CANCER DIAGNOSIS & PROGNOSIS *6*: 383-392 (2026)
doi: 10.21873/cdp.10537

The Prognostic Role of Inflammation on Hepatocellular Carcinoma

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Abstract

Background/Aim: Advanced hepatocellular carcinoma has dismal prognosis. The choice of optimal therapy for each patient is not characterized well. There is a growing need to describe the relation of predictive and prognostic factors with survival. In this study, we aimed to examine the impact of clinical factors and inflammatory markers on the prognosis.

Patients and Methods: A total of 125 patients who were diagnosed between January 2011-April 2018 were enrolled retrospectively. Patients' demographics, performance status, tumoral characteristics and inflammation-based prognostic scores (neutrophil/lymphocyte ratio (NLR), prognostic nutritional index (PNI), aspartate aminotransferase/platelet count ratio (APRI)) were recorded. Univariate and multivariate analyses were performed to determine the prognostic factors for survival.

Results: Median age of patients was 64 (range=22-85) with male dominancy (*n*=105; 84%). Etiology was hepatitis B virus in 74 patients, and hepatitis C virus in 9 cases. Median overall survival (mOS) of the overall study population was 11.9 months (95% CI=7.1-16.9). Local treatment options yielded a median OS of 24.8 months (95% CI=12.8-36.8) in intermediate BCLC stage B patients. Patients who received sorafenib had an OS of 19.7 (95% CI=11.2-28.2 months). Initial ECOG performance status, Child Pugh Score, tumor size, presence of portal vein thrombosis was found to be significantly associated with worse OS in univariate analyses.

continued

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Received December 22, 2025 | Revised February 1, 2026 | Accepted February 4, 2026

Conclusion: Inflammation based scores, NLR and APRI were found to be associated with worse mOS. Larger tumor size, older age and ECOG PS were found to be independent prognostic factors.

Keywords: Inflammation, prognosis, aspartate aminotransferase, platelet count ratio index, neutrophil lymphocyte ratio, albumin.

Introduction

Hepatocellular carcinoma (HCC) is the third leading cause of cancer-associated mortality (1). HCC has a rapidly progressive course and unfavorable prognosis. Treatment options include locally ablative therapies, surgical resection, liver transplantation and systemic treatments, depending on the stage of the disease. Recurrence rate is high despite the curative therapies.

Systemic inflammatory reactions have been shown to impact the outcome in various malignancies (2, 3). In case of chronic inflammatory disease existing in hepatic parenchyma, inflammation and increased hepatic turnover may result in chronic hepatic injury, dysplasia and fibrosis. Due to the upregulation of cytokines and inflammatory mediators, DNA damage, angiogenesis, and inhibition of apoptosis may lead to malignant transformation and/or progression of HCC (4, 5).

Patient associated factors such as age, ECOG performance score (PS), comorbid diseases, extent and clinical reflections of chronic liver disease at the time of diagnosis as well as disease associated factors (stage, Barcelona Clinic Liver Classification-BCLC, vascular invasion status, multicentricity) were related to prognosis in previous studies (6, 7). Inflammatory markers measured before and after treatment have been studied to detect high risk patients for disease recurrence, *i.e.,* platelet/lymphocyte ratio, neutrophil/lymphocyte ratio (NLR), neutrophil/monocyte ratio, and aspartate aminotransferase (AST)/platelet count ratio (APRI score), are tests for determining prognosis. APRI score was found to be associated with poor prognosis. However, independent prognostic influence of inflammation on prognosis of HCC is an area of growing interest. The aim of the present study was to investigate the effect of inflammatory markers on prognosis and its relations to patient associated and disease associated prognostics.

Patients and Methods

The study included patients diagnosed with HCC histopathologically *via* biopsy, or by two radiologists using MRI imaging. Data from January 2011 to April 2018 were analyzed retrospectively. The study included Barcelona stage A, B, C, and D patients aged 18 and over who were unsuitable for local ablative treatments. Patients who had undergone transplantation were excluded. Laboratory and imaging test results were obtained individually from our clinic's electronic record system. Patient characteristics (age, sex, ECOG PS, etiology of disease, use of antiviral therapies, Child Pugh Score-CPS at diagnosis) and disease characteristics (tumor size, multicentricity, portal vein thrombosis) were recorded. Primary treatment modalities, surgery, transplantation or usage of local ablative techniques were also recorded. The etiology of HCC was classified according to molecular types as proliferative group associated with hepatitis B virus and non-proliferative group associated with hepatitis C virus and alcohol use.

Inflammation based prognostic scores were studied. NLR, prognostic nutritional index (PNI) and APRI score were the main analyzed measures for prognosis. The formulas for NLR, PNI and APRI scores are described herein. NLR: Neutrophil count/lymphocyte count; PNI: 10× serum albumin (g/dl) + 0.005× total lymphocyte count per mm^3; APRI: (AST/upper limit normal)/ platelet count ($\times 10^9$/l) ×100. Hepatic transferase levels at diagnosis were recorded and upper limit of normal for AST and ALT was accepted as 50 IU/l according to local laboratory calibration.

The date of diagnosis was accepted as the index date and all calculations were made accordingly. The progression free survival (PFS) was calculated as the duration from the index date until the event of first progression or death. Disease monitoring was performed radiologically with imaging every 3 months. Imaging was performed following an increase in AFP levels. Based on the imaging results, patients with progression in target lesions and the development of new lesions according to the RECIST criteria were considered to have progressive disease. The median overall survival (mOS) was defined as the duration between the index date and the time of exitus or lost to follow-up. Inflammation related markers and scores as well as disease and tumor related factors were analyzed in regard to relation with OS and PFS.

The study was approved by the committee of University of Health Sciences, Ankara Oncology Education and Research Hospital (TUEK meeting number: 57-04.12.2018). The principles outlined in the Declaration of Helsinki were followed. Given the retrospective nature of the study, written informed consent was not mandatory according to local regulations.

Statistical analysis. This study was designed as a single center retrospective cohort study. Data was analyzed using the IBM Statistical Package for Social Sciences (SPSS) v.21 (IBM Inc., Armonk, NY, USA). Safety margin was accepted as 95% throughout the study. Receiver operative characteristic (1) analysis depending on mOS was used to determine the cut-off values of prognostic scores. ROC analysis was constructed based on the 12-month OS (alive *vs.* deceased). Time-dependent ROC analysis was not performed due to retrospective design. Kaplan-Meier method was employed for survival analysis, log-rank test for comparison in subgroups, and cox-regression model for multivariate analysis.

Results

A total of 125 HCC patients were included. The median age of the patients was 64 years (range=22-85), and 84% of them were males. Most of the patients were diagnosed with HCC in the presence of chronic HBV infection (74 cases, 59.2%). ECOG PS was 1 in 60% of study population. At least one comorbid condition was identified in 95 patients, with diabetes mellitus being the most prevalent. Patient characteristics and the choices of treatment are outlined in Table I.

Table I. *Patient characteristics (n=125).*

Characteristic	
Age, mean (2), year	64 (22-85)
Male/female ratio	5.2/1
	No. (%)
Stage at diagnosis	
Locally advanced	87 (69.6)
Metastatic	38 (30.4)
Histopathologic diagnosis	79 (63.2)
Wash-out sign in MRI	66 (52.8)
Etiopathology	
HBV	74 (59.2)
HCV	9 (7.2)
NASH	14 (11.2)
Alcohol induced	8 (6.4)
Cryptogenic	20 (16)
ECOG Performance Status at diagnosis	
ECOG 0-1	75 (60.5)
ECOG 2	34 (27.4)
ECOG 3	15 (12.1)
Child Score at diagnosis	
Child A	84 (67.2)
Child B	25 (20)
Child C	16 (12.8)
Metastatic sites	
Lung	8 (6.4)
Peritoneal and abdominal LN	17 (13.6)
Suprarenal gland	4 (3.2)
Skeletal	11 (8.8)

MRI: Magnetic resonance imaging; HBV: Hepatitis B Virus; HCV: Hepatitis C Virus; NASH: non-alcoholic steatohepatitis; ECOG: Eastern Cooperative Oncology Group; LN: lymph node.

Surgery was the main treatment in 12 cases (9.6%). Forty-four patients received local treatment [transarterial chemotherapy (TACE) or transarterial radioembolization (TARE) or radiofrequency ablation (RF)]. Seventeen patients received sorafenib. Metastatic disease was detected in 38 cases (30.4%); distribution was as follows: intraabdominal lymph nodes (31.5%), lung metastasis

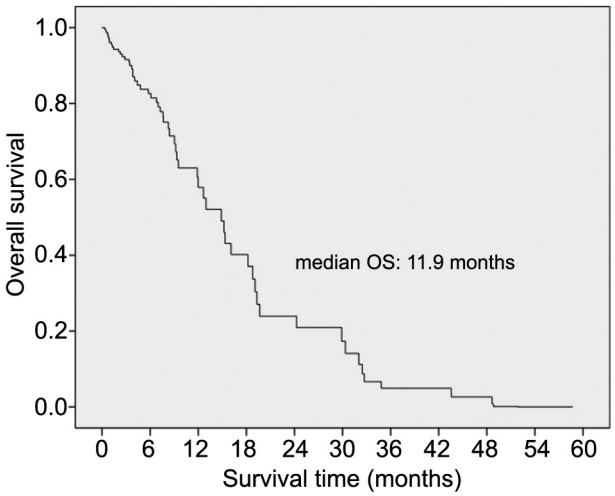
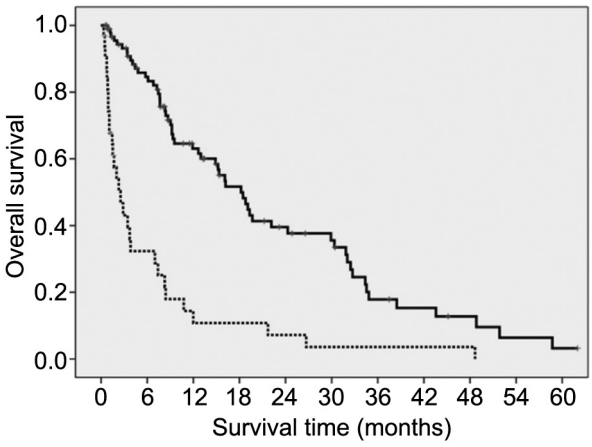


Figure 1. *Kaplan Meier curve for overall survival (OS).*



	Median OS (months)	95% Confidence interval
BSC	2.5	1-4
Any treatment option	18.2	13.9-22.4

Figure 2. *Comparison of overall survival (OS) according to treatment eligibility.*

(21), and bone metastasis (15.7%). Forty-seven patients were treated with sorafenib. Of the sorafenib received cases, 13 were treated without preceding local ablative treatment approaches. Best supportive care (BSC) was the most suitable option for 32 cases (25.6%). After failure of first line treatments, further options (n=30) were as follows: sorafenib (n=26), capecitabine (n=1) and systemic adriamycin (n=3).

Median OS of the study population was 11.9 months (95% CI=7.1-16.9, Figure 1). At the time of data analysis, 87 cases had died (69.6%). One-year, 2- and 3-year OS rates were 48.4%, 29.8% and 14.2% respectively. Local treatment options yielded a median OS of 24.8 months (95% CI=12.8-36.8) in intermediate BCLC stage B patients. Patients who were suitable for at least one type of treatment modality had better OS compared to patients who followed with BSC (18.2 *vs.* 2.5 months, p<0.0001, Figure 2). Patients who received sorafenib had an OS of 19.7 (95% CI=11.2-28.2 months). In the group of patients to whom local ablative techniques were applied, median OS was 31.8 months (95% CI=20.7-42.9). On the other hand, a statistically significant difference was found for cases who were treated with sorafenib alone (mPFS=9.5 months, 95% CI=3.2-15.8). Of note, this comparison should be interpreted cautiously due to potential immortal-time bias and baseline differences, as patients receiving BSC had poorer performance status and liver function.

Median PFS of patients treated with sorafenib was 6.4 months (95% CI=3-8.5). In patients who were treated with local ablative approaches, sorafenib achieved a mPFS of 6.4 months (95% Cl=2-10.8). On the contrary, patients who did not receive any local treatment before sorafenib had a mPFS of 5.8 months (95% Cl=2.4-9.4).

ROC analysis was used to define the cut-off values of APRI-PNI and NLR indices; 0.63 for APRI, 44.27 for PNI and 2.6 for NLR were determined. Subsequently, univariate analysis for the survival of patients was performed, based on these predefined subgroups. Patients with lower APRI scores have higher statistically significant survival rates compared to higher scores. On the other hand, there was a positive trend for patients with higher PNI and lower NLR scores which did not reach a statistically significant level (Figure 3A-C).

A weak correlation was found between Child Pugh score and NLR (r=0.27, p=0.002). A moderate correlation was found between Child Pugh score and PNI (r=0.4, p=0.00),

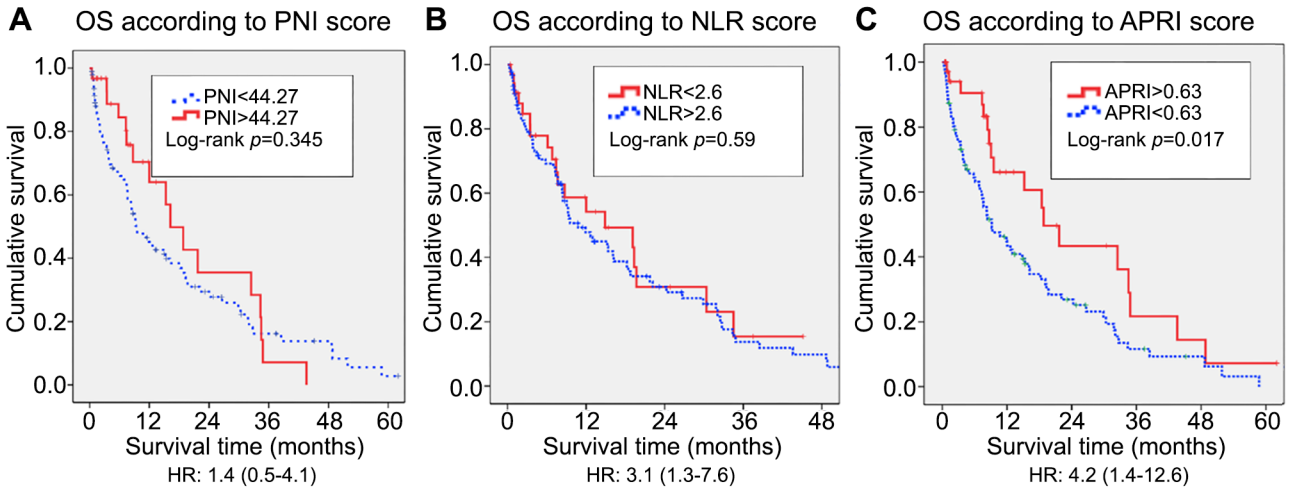


Figure 3. *Overall survival according to PNI, NLR, and APRI score. PNI: Prognostic nutritional index; NLR: neutrophil-lymphocyte ratio; APRI: aspartate aminotransferase platelet count index.*

while a weak correlation was identified between Child Pugh score and APRI (r=0.29, p=0.001). However, when adjusted for multivariate analysis, APRI was an independent factor.

In univariate analysis, initial ECOG PS, Child Pugh Score, tumor size, multicentricity, and portal vein thrombosis was found to be significantly associated with OS. Initial tumor size (>5 cm), older age (>65 years), ECOG PS 2-3, applicability of local treatment options, lower NLR scores and higher APRI index were found to be statistically significant independent prognostic factors for OS in multivariate analysis (Table II).

Discussion

Inflammation is the key factor in the tumorigenesis and progression of HCC. In this study, we showed that systemic inflammatory indices (APRI, PNI and NLR) were related with prognosis. In this patient cohort, patients with lower APRI scores have higher statistically significant OS rates compared to higher scores. In the present study, NLR did not reach statistical significance in univariate analysis or Kaplan–Meier comparison. However, after adjustment for key clinical and tumor-related variables in the multivariate Cox regression model, NLR emerged as an independent prognostic factor for mOS. This finding indicates that the prognostic effect of NLR may be masked by confounding factors such as performance status, tumor burden, and treatment modality in unadjusted analyses, and becomes evident only after multivariable adjustment.

In previous studies, antiviral therapy has been shown to possibly contribute to the liver healing process, sustaining liver function and reserve, and improve prognosis in HCC (8). Kuang *et al.* supported this hypothesis *via* demonstrating increased neutrophils in the peritumoral stroma (9). Besides that, in the previous trials, increased NLR was associated with worse prognosis in patients who had undergone TACE, RFA, transplantation and surgical resection (10-13).

This study has important and different details and end points. Our patient cohort was heterogeneous, with a variety of treatment modalities applied. In addition, the APRI score which had been previously studied in the staging of liver fibrosis and NLR index was analyzed within the same population. Median OS of the study population was 11.9 months; 1-, 2- and 3-year OS rates were 48.4%, 29.8% and 14.2%, respectively. Local treatment options yielded a median OS of 24.8 months (95% CI=12.8-36.8) in intermediate stage HCC. Patients who were suitable for at least one type of treatment modality had better OS compared to patients who followed with BSC.

Table II. *Independent prognostic factors of overall survival.*

Characteristic	Value (n/%)	Univariate analyses		Multivariate analyses	
		Survival (mo.)	*p*-Value	HR (95% CI)	*p*-Value
Age, y					
<65 y	45 (36)	9.2	0.065		
>65 y	80 (64)	16.1		0.4 (0.2-0.8)	**0.008**
ECOG Performance Status					
ECOG 0-1	76 (60.8)	18.8	**0.0001**		
ECOG 2-3	49 (39.2)	6.9		3.2 (1.4-6.9)	**0.004**
Child Pugh Score at diagnosis					
Child A	80 (67.7)	16.1	**0.002**		
Child B	22 (18.6)	7		0.7 (0.3-1.9)	0.52
Child C	16 (13.5)	2.5		0.5 (0.1-1.8)	
Tumor size (Initial status)					
<5 cm	45 (36)	22.1	**0.0001**		
>5 cm	80 (64)	8.4		3.2 (1.5-6.8)	**0.003**
Portal vein thrombosis					
Absent	80 (65)	18.5	**0.0001**	Ref.	
Present	43 (34.4)	5.8		0.8 (0.4-1.8)	0.5
Primary modality of treatment					
Local treatment options (TACE/TARE/RFA)	44 (35.2)	29.9	**0.0001**		
Sorafenib	17 (13.6)	7.7		3.8 (1.1-13.8)	**0.01**
BSC	42 (33.6)	2.9		4.4 (1.3-15)	
Systemic Adriamycin	10 (8)	18.8		1.6 (0.4-6.3)	
Surgery	12 (9.6)	19.7		1.3 (0.4-4.5)	
NLR					
≤2.6	35 (28)	14.9	0.59		
>2.6	90 (72)	10.7		3.1 (1.3-7.6)	**0.01**
PNI					
>44.27	31 (24.8)	16.2	0.35		
≤44.27	94 (75.2)	9.3		1.4 (0.5-4.1)	0.54
APRI			**0.01**		
<0.63	38 (30.4)	18.8			
>0.63	87 (69.6)	9.2		4.2 (1.4-12.6)	**0.01**

Not all case data are available. HBV: Hepatitis B Virus; HCV: Hepatitis C Virus; ECOG: Eastern Cooperative Oncology Group; TACE: transarterial chemoembolization; TARE: transarterial radioembolization; RFA: radiofrequency ablation; NLR: neutrophil-lymphocyte ratio; PNI: prognostic nutritional index; APRI: aspartate aminotransferase platelet count index. Statistically significant *p*-values are shown in bold.

In this study, the cut-off value was determined by ROC analysis and the values of 2.6, 0.63 and 44.27 were found for NLR, APRI and PNI, respectively. For these indices, a constant cut-off value cannot be assigned due to different reference values in different centers and different study populations. Tumor size, multiplicity, invasion status and grade of HCC were found to be associated with increased NLR (15).

NLR is a biochemical marker that shows inflammation and is thought to have a potential role in cancer progression (16). Increased NLR in many solid tumors has been found to be a negative prognostic factor for survival. NLR was found to be associated with HCC recurrence and overall poor long-term survival (17). Increased NLR level has also been associated with an aggressive tumor phenotype. A meta-analysis of 20,475 patients and a systematic review showed that overall HCC patients with lower baseline NLR had better survival (HR=1.80; 95% CI=1.59–2.04; $p<0.00001$) and recurrence-free or disease-free survival (HR=2.23; 95% CI=1.80–2.76; $p<0.00001$) (18). Increased infiltration of tumor-associated macrophages by the formation of immune

microenvironment and cytokine release causes tumor vascular invasion; the host immunity is suppressed, and this leads to tumor progression. Additionally, preoperative NLR was found to be associated with worse survival, and this negative association was not found to be associated with treatment modalities (19). In our study, patients with lower NLR had better survival compared to those with higher NLR (14.9 *vs.* 10.7 months, p=0.01). The mechanism of this association is not well understood. Increased NLR may lead to relatively low levels of lymphocytes and decreased immunity against tumoral tissue (20). In recent years, in order to avoid an invasive biopsy approach, APRI index was proposed to assess the hepatic reserve and prognosis in chronic liver diseases (21, 22).

Advanced stage liver injury is associated with mitochondrial injury and increased AST levels. In liver fibrosis and cirrhosis, the clearance of AST also decreases, which further elevates the plasma levels of AST and APRI scores. Hung *et al.* demonstrated the degree of hepatic fibrosis and recurrence of HCC (23). In this patient cohort, 30.4% of patients with the lowest APRI score had a median OS of 18.8 months, whereas patients with higher APRI scores (69.6%) had 9.2 months (p=0.01). Shen *et al.* demonstrated the negative prognostic relation between the preoperative APRI score and HCC (24). Similarly, in surgically resected HCC cases and for patients treated with RFA, APRI was found to be prognostic (24). In relation to the etiopathogenetic mechanism of HCC, in patients with NASH and HBV, APRI was shown to be beneficial for HCC risk (25). Ballester MP *et al.* evaluated the real-world efficacy and safety of atezolizumab plus bevacizumab over a two-year period in patients with HCC and demonstrated that the ALBI score is an important tool for detecting changes in liver function and guiding treatment selection (26). Inflammatory markers can provide prognostic information in patients receiving local therapies. In this context, Hashimoto *et al.* demonstrated that the HALP score, incorporating hemoglobin, albumin, lymphocyte, and platelet counts, serves as a simple and inexpensive predictor of prognosis after hepatectomy in hepatocellular carcinoma (27).

Combination therapies incorporating immune checkpoint inhibitors have become the standard of care for advanced hepatocellular carcinoma (HCC). In this context, inflammatory markers are considered important for predicting both treatment efficacy and immune-related adverse events. Ishikawa *et al.* demonstrated that continued treatment with durvalumab and tremelimumab may be effective in patients with HCC who show improvement in NLR following locoregional therapy (28).

In addition, Kuwano *et al.* demonstrated that a NLR <2.04 at three weeks after treatment initiation may serve as an important biomarker for predicting immune-related adverse events in patients with HCC treated with atezolizumab plus bevacizumab (29).

PNI which is related to the lymphocyte count and serum albumin levels, is a marker related to the systemic inflammatory response. In a meta-analysis, Wang *et al.* demonstrated a negative association between the low PNI and survival rates (30). Low PNI may be the result of hypoalbuminemia and lymphopenia. In HCC, in the cirrhotic hepatic parenchyma, synthetic functions of the liver diminish and serum albumin concentration decreases. Both the decrease in albumin levels and lymphopenia are associated with a worse prognosis due to malfunction of the immune system (31). Alternatively, serum albumin concentration may decrease due to malnutrition, or as a negative serum inflammation marker which is commonly observed in extensive stage malignancies, especially in HCC. In parallel to these hypotheses, our results also demonstrated that lower PNI levels had a negative trend for prognosis (9.3 *vs.* 16.2 months, p=0.35). Although our results were clinically relevant, the lack of statistical significance may be related to the heterogenous patient population (various stages of disease), diverse treatment approaches and small sample size. Patients with Child–Pugh class A liver function are preferentially evaluated in clinical studies because they are candidates for systemic therapy. However, in Child–Pugh class B patients, HCC prognosis is strongly influenced by hepatic reserve, highlighting the need for further research to establish optimal therapeutic approaches (32).

Study limitations. The retrospective design may introduce data collection bias, while potential confounding from inflammatory or infectious conditions and the absence of prospective evaluation limit a deeper understanding of the relationship between inflammation and HCC prognosis. The single-center patient cohort limited the size of the study population. On the other hand, 4 different scoring systems were analyzed in parallel with each other in the same patient cohort, which helped to eliminate biases and may give an answer to the clinical implication of inflammation in the molecular level.

Conclusion

In conclusion, with different etiologies related to hepatic injury, inflammation-based indices like APRI score, NLR and PNI may have a role in clinical follow-up, in treatment selection and determining prognosis. The results of our study provide important information contributing to understanding the predictive and prognostic factors of HCC. Further studies with prospective design, including serum inflammatory biomarker tests, are needed to prove the role of inflammation in HCC.

Availability of Data and Materials

The first author and the corresponding author have full access to the database regarding the patient population of this manuscript. The authors are willing to share the data if needed.

Conflicts of Interest

The Authors declare no conflicts of interest.

Authors' Contributions

Irem Bilgetekin, Ece Esin and Umut Demirci contributed to the conception and design of the study. Irem Bilgetekin, Ece Esin, Ilknur Deliktas Onur, Guliz Ozgun, Necla Demir, Ayse Ocak Duran, and Berna Oksuzoglu were involved in data collection. Irem Bilgetekin, Umut Demirci, and Ece Esin performed data analysis and interpretation. Irem Bilgetekin drafted the manuscript. Ece Esin did the statistical analysis. Hasan Çagri Yildirim worked to edit. All Authors critically revised the manuscript for important intellectual content, approved the final version.

Artificial Intelligence (AI) Disclosure

No artificial intelligence (AI) tools, including large language models or machine learning software, were used in the preparation, analysis, or presentation of this manuscript.

References

1 El-Serag HB: Hepatocellular carcinoma. N Engl J Med 365(12): 1118-1127, 2011. DOI: 10.1056/NEJMra1001683
2 Cammà C, Cabibbo G: Prognostic scores for hepatocellular carcinoma: none is the winner. Liver Int 29(4): 478-480, 2009. DOI: 10.1111/j.1478-3231.2009.01994.x
3 Edge SB, Byrd DR, Compton CC: AJCC cancer staging manual. AJCC Cancer Staging Manual 7th ed. New York, NY, USA, Springer, 2010.
4 Balkwill F, Mantovani A: Inflammation and cancer: back to Virchow? Lancet 357(9255): 539-545, 2001. DOI: 10.1016/S0140-6736(00)04046-0
5 Jackson JR, Seed MP, Kircher CH, Willoughby DA, Winkler JD: The codependence of angiogenesis and chronic inflammation. FASEB J 11(6): 457-465, 1997.
6 Mazzaferro V, Regalia E, Doci R, Andreola S, Pulvirenti A, Bozzetti F, Montalto F, Ammatuna M, Morabito A, Gennari L: Liver transplantation for the treatment of small hepatocellular carcinomas in patients with cirrhosis. N Engl J Med 334(11): 693-700, 1996. DOI: 10.1056/NEJM199603143341104
7 Yao FY, Ferrell L, Bass NM, Watson JJ, Bacchetti P, Venook A, Ascher NL, Roberts JP: Liver transplantation for hepatocellular carcinoma: expansion of the tumor size limits does not adversely impact survival. Hepatology 33(6): 1394-1403, 2001. DOI: 10.1053/jhep.2001.24563
8 Breitenstein S, Dimitroulis D, Petrowsky H, Puhan MA, Müllhaupt B, Clavien PA: Systematic review and meta-analysis of interferon after curative treatment of hepatocellular carcinoma in patients with viral hepatitis. Br J Surg 96(9): 975-981, 2009. DOI: 10.1002/bjs.6731
9 Kuang DM, Zhao Q, Wu Y, Peng C, Wang J, Xu Z, Yin XY, Zheng L: Peritumoral neutrophils link inflammatory response to disease progression by fostering angiogenesis in

hepatocellular carcinoma. J Hepatol 54(5): 948-955, 2011. DOI: 10.1016/j.jhep.2010.08.041
10 Huang ZL, Luo J, Chen MS, Li JQ, Shi M: Blood neutrophil-to-lymphocyte ratio predicts survival in patients with unresectable hepatocellular carcinoma undergoing transarterial chemoembolization. J Vasc Interv Radiol 22(5): 702-709, 2011. DOI: 10.1016/j.jvir.2010.12.041
11 Chen TM, Lin CC, Huang PT, Wen CF: Neutrophil-to-lymphocyte ratio associated with mortality in early hepatocellular carcinoma patients after radiofrequency ablation. J Gastroenterol Hepatol 27(3): 553–561, 2012. DOI: 10.1111/j.1440-1746.2011.06910.x
12 Halazun KJ, Hardy MA, Rana AA, Woodland DC 4th, Luyten EJ, Mahadev S, Witkowski P, Siegel AB, Brown RS Jr, Emond JC: Negative impact of neutrophil-lymphocyte ratio on outcome after liver transplantation for hepatocellular carcinoma. Ann Surg 250(1): 141-151, 2009. DOI: 10.1097/SLA.0b013e3181a77e59
13 Gomez D, Farid S, Malik HZ, Young AL, Toogood GJ, Lodge JP, Prasad KR: Preoperative neutrophil-to-lymphocyte ratio as a prognostic predictor after curative resection for hepatocellular carcinoma. World J Surg 32(8): 1757-1762, 2008. DOI: 10.1007/s00268-008-9552-6
14 Rimassa L, Santoro A: Sorafenib therapy in advanced hepatocellular carcinoma: the SHARP trial. Expert Rev Anticancer Ther 9(6): 739-745, 2009. DOI: 10.1586/era.09.41
15 Peng W, Li C, Wen TF, Yan LN, Li B, Wang WT, Yang JY, Xu MQ: Neutrophil to lymphocyte ratio changes predict small hepatocellular carcinoma survival. J Surg Res 192(2): 402-408, 2014. DOI: 10.1016/j.jss.2014.06.039
16 Aggarwal BB, Vijayalekshmi R, Sung B: Targeting inflammatory pathways for prevention and therapy of cancer: short-term friend, long-term foe. Clin Cancer Res 15(2): 425-430, 2009. DOI: 10.1158/1078-0432.CCR-08-0149
17 Bruix J, Sherman M, Practice Guidelines Committee, American Association for the Study of Liver Diseases: Management of hepatocellular carcinoma. Hepatology 42(5): 1208-1236, 2005. DOI: 10.1002/hep.20933
18 Qi X, Li J, Deng H, Li H, Su C, Guo X: Neutrophil-to-lymphocyte ratio for the prognostic assessment of hepatocellular carcinoma: A systematic review and meta-analysis of observational studies. Oncotarget 7(29): 45283-45301, 2016. DOI: 10.18632/oncotarget.9942
19 Yin L, Li H, Li AJ, Lau WY, Pan ZY, Lai EC, Wu MC, Zhou WP: Partial hepatectomy *vs.* transcatheter arterial chemoembolization for resectable multiple hepatocellular carcinoma beyond Milan criteria: A RCT. J Hepatol 61(1): 82-88, 2014. DOI: 10.1016/j.jhep.2014.03.012
20 Poon RT, Fan ST, Lo CM, Ng IO, Liu CL, Lam CM, Wong J: Improving survival results after resection of hepatocellular carcinoma: a prospective study of 377 patients over 10 years. Ann Surg 234(1): 63-70, 2001. DOI: 10.1097/00000658-200107000-00010
21 Boursier J, Brochard C, Bertrais S, Michalak S, Gallois Y, Fouchard-hubert I, Oberti F, Rousselet M, Calès P: Combination of blood tests for significant fibrosis and cirrhosis improves the assessment of liver-prognosis in chronic hepatitis C. Aliment Pharmacol Ther 40(2): 178-188, 2014. DOI: 10.1111/apt.12813
22 Lin ZH, Xin YN, Dong QJ, Wang Q, Jiang XJ, Zhan SH, Sun Y, Xuan SY: Performance of the aspartate aminotransferase-to-platelet ratio index for the staging of hepatitis C-related fibrosis: an updated meta-analysis. Hepatology 53(2): 726-736, 2011. DOI: 10.1002/hep.24105
23 Hung HH, Su CW, Lai CR, Chau GY, Chan CC, Huang YH, Huo TI, Lee PC, Kao WY, Lee SD, Wu JC: Fibrosis and AST to platelet ratio index predict post-operative prognosis for solitary small hepatitis B-related hepatocellular carcinoma. Hepatol Int 4(4): 691-699, 2010. DOI: 10.1007/s12072-010-9213-3
24 Shen S, Fu S, Chen B, Kuang M, Li S, Hua Y, Liang L, Guo P, Hao Y, Peng B: Preoperative aspartate aminotransferase to platelet ratio is an independent prognostic factor for hepatitis B-induced hepatocellular carcinoma after hepatic resection. Ann Surg Oncol 21(12): 3802-3809, 2014. DOI: 10.1245/s10434-014-3771-x
25 Kawamura Y, Arase Y, Ikeda K, Seko Y, Imai N, Hosaka T, Kobayashi M, Saitoh S, Sezaki H, Akuta N, Suzuki F, Suzuki Y, Ohmoto Y, Amakawa K, Tsuji H, Kumada H: Large-scale long-term follow-up study of Japanese patients with non-alcoholic Fatty liver disease for the onset of hepatocellular carcinoma. Am J Gastroenterol 107(2): 253-261, 2012. DOI: 10.1038/ajg.2011.327
26 Ballester MP, Abril C, Merino V, Alós M, Segarra G, Tosca J, Montón C, Casasus N, Lluch P: Atezolizumab plus bevacizumab treatment for unresectable hepatocellular carcinoma: real-life experience from a single tertiary centre in Spain and ALBI score as a survival prognostic factor. Cancer Diagn Progn 4(5): 623-630, 2024. DOI: 10.21873/cdp.10373
27 Hashimoto K, Kanno H, Sakai H, Miyazaki D, Fukutomi S, Arai S, Goto Y, Akashi M, Isobe T, Mori N, Ishibashi N, Fujita F, Hisaka T: Hemoglobin, albumin, lymphocyte, and platelet (HALP) score as a predictor of prognosis after hepatectomy. Anticancer Res 44(8): 3669-3678, 2024. DOI: 10.21873/anticanres.17191
28 Ishikawa T, Sato R, Natsui H, Iwasawa T, Ogawa M, Kobayashi Y, Sato T, Yokoyama J, Honma T: Efficacy of durvalumab-tremelimumab treatment in combination with locoregional therapy in unresectable hepatocellular carcinoma: a preliminary study. Cancer Diagn Progn 5(5): 591-596, 2025. DOI: 10.21873/cdp.10473
29 Kuwano A, Yada M, Tanaka K, Koga Y, Nagasawa S, Masumoto A, Motomura K: Neutrophil-to-lymphocyte ratio predicts immune-related adverse events in patients with hepatocellular carcinoma treated with atezolizumab plus bevacizumab. Cancer Diagn Progn 4(1): 34-41, 2024. DOI: 10.21873/cdp.10282

30 Wang Z, Wang J, Wang P: The prognostic value of prognostic nutritional index in hepatocellular carcinoma patients: A meta-analysis of observational studies. PLoS One 13(10): e0202987, 2018. DOI: 10.1371/journal.pone.0202987
31 Wada Y, Nakashima O, Kutami R, Yamamoto O, Kojiro M: Clinicopathological study on hepatocellular carcinoma with lymphocytic infiltration. Hepatology 27(2): 407-414, 1998. DOI: 10.1002/hep.510270214
32 Kuwano A, Yada M, Tanaka K, Koga Y, Nagasawa S, Masumoto A, Motomura K: Systemic chemotherapy for advanced hepatocellular carcinoma in patients with Child-Pugh class B. Cancer Diagn Progn 4(2): 111-116, 2024. DOI: 10.21873/cdp.10295