful for assessing liver function and treatment response. For instance, the AST/ALT ratio, also known as the De Ritis ratio, has been shown to be a significant predictor of outcomes in HCC patients. An elevated AST/ALT ratio ( $\geq 1$ ) has been associated with poorer survival outcomes in patients undergoing surgery, liver transplantation, or other therapies. This is because a higher ratio often reflects advanced liver fibrosis or cirrhosis, which is a negative prognostic factor in HCC [35-37].

While each of these markers - NLR, PLR, SII, ALBI and AST/ALT - offers valuable prognostic information in HCC, their utility may vary depending on the clinical context. NLR, PLR, and SII are more reflective of the systemic inflammatory response and immune status, while PNI and ALBI provide insights into the nutritional and hepatic function of patients. In clinical practice, combining these scores could offer a more comprehensive understanding of patient prognosis, guiding treatment decisions and tailoring therapeutic approaches. For instance, patients with high NLR or SII may benefit from early initiation of systemic therapies or inclusion in clinical trials for novel immunotherapies. On the other hand, low PNI and high ALBI grades may prompt more aggressive nutritional support or earlier consideration of liver transplantation.

Despite their prognostic value, these inflammation scores have certain limitations. They are influenced by a variety of factors, including infections, comorbidities, and liver function, which may confound their interpretation in certain clinical scenarios. Moreover, most studies on these markers are retrospective, and prospective validation in larger, multicentric cohorts is needed to establish standardized cut-offs and further elucidate their role in clinical decision-making. In this regard, our study included a data from a national data base coming for five tertiary centers, revealing the patients' profiles from our geographical area. To our knowledge, the data from this study concerning inflammatory markers related to HCC from our geographical area represents the first of its kind, with a notably long follow-up period, marking a significant contribution to the understanding of HCC in this region. While our study provides the first valuable dataset on HCC disease and patient profiles at diagnosis and their prognostics, we recognize its significant limitations. The most prominent limitation is the absence of data on therapeutic choices, though this was beyond the original scope of the project, and on the other hand, there is a bias in HCC diagnosis and follow up coming from inherent registry-based designs with data gathered from multiple centers.

Future research should also focus on exploring the potential of these scores in predicting responses to emerging treatments, such as immune checkpoint inhibitors, and incorporating them into predictive models that account for the heterogeneity of HCC. By integrating inflammation scores with molecular and genetic markers, we may develop more personalized treatment strategies that improve outcomes for patients with HCC.

## CONCLUSION

Inflammation-based scores, including NLR, PLR, SII, PNI, and ALBI, provide important prognostic insights in patients

with HCC. Their ability to predict survival outcomes, response to treatment, and complications makes them valuable tools in both clinical practice and research. Incorporating these markers into routine assessment and combining them with emerging biomarkers could enhance personalized care and optimize therapeutic outcomes in HCC.

**Conflicts of interest:** None to declare.

**Authors' contributions:** D.C., B.P., H.S. and M.G. conceived and designed the study. L.G., I.S., L.D.S, A.T., Z.S., M.D., I.R., R.C., C.C., R.S., C.M.U., C.B., L.M., N.A. collected data. D.C., M.R. and T.C. performed the statistical analysis and analyzed the data. D.C., R.C., B.P. and M.G. drafted the manuscript. All authors critically revised the manuscript, approved the final version to be published, and agreed to be accountable for all aspects of the work.

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