Zagazig University Medical Journal
www.zumj.journals.ekb.eg
https://dx.doi.org/10.21608/zumj.2022.141934.2577 Volume 29, Issue 2, March 2023, Page (650-663)
Manuscript ID ZUMJ-2205-2577 (R1)
DOI **10.21608/zumj.2022.141934.2577**

ORIGINAL ARTICLE

Impact of Prognostic Nutritional Index and Systemic Immune-Inflammation Index on the Clinical Outcome of Patients with Advanced Hepatocellular Carcinoma Treated with Sorafenib

Ahmad Barakat Waley [1*], Rasha Haggag [1], Amir Abd-elhameed Ahmed Barakat [2], Hanaa Ahmed Rashied [3], Ahmed Abdul-Saboor [4], Marwa Mohammed Esawy [4], Yasser Ali Orban [5], Adel Bakry [1]

1 Department of Medical Oncology, Faculty of Medicine, Zagazig University, 44519, Egypt

2 Department of Internal Medicine, Faculty of Medicine, Zagazig University, 44519, Egypt

3 Department of Clinical Oncology, El-Mabara Hospital, Zagazig, 44519, Egypt

4 Department of Clinical Pathology, Faculty of Medicine, Zagazig University, 44519, Egypt

5 Department of General Surgery, Faculty of Medicine, Zagazig University, 44519, Egypt

*** Corresponding author**:
Ahmad Barakat Waley
Medical Oncology Department, Faculty of Medicine, Zagazig University, 44519, Zagazig, Egypt.
E-mail address: abowaley@gmail.com

Submit Date 2022-06-05
Revise Date 2022-06-15
Accept Date 2022-06-20

ABSTRACT

Background: Hepatocellular carcinoma (HCC) is one of the most common cancers of the gastrointestinal tract worldwide. In Egypt, it is the leading cause of cancer-related mortality and morbidity. Sorafenib has been the treatment of choice for patients with advanced HCC since 2008. Currently, no specific biomarker has proven successful in predicting sorafenib efficacy. Inflammation is believed to be one of the drivers of cancer progression and metastasis development. The systemic immune inflammation index (SII) has been identified as a predictor for the outcome of cancer patients. Nutritional status appears to influence outcomes in various solid tumors. The Prognostic Nutritional Index (PNI) was introduced to assess the immune nutritional status of cancer patients. The aim of our study was to evaluate the prognostic and predictive value of SII and PNI in sorafenib-treated patients with advanced HCC

Method: This prospective, non-randomized study aimed to evaluate the prognostic value of SII and PNI in patients with advanced hepatocellular carcinoma (HCC) receiving sorafenib. One hundred and ten patients were included.

Results: The optimal cutoff values for PNI and SII using the Receiver Operating Characteristic (ROC) curve were 47.6 and 278, respectively. PNI and SII were significantly associated with disease control rate. Multivariate analyzes showed that low PNI and high SII were independent predictors of poor progression-free and overall survival.

Conclusions: There is cumulative evidence support ing the utility of pre-treatment PNI and SII as prognostic factors in sorafenib-treated HCC patients.

Keywords: Systemic inflammation index, prognostic nutritional index, hepatocellular carcinoma, sorafenib

INTRODUCTION

Hepatocellular carcinoma (HCC) is one of the most common malignant gastrointestinal tumors with a significant mortality and morbidity rate worldwide **[1].** It is the sixth and fourth most common cancer worldwide **[2]** and in Egypt **[3].**

Egyptian health authorities consider HCC to be a major health challenge. Several national hospital studies have shown an increasing incidence of HCC over the past two decades **[4].** This increased incidence could be attributed to the introduction of screening programs and improvement of diagnostic tools **[5],** as well as more successful HCV antiviral treatment leading to longer survival rates of cirrhotic patients and thus increasing the likelihood of progression to HCC [**4]** given the HCV infection is the most important risk factor for developing HCC in Egypt **[6].** Meanwhile, the treatment of HCC patients depends on the stage of the disease. Radiofrequency ablation, percutaneous ethanol injection, and liver resection are limited in early-stage localized disease. Targeted therapies and immunotherapy are currently the most accepted therapies for patients with advanced HCC **[7].** Sorafenib, an oral multikinase inhibitor, has been the treatment of choice for patients with advanced HCC since 2008 **[8].** Currently no specific biomarker has been proven to predict the efficacy of sorafenib **[9].** Multiple clinical and biochemical factors such Body Mass Index (BMI), as Child-Pugh Score (CPS), Aspartate Aminotransferase (AST), Albumin Bilirubin (ALBI) grade , alpha-fetoprotein (AFP), lactate dehydrogenase (LDH), Macroscopic Vascular Invasion (MVI) and Barcelona Clinic Liver Cancer (BCLC), were examined to predict the outcome of HCC patients treated with sorafenib **[10].** None of these factors have been shown to be predictive of outcome or have been approved for use in clinical decisions. **[11].** One of the enabling properties in carcinogenesis, the development of metastases, is inflammation. Chronic inflammation has been linked to increased risk of cancer; For example, HBV can lead to HCC, EBV has been implicated in nasopharyngeal carcinoma, and Helicobacter pylori has been associated with gastric lymphoma **[12].** As our knowledge of cancer-related inflammation has grown, biomarkers of systemic inflammatory responses, such as platelet-to-lymphocyte ratio, neutrophil-to-lymphocyte ratio, lymphocyte-to-monocyte ratio, and C-reactive protein **[13],** have been shown to predict the outcome of patients with various types of cancer, including those with renal cell carcinoma, colon and lung cancer **[14].** All of these biomarkers integrate only two inflammatory cells. Instead, the systemic immune-inflammatory index (SII), an innovative inflammatory biomarker that may help predict cancer patient outcomes, uses platelet, neutrophil, and lymphocyte counts **[15].** Apparently, nutritional status is also associated with surgical outcomes in different solid tumors. Recently, multiple indices encompassing various nutritional and inflammatory variables have been shown to predict prognosis of cancer patients, including colorectal cancer and esophageal cancer **[16].** The Prognostic Nutritional Index (PNI), which is calculated from serum albumin and lymphocyte count **[17],** has been validated as a useful prognostic biomarker in a variety of cancer types, including esophageal carcinoma and osteosarcoma **[18].** Wang and colleagues recently found that PNI and SII can predict clinical outcomes in localized HCC patients after surgical resection **[17].** Although accumulating data demonstrate that SII and PNI can predict prognosis in cancer, the correlation between PNI, SII and outcomes in patients with advanced HCC treated with sorafenib is not fully understood. In this study, our objective was to assess the prognostic and predictive value of SII and PNI in sorafenib-treated patients with advanced HCC.

Methods:

Compliance with Ethical Standards

This study was approved by Zagazig University Institutional Review Board (IRB), and carried out from May 2020 to November 2021 at Zagazig University and El-Mabara Hospitals.

Study design and settings:

This prospective study included 110 patients with advanced histologically or radiologically proven HCC (according to the criteria of the American Association for the Study of Liver Diseases) **[19]** that is refractory or not amenable for locoregional therapies. Patients were eligible to participate from the age of 18 years with no prior radiation or chemotherapy and no medical contraindications to taking sorafenib. Patients were excluded if they were pregnant, breastfeeding, or had an autoimmune disease. Patients with non-HCC liver cancer or patients who do not have access to sorafenib were also excluded.

Pretreatment Evaluation:

The pre-treatment evaluation included a detailed medical history; complete physical examination; complete blood count including differential (lymphocytes, neutrophils) and platelet count (PLT), comprehensive liver function panel including alanine aminotransaminase (ALT), aspartate aminotransaminase (AST), serum bilirubin and serum albumin; prothrombin time (PT), activated partial thromboplastin time (APTT) and viral serology (HCV-Ab, HBs-Ag, HBc-Ab, PCR for serologically positive patients); along with serum alpha-fetoprotein (AFP) and renal function tests. Staging radiology included positron emission tomography-computed tomography (PET-CT) scan and/or CT scans of the chest, abdomen, and pelvis; Bone scan. Patients were classified according to the Barcelona Clinic Liver Cancer System (BCLC) **[20].** Performance status was reported according to the ECOG performance scale and CPS was calculated for all patients.

Pretreatment PNI and SII:

The PNI was calculated as the level of albumin (g/L) summed to the total number of lymphocytes (10^9 /L) multiplied by five **[18].** The SII was defined as the number of platelets multiplied by neutrophils (10^9 /L) and divided by the number of lymphocytes (10^9 /L) **[15].** PNI and SII cutoff values were determined according to patient overall survival (OS) using Receiver Operating Characteristic (ROC) curves.

Treatment Schedule:

Patients with CPS A and early B who met the previous eligibility criteria were scheduled to receive sorafenib 400 mg twice daily continuously; An initial lower dose was used in elderly patients or patients with poor performance status. Dose reduction or discontinuation of the drug owing to adverse effects was performed according to the drug monograph **[21].** Treatment continued until radiographic disease progression or unacceptable toxicity. Adverse events were reported and classified according to the Common Terminology Criteria for Adverse Events of (CTCAE v4.0).

Laboratory Methods

Blood samples were obtained in BD Vacutainers **(Becton, Dickinson and Company, Franklin Lakes, NJ).** Three tubes were collected, including one citrate, one plain, and one EDTA tube from each patient. The citrate tube was immediately centrifuged at 2000 x g for 15 minutes. 30 minutes after removal from the plain tube, the serum was separated by centrifuging the tube at 1200 x g for 10 minutes. Complete blood count was performed from the EDTA tube using the XS500i hematology analyzer **(Sysmex, Kobe, Japan).** The differential cell number was estimated from the blood smear. Prothrombin time was measured with Sysmex CS2100i **(Siemens, Munich, Germany).** The Cobas 8000 Modular Analyzer **(Roche**

Diagnostics, Mannheim, Germany) was used to evaluate all biochemical tests including liver function panel and AFP.

Response Assessment:

Tumor response was assessed based on radiological evaulations such as CT/PETCT scans every 8 weeks or as clinically indicated using Response Evaluation Criteria In Solid Tumors (RECIST) **[22]**.

Statistical Analysis:

The data distribution was non-parametric (Shapiro-Wilk test). Thus, quantitative parameters were presented as median and range, while categorical parameters were presented as frequencies and percentages. The chi-square test was used to compare categorical variables. ROC curve analysis was used to determine PNI and SII cut-offs according to patient survival. Index association was assessed by Spearman's correlation test. KaplanMeier survival curves were constructed to assess survival patterns and significance was demonstrated by the log-rank test. The Cox proportional hazards model was used to estimate the unadjusted and adjusted hazard ratio (HR) and its 95% confidence interval (CI). A p-value below 0.05 was considered significant. These statistical tests were performed using SPSS 17 software **(SPSS Inc., IL, USA).** Overall survival rate was calculated from the date of diagnosis to date of death or last follow up. Progression-free survival (PFS) was calculated as the period of time the patient lived without evidence of disease progression, death, or lost follow up (for responding patients).

RESULTS

Baseline Characteristics:

The clinical characteristics of the 110 sorafenib-treated HCC patients are presented in Table 1. Of the 110 patients included in the study, 96 patients (87.3%) were male and 14 patients (12.7%) were female. The median age at presentation was 62 years (range: 46-71 years). The most important etiological factor was viral hepatitis (69.1%). The prevalence of HCV and HBV infection was 67.3% and 1.8%, respectively. The other causes identified were schistosomiasis (1.8%), metabolic causes (0.9%) and autoimmune hepatitis (0.9%). In the remaining patients, viral hepatitis status was unknown and no other etiological factors were revealed. Fourteen patients had diabetes mellitus and hypertension was evident in 11 patients. Other reported comorbidities were interstitial lung disease, gallbladder stones, bronchial asthma and hyperlipidemia. Twenty-nine patients (26.4%) had received prior treatment for limited-stage HCC; 28 patients received at least one or more locoregional treatment modalities and only one patient underwent liver transplantation.

All patients had a CPS of 8 or better [Only one patient had a CPS of B8, five patients had a CPS of B7, while the rest of the patients had a CPS of A5-6]. Liver cirrhosis was evident in 74.5% of patients and signs of portal hypertension were noted in 52.7% of patients. Only 15 individuals showed histological evidence of HCC, while the majority were diagnosed solely on the basis of radiological criteria. At presentation, evidence of distant metastases was identified in 38 patients (34.5%); five patients had multiple metastases at more than one site. Lung (20/38) was the most commonly reported metastatic site, followed by bone (17/38). Other metastatic sites involved were adrenal glands, omentum, peritoneum, and mediastinal lymph nodes. Vascular and regional lymph node involvement were evident in 57.3% and 40.9% of patients, respectively.

The median serum albumin level was 3.8 [2.6-4.8] g/dl. Median neutrophil, lymphocyte, and platelet

counts were 3.65 [2.6-14]*109/L, 1.5 [0.4-5.7]*109/L, and 141.4 [19-430], respectively]*109/l. Median AST and ALT were 29 [12-180] IU/L and 44 [10-220] IU/L, respectively; the median total bilirubin was 0.9 [0.3-2.1] mg/dL. Regarding AFP, the median value was 232 ng/dl [2-121444] and about one third of the patients had an elevated AFP value above 400 ng/dl.

PNI and SII Cutoff Values:

The median PNI was 46.5 [range: 29.5-64]. On the other hand, the median SII was 330 [range 74-2236]. We evaluated the optimal cutoff values for PNI and SII to predict OS using the area under the ROC curve. In the current study, the cutoff value for PNI was 47.6 (Figure 1A) and the corresponding value for SII was 278 (Figure 1B). With a PNI value of 47.6, the sensitivity was 78.6% and the specificity was 76.9%; while the SII cutoff value of 278 corresponded to sensitivity and specificity values of 76.2% and 76.9%, respectively. According to the PNI cutoff, 74 patients (67.3%) had a low PNI, while the remaining 36 patients (32.7%) had a high PNI. Regarding SII, 41 patients (37.3%) were classified as SII low group while the remaining 69 patients (62.7%) were classified as SII high group. Spearman's correlation analysis showed a negative correlation between PNI and SII ($r = -0.739$, $p < 0.0001$).

Treatment and toxicity:

All patients received sorafenib in a dose range of 400 to 800 mg per day in two divided doses. Twenty-two patients (20%) were started on the lower dose (200 g twice daily) (Table 2). The median duration of treatment was four months. Dose adjustments due to sorafenib-related adverse events were required in 50 patients (45.5%). Treatment discontinued due to disease progression in 47 patients (36.3%); an additional 17 patients (15.5%) discontinued treatment for Grade 3 or greater toxicity. The overall incidence of treatment-emergent adverse events of any grade was 77.3% (Table 2). The most frequently reported adverse reactions were liver dysfunction (31.8%), fatigue (14.5%) and hand-foot syndrome (14.5%). Seven patients (6.4%) experienced grade 3 or greater treatment-emergent hepatic impairment and died of progressive hepatic failure; Four of them were reported to have detectable pre-treatment HCV viraemia and the virology status of the other three was unknown. Another patient died of life-threatening gastrointestinal bleeding with no history of variceal bleeding prior to treatment initiation.

Response and Survival:

Among the 110 patients included in this study, 26 patients were not eligible for response assessment either due to early treatment discontinuation or lack of follow-up prior to the initial response assessment, and for these patients OS and PFS were censored at the last visit. Complete response (CR) was achieved in 4 patients (3.6%); Twelve patients (10.9%) had a partial response (PR) and 23 patients (20.9%) had stable disease (SD), while 45 patients (40.9%) had progressive disease (PD) (Table 2). After a median follow-up of 4 months; Twenty-six cases (23.6%) were alive, 75 patients (68.2%) were reported dead, and nine patients lost follow-up. The cause of death was disease progression in 67 cases and eight patients died from treatment-related toxicities. With a maximum follow-up of 17 months, the median OS was 5 months (95% CI, 4.64-5.36). The median PFS for the 39 disease-controlled patients (CR+PR+SD) was 3.5 months (95% CI, 2.62-4.38).

PNI, SII and Response Rates:

PNI and SII were not associated with objective response rates (CR+PR). Conversely, PNI and SII

were significantly associated with disease control rate (CR+PR+SD). High PNI patients showed a higher disease control rate (DCR) compared to low PNI cohorts [25% vs. 21.4% (p=0.001)]. In addition, DCR was better in patients with low SII than in high SII cases [26.1% vs. 20.2% (p=0.003)] (Table 3).

The Prognostic Value of PNI and SII in HCC Patients:

We examined the prognostic value of PNI and SII in HCC patients. The median OS in the low and high PNI groups was 4 and 7 months, respectively (p<0.001, Figure 2A), and 6 and 4 months in the low and high SII groups (p<0.001, Figure 2B). The median PFS times in the low PNI and high PNI groups were 3 and 6 months, respectively (p<0.001, Figure 2C), and the median PFS times in the low and high SII groups were 6 and 3 months, respectively (P<0.001, Figure 2D).

Univariate & multivariate Analyses for Prognostic Variables:

In the univariate analysis, a low PNI was predictive of overall survival with a HR of 3.6 (95% CI: 2.1-6.3; p<0.001), and a high SII was significantly associated with a worse OS outcome (HR: 2.94; 95% CI: 1.78-4.87; p<0.001). In addition, age, albumin and lymphocyte count were significant prognostic factors associated with overall survival (Table 4). Regarding PFS, PNI, SII, albumin, and lymphocyte count were predictive of a poor outcome.

Multivariate analyzes with strong prognostic factors showed that PNI, SII and age were independent predictors for overall survival. A low PNI was associated with a HR of 2.82 (95% CI: 1.18-6.7; p<0.019); high SII was associated with a HR of 2.3 (95% CI: 1.03-5.21; p=0.043), and the HR for the elderly (age > 60) was 1.8 (95%- CI: 1.03-3.15, p=0.039). On the other hand, low PNI (HR: 4; 95% CI: 1.05-15.7; p<0.04), high SII (HR: 4.7; 95% CI: 1.45-15.38 ; p = 0.01) independent predictors of poor PFS when adjusted for other factors.

Table (1): Baseline patients' clinical characteristics

Variable	Frequency (N=110)	Percent/ Range
Gender		
Male	96	87.3%
Female	14	12.7%
Median Age (years) (range)	62 (46-71)	--------
Etiology		
Viral	76	69.1
HCV	*47*	*67.3%*
HBV	*2*	*1.8%*
Bilharziasis	2	1.8%
Autoimmune	1	0.9%
Metabolic	1	0.9%
Unknown	30	27.3%
Comorbidities		
Diabetes Mellitus	14	12.7%
Hypertension	11	9.9%
Interstitial lung disease	2	1.8%
Gall bladder stones	2	1.8%
Bronchial asthma	1	0.9%
Hyperlipidemia	1	0.9%

Variable	Frequency (N=110)	Percent/ Range
Signs of Chronic Liver Disease		
Cirrhosis	82	74.5%
Splenomegaly	59	53.6%
Portal hypertension	58	52.7%
Ascites (mild)	6	5.5%
Prior Treatment for HCC		
TACE	13	11.8%
Multiple TACE	9	8.1%
RFA	5	4.5%
Combined TACE & RFA	1	0.9%
Liver transplantation	1	0.9%
Child-Pugh Score		
A5	80	72.7%
A6	24	21.8%
B7	5	4.5%
B8	1	0.9%

Table (1): Baseline patients' clinical characteristics cont'd

Variable	Frequency (N=110)	Percent/ Range
HCC lobar distribution		
Single Right Hepatic focal lesion	57	51.8%
Multiple Right Hepatic focal lesions	20	18.2%
Single Left Hepatic focal lesion	17	15.5%
Multiple Left Hepatic focal lesions	6	5.5%
Bilobar Hepatic focal lesions	34	30.9%
Vascular Involvement	**63**	**57.3%**
Main portal vein invasion	45	40.9%
Right portal vein invasion	13	11.8%
Left portal vein invasion	5	4.5%
Lymph Node Involvement	**69**	**62.7%**
Porta hepatis lymph nodes	45	40.9%
Abdominal Lymph nodes	24	21.8%
Distant Spread	**38**	**34.5%**
Lung	20	18.1%
Bone	17	15.5%
Adrenals	2	1.8%
Omentum & peritoneum	2	1.8%
Mediastinal lymph nodes	1	0.9%
Multiple sites	5	4.5%
Diagnostic Modality		
Radiological	95	86.4%
Pathological	15	13.6%
CBC Parameters	Median	Range
Neutrophils, $*10^9$/L	3.65	[2.6-14]
Lymphocytes, $*10^9$/L	1.5	[0.4-5.7]
Platelets, $*10^9$/L	141.4	[19-430]
Liver Function Parameter		
Prothrombin time, sec	12.55	[11.2-22]
Total bilirubin, mg/dL	0.9	[0.3-2.1]
Albumin, g/dL	3.8	[2.6-4.8]

Variable	Frequency (N=110)	Percent/ Range
AST, IU/L	29	[12-180]
ALT, IU/L	44	[10-220]
AFP, ng/mL	232	[2-121444]
AFP elevation	Frequency	Percent
AFP, ≥ 200	56	50.9%
AFP, ≥ 400	39	35.5%
PNI (median-range)	46.5	[29.5-64]
Cutoff	**47.6**	
Low	74	67.3%
High	36	32.7%
SII (median-range)	330	[74-2236]
Cutoff	**278**	
Low	41	37.3%
High	69	62.7%

Table 2: Outcome of treatment with sorafenib

Parameters	HCC patients (No.: 110)	
Duration of Treatment (months/range)	4 months [1-7]	
Lower Initial dose	22 (20%)	
Dose Adjustment	50 (45.5%)	
Withdrawal of Treatment	62 (56.4%)	
Progressive disease	45 (40.9%)	
Treatment related toxicity	17 (15.5%)	
Liver cell failure	7 (6.4%)	
Dermatological toxicity	4 (3.6%)	
Gastrointestinal toxicity	3 (2.7%)	
Fatigue	2 (1.8%)	
Vascular toxicity	1 (0.9%)	
Adverse Events	All grades	Grade ≥ III
Overall incidence	85 (77.3%)	19 (17.3%)
Liver dysfunction	35 (31.8%)	7 (6.4%)
Hand-foot syndrome	16 (14.5%)	5 (4.5%)
Fatigue	16 (14.5%)	2 (1.8%)
Diarrhea	11 (10%)	4 (3.6%)
Bleeding	3 (2.7%)	1 (0.9%)
Rash	1 (0.9%)	-
Radiological Response		
Complete response	4 (3.6%)	
Partial response	12 (10.9%)	
Stable disease	23 (20.9%)	
Disease control rate	39 (35.4%)	
Progressive disease	45 (40.9%)	
Non evaluable	26 (23.6%)	
Survival Status		
Alive	26 (23.6%)	
Dead	75 (68.2%)	
Lost Follow Up	9 (8.2%)	

Parameters	HCC patients (No.: 110)
Median Overall Survival	5 months (95% CI, 4.64-5.36)
Median Progression Free Survival	3.5 months (95% CI, 2.62-4.38)
Mortality Cause	
Progressive Disease	67/75 (89.4%)
Treatment Related	8/75 (10.6%)

Table 3: Association between PNI, SII, and response

Response (84 patients)	PNI			SII		
	<47.6	**≥47.6**	***P value***	**<278**	**≥278**	***P value***
Objective Response Rate						
CR+PR	7 (8.3%)	9 (10.7%)	*0.06*	9 (10.7%)	7 (8.3%)	*0.12*
SD+PD	47 (56%)	21 (25%)		24 (28.6%)	44 (52.4%)	
Disease Control Rate						
CR+PR+SD	18 (21.4%)	21 (25%)	***0.001****	22 (26.1%)	17 (20.2%)	***0.003****
PD	36 (42.9%)	9 (10.7%)		11 (13.1%)	34 (40.5%)	

**: Statistically Significant*

Table 4: Univariate analysis for overall survival and progression-free survival

Covariate	Overall survival		Progression free survival	
	HR (95%CI)	***p-value***	**HR (95%CI)**	***p-value***
Age (>60 years)	2.02 (1.27-3.2)	***0.003****	1.82 (0.96-3.46)	*0.07*
Sex (Male)	1.04 (0.54-2)	*0.91*	0.84 (0.39-1.81)	*0.84*
Etiology (viral)	0.78 (0.49-1.25)	*0.31*	0.79 (0.39-1.6)	*0.51*
Comorbidities	0.87 (0.55-1.35)	*0.50*	0.55 (0.27-1.07)	*0.08*
Child-Pugh (A5)	1.02 (0.71-1.46)	*0.91*	1.17 (0.76-1.79)	*0.48*
Distant metastasis	0.84 (0.53-1.32)	*0.45*	0.55 (0.28-1.08)	*0.08*
Adverse effects	0.82 (0.5-1.28)	*0.39*	1.16 (0.47-2.88)	*0.75*
Total bilirubin	0.77 (0.39-1.58)	*0.46*	0.61 (0.33-1.15)	*0.19*
Albumin	0.5 (0.32-0.77)	***0.002****	0.49 (0.27-0.88)	***0.02****
AST	1.05 (0.68-1.61)	*0.84*	0.89 (0.48-1.67)	*0.72*
ALT	0.87 (0.56-1.35)	*0.53*	1.42 (0.71-2.82)	*0.32*
Lymphocytes	0.72 (0.56-0.92)	***0.01****	0.57 (0.38-0.86)	***0.007****
Neutrophils	1.04 (0.94-1.16)	*0.46*	1.11 (0.95-1.29)	*0.13*
Platelets	1 (0.99-1.003)	*0.26*	1 (0.94-1.004)	*0.30*
AFP (>400)	1.42 (0.91-2.2)	*0.12*	1.54 (0.85-2.79)	*0.16*
PNI (<47.6)	3.6 (2.1-6.3)	***<0.001****	3.98 (1.89-8.37)	***<0.001****
SII (≥278)	2.94 (1.78-4.87)	***<0.001****	5.34 (2.5-11.4)	***<0.001****

**: Statistically Significant*

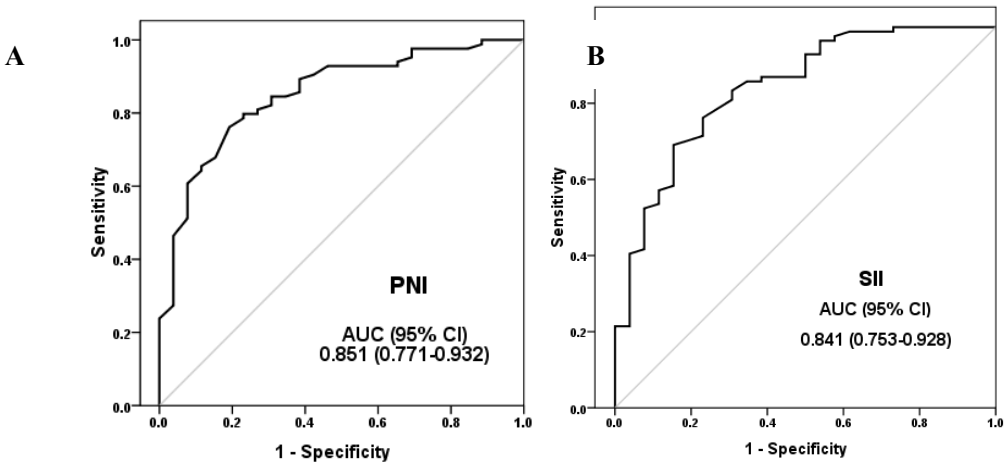

Figure 1: ROC curves analysis of SII, PNI for survival. **A.** PNI ROC curve; **B.** SII ROC curve.

AUC: Area under the curve; CI: Confidence interval

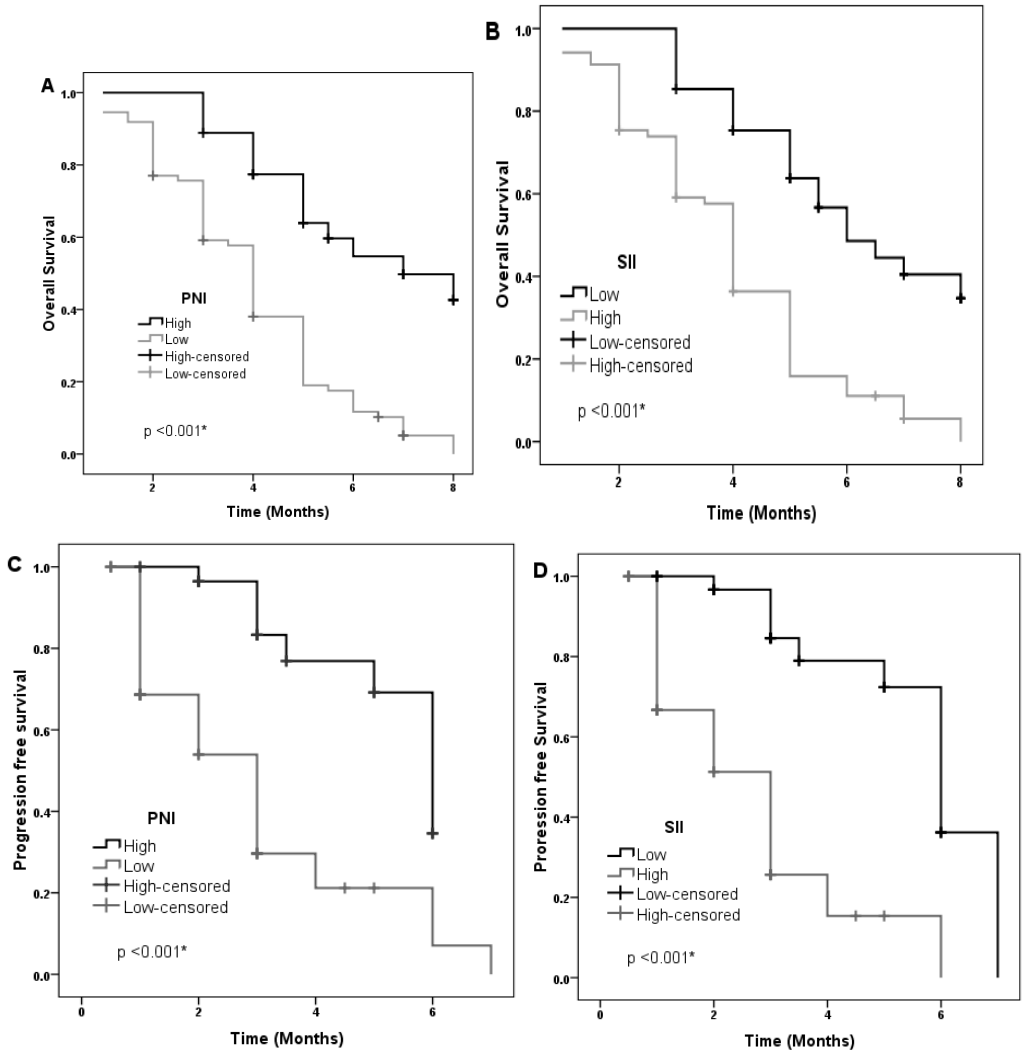

Figure 2: Survival curves according to PNI and SII. **A.** OS in relation to PNI; **B.** OS in relation to SII; **C.** PFS in relation to PNI; **D.** PFS in relation to SII

*OS: Overall survival; PFS: Progression-free survival; *: Significant*

DISCUSSION

Hepatocellular carcinoma (HCC) is one of the most common malignant tumors of the gastrointestinal tract and has a high mortality and morbidity worldwide **[1]** and in Egypt **[3].** Since the introduction of sorafenib in HCC patients, no specific biomarker has been proven to predict the efficacy of sorafenib **[9].** Inflammation is regarded as a promoter status for tumor development and metastasis **[12].** In addition, nutritional status is also associated with outcomes in different solid tumors. Multiple indices encompassing various nutritional and inflammatory variables have been shown to predict prognosis in cancer patients **[16].** In this study, we evaluated the clinical outcomes and the role of pre-treatment PNI and SII as prognostic factors in advanced HCC patients treated with sorafenib in terms of OS, PFS, ORR, and DCR rates.

With a maximum follow-up of 17 months, the median PFS for the disease-controlled patients was 3.5 months, while the median OS of our entire cohort was 5 months. These numbers are far shorter than the OS results reported in the Sharp study (10.7 months for the sorafenib arm versus 7.9 months for the placebo arm) **[8].** Similarly, an Indian group reported a median OS of 3.8 months in sorafenib-treated HCC patients **[23].** In an Egyptian precedent study, the median OS in 41 HCC patients treated with sorafenib was 6.25 months **[24].** Apparently, the OS of HCC patients treated with sorafenib is lower in real life compared to trial settings. Possible explanations for shorter survival times reported in our cohort include a predominant distinctive etiology, poorer baseline liver function parameters reflecting the impact of widespread chronic viral hepatitis and cirrhosis, more frequent lower starting doses to account for poorer baseline PS, more frequent need for dose adjustment or treatment withdrawal due to poor treatment tolerance, more frequent disease burden, and predominance of advanced HCCs at diagnosis. Given the very short outcomes of untreated Egyptian HCC patients (median OS 2.3 months) **[25]** the overall outcome of HCC in Egypt remains apparently poor.

We also assessed the optimal cutoff values for PNI and SII to predict OS using the ROC curve. Using these cutoff values, we divided the patients into low and high groups. Correlation analysis failed to identify any correlation between PNI and SII.

In our study, the PNI cutoff generated by the ROC curve was 47.6, and this value was close to that reported by Wang and colleagues (50.25) **[17]** but higher than that reported by Caputo and his colleagues (31.1) **[10].** Accordingly, the cutoff value of SII in our patients was 278, and this value was also lower than the cutoff value reported by previous investigators **[9, 17].** These observed differences could be due to the unique nature of the disease in Egypt, including variable etiological and biological determinants with predominant viral etiology and previous chronic liver disease, which may have influenced baseline serum albumin and blood counts.

Our results showed that PNI and SII did not correlate with objective response rates. Conversely, both high PNI and low SII cohorts showed higher disease control rates compared to low PNI and high SII cases. This finding could be explained by a relatively low percentage of PR and CR achieved in our study group.

In the multivariate analysis, low SII was significantly predictive of better PFS and OS outcomes. These observations are consistent with the findings of an Italian group that evaluated pretreatment SII and NLR in 56 patients with advanced HCC who received sorafenib. Their

conclusion was that SII is an independent prognostic determinant for OS **[9]**.

Furthermore, a meta-analysis of ten retrospective studies involving 2796 HCC patients treated with resection or systemic treatment showed that high SII is a poor prognostic factor for OS in HCC, while low SII is associated with better clinical outcomes **[26]**.

On the other hand, a high PNI was independently associated with better OS and PFS. These results are consistent with earlier studies assessing the impact of PNI in HCC. Wang et al. found that the PNI predicts tumor recurrence and survival in localized HCC patients with surgical resection **[17];** Hatanaka et al. showed that it is also associatedwith the survival of HCC cases treated with sorafenib in Japanese patients **[27].** In the European experience of Caputo et al. **[10],** along with other baseline characteristics, PNI was an independent predictor of overall survival in HCC patients treated with sorafenib.

Consistent with the above results, we demonstrated the prognostic role of PNI and SII in relation to DCR, PFS and OS in an Egyptian cohort of patients with HCC treated with sorafenib.

The present study has several limitations. First, this was a single institute study. Second, there were no predetermined PNI and SII cut-off values. Third, the lack of a control cohort that did not receive sorafenib precluded evaluating the predictive role of both indices. Finally, the HCC treatment landscape has changed in the last two years to include atezolizumab plus bevacizumab, making it prudent to continue evaluating PNI and SII in the era of immunotherapy, yet being in a developing country like Egypt limits access to more expensive novel therapies. This precludes the availability of an adequate sample size to draw meaningful conclusions about the importance of these prognostic parameters in the era of immunotherapy.

CONCLUSION

There is cumulative evidence supporting the utility of pretreatment PNI and SII as easy-to-apply prognostic factors in HCC patients receiving sorafenib. Both are also readily available and could be used in future clinical trials design in patients with HCC. However, larger multi-center clinical trials are required to obtain standardized PNI and SII cut-offs and accurately predict the prognosis of HCC patients, especially in the approaching immunotherapy era.

Disclosure of potential conflicts of interest

The authors declare no conflicts of interest.

Funding Declaration:

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

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To cite:

Waley, A., Haggag, R., Ahmed Barakat, A., Rashied, H., Abdul-Saboor, A., Esawy, M., Orban, Y., Bakry, A. Impact of Prognostic Nutritional Index and Systemic Immune-Inflammation Index on the Clinical Outcome of Patients with Advanced Hepatocellular Carcinoma Treated with Sorafenib. *Zagazig University Medical Journal*, 2022; (650-663): -. doi: 10.21608/zumj.2022.141934.2577