

Prognostic role of inflammatory markers in hepatocellular cancer patients receiving sorafenib therapy

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Abstract

Objective: Systemic inflammatory markers have been shown to have prognostic value in many types of cancers. Although the prognostic role of the systemic immune-inflammation index (SII), derived neutrophil-lymphocyte ratio (dNLR) and platelet lymphocyte ratio (PLR) has been shown in hepatocellular cancer (HCC) patients who underwent transplantation, its prognostic value has not been investigated in HCC patients under sorafenib treatment. We investigated the prognostic value of inflammatory indices in patients with HCC under sorafenib treatment.

Materials and Methods: The data of 46 patients with stage III unresectable and stage IV HCC were evaluated retrospectively. SII and dNLR were dichotomized based on receiver operating characteristic (ROC) curve analysis (cut-off values: 355 and 1.8). No cut-off value could be determined for PLR; therefore, the median value was defined as the cut-off for PLR. At the time of diagnosis, values of these three inflammatory markers were analyzed to determine their association with clinicopathologic characteristics and to assess their prognostic values via the Kaplan-Meier method and multivariate Cox regression analysis.

Results: Overall survival (OS) was significantly shorter in patients with a high SII, dNLR, or PLR. In univariate analyses, tumor stage, tumor focus count, and presence of extrahepatic lesions seemed to affect survival. Multivariate analysis revealed SII and the presence of extrahepatic lesions as independent risk factors for survival.

Conclusion: The findings of the present study suggest that a high SII is an independent risk factor for survival in patients with HCC under sorafenib treatment.

Keywords: Sorafenib, hepatocellular cancer, systemic immune-inflammation index, derived neutrophil-lymphocyte ratio, platelet lymphocyte ratio

Introduction

Hepatocellular cancer (HCC) is the fourth leading cause of cancer-related death and leads to an annual number of fatalities around 800,000 worldwide (1). It is the ninth most common cancer in women and the fifth most common cancer in men (2). Treatment options include surgery, local ablative treatments, and systemic therapies for HCC. Sorafenib is an oral tyrosine kinase inhibitor that inhibits the rapidly accelerated fibrosarcoma (RAF) kinase and vascular endothelial growth factor (VEGFR) kinase pathways (3). Sorafenib was shown to improve overall survival (OS) and slow radiological progression of the disease compared with placebo in patients with Child Plough class A cirrhosis and inoperable HCC in the multicenter SHARP trial (4). Whereas adverse events related to treatment and decreases in baseline plasma biomarkers such as AST, ALT, and AFP have been proposed as prognostic markers of response to sorafenib, no marker has been widely accepted in this regard (5-7).

The cellular immune system is known to be related to cancer and a marker of the systemic inflammatory response (8). Recently, inflammatory markers such as platelet lymphocyte ratio (PLR), derived neutrophil-lymphocyte ratio (dNLR), and systemic immune-inflammation index (SII) which are calculated from blood count parameters have been proposed to predict survival in various disorders (9-11). In 2012, Hu et al. (12) developed SII as a marker of prognosis in patients with HCC who underwent curative surgery. SII is calculated by multiplying NLR per liter by platelet count (12). Afterward, SII has been shown to predict postoperative prognosis and response to treatment in various types of cancers (13,14). Similarly, dNLR and PLR have been reported to be associated with survival and response to treatment in patients with malignancies such as colorectal and prostate cancers (10,11). Shao et al. (15) reported that a decrease of more than 20% in alpha-fetoprotein levels could be used to predict response to



treatment in patients with advanced HCC under anti-androgen treatment. Based on all these findings, we aimed to investigate the role of SII, PLR, and dNLR in predicting survival in patients with HCC under sorafenib treatment.

Materials and Methods

Study population and definition

Patient data have been collected from their files and electronic records. A total of 46 patients with stage 4 or stage 3 inoperable HCC with respect to the eighth edition of American Joint Committee on Cancer (AJCC) TNM classification and also Child-Pugh class A cirrhosis and an AFP level above 20 ng/ml who were diagnosed radiologically or pathologically and were under sorafenib (Nexavar) treatment for a minimum of eight weeks were enrolled to this retrospective study.

Before the initiation of sorafenib treatment, all of the patients underwent an evaluation including complete blood count analysis; AFP; albumin, INR, and bilirubin (for Child-Pugh classification); and ultrasound to scan for the presence of ascites. For inclusion to the study, the patients had to have an Eastern Cooperative Oncology Group (ECOG) performance score of lower than two.

The age, sex, ECOG, PS, underlying liver disease, TNM stage, number of tumor foci in liver parenchyma on imaging, extrahepatic metastases, and pre-treatment laboratory values of the patients were recorded.

The initial dose of sorafenib was 400 mg bid. Sorafenib was discontinued only in case of disease progression or grade III unmanageable or grade IV toxicity. In the case of grade III manageable toxicity, sorafenib dose was reduced to 200 mg bid.

Sorafenib was discontinued in these patients only if grade III toxicity recurred under the reduced dose regimen. A decrease of more than 20% in AFP level after eight weeks of sorafenib treatment was defined as a response to treatment. In order to calculate pre-treatment SII, dNLR, and PLR values, respectively, platelet count X(neutrophil count/lymphocyte count), absolute neutrophil count/(white blood cell count-absolute neutrophil count) and platelet count/lymphocyte count formulas were used. The overall survival (OS) was calculated for all patients as the duration between the initiation of treatment and death or the last follow-up time for that patient.

Statistical analysis

To determine the cut-off values for SII and dNLR, ROC curve analysis was used. The log-rank test was used in univariate analyses, and Cox-regression model was used in multivariate analysis. Kaplan-Meier analysis was used to calculate OS duration, and survival graphics were presented. In the comparison of survival between groups, the log-rank test was used.

The variables consisted of age, sex, ECOG, PS, etiology, tumor stage, number of tumor foci, extrahepatic metastasis, albumin, SII, dNLR, PLR, the need for sorafenib dose modification, development of adverse events, response to

sorafenib, and OS. No cut-off could be determined for PLR using ROC curve analysis, so its median value was used as the cut-off for PLR. Prognostic significance of SII, dNLR, and PLR were evaluated using univariate and multivariate analyses.

The odds ratio and 95% confidence interval were determined by cox regression analysis.

SPSS version 21.0 (IBM Inc., Chicago, IL, ABD) was used for statistical analyses. Statistical significance was set at $p < 0.05$.

Results

Patient characteristics

A total of 46 patients with HCC who used sorafenib treatment were included. The most sensitive and specific values for study variables were determined using receiver-operating characteristics (ROC) curve analysis: cut-off values were 355 for SII and 1.8 for dNLR (Figure 1). The baseline characteristics of the patients are summarized in Table 1.

The median age was 58 (39-82), and 8.6% of the study population were females. Most of the patients (78.2%) had an ECOG PS of 0. The etiology of liver disease was HBV in 71.7% and HCV in 21.8%, and 4.3% of the study population reported alcohol use.

Survival outcomes

The median OS was 10.2 months, and the median duration of follow up was 9.8 months. In univariate analyses, the median OS was 10.8 months in stage III patients and 8.7 months in stage IV patients ($p = 0.024$).

While patients with a single tumor focus had a median OS of 10.5 months, those with multiple tumor foci had a median OS of 9.6 months ($p = 0.047$).

The patients with extrahepatic lesions had a median OS of 7.3 months, and those without extrahepatic lesions had a median OS of 10.4 months ($p = 0.011$).

While the median OS was 11.7 months in the patients with an $SII \leq 355$, it was 7.9 months in those with an $SII > 355$ ($p = 0.008$).

The median OS was 10.5 months in the patients with a $dNLR \leq 1.8$, and it was 8.2 months in those with a $dNLR > 1.8$ ($p = 0.025$). The median OS was 10.2 months in the patients with a $PLR \leq 184$ while it was 8.9 months in those with a $PLR > 184$ ($p = 0.038$). The patients with and without response to sorafenib had a median OS of 11.2 and 9.5 months, respectively ($p = 0.032$).

There was no significant association between OS and age, sex, ECOG PS, etiology, albumin, need for sorafenib dose modification, and development of adverse events ($p = 0.117$, $p = 0.145$, $p = 0.684$, $p = 1.125$, $p = 1.187$, $p = 0.251$, and $p = 0.148$, respectively). Multivariate analysis revealed that OS was independently associated with the presence of extrahepatic lesions and a high SII ($p = 0.014$ and $p = 0.016$, respectively, Table 2). Figure 2 demonstrates the survival graphs.

Table 1. Baseline characteristics in hepatocellular carcinoma patients treated with sorafenib (n:46)

		Number of patients n (%)
Age	≤65	24 (52,1%)
	>65	22 (47,9%)
Gender	Female	4 (8,6%)
	Male	42 (91,4%)
ECOG PS	0	36 (78,2%)
	1	10 (21,8%)
Etiology	HBV	33 (71,7%)
	HCV	10 (21,8%)
	Alcohol	2 (4,3%)
	Unknown	1 (2,2%)
TNM stage	Stage III inoperabl	9 (19,5%)
	Stage IV	37 (80,5%)
Tumor focus count	Single	10 (21,8%)
	Multiple	36 (78,2%)
Extrahepatic lesion	Yes	5 (10,8%)
	No	41 (89,2%)
Albumin <3.5 (g/dL)	Yes	18 (39%)
	No	28 (61%)
WBC counts (x10 ⁹ /L), median(min-max)		7,25 (2,58-22,52)
Neutrophil counts (x10 ⁹ /L), median(min-max)		2,37 (1,58-3,87)
Lymphocyte counts (x10 ⁹ /L), median(min-max)		1,12 (0,68-1,76)
Platelet counts (x10 ⁹ /L), median(min-max)		102.0 (65.2-278.0)
SII	≤355	26 (56,5%)
	>355	20 (43,5%)
dNLR	≤1,8	18 (39,1%)
	>1,8	28 (60,9%)
PLR	≤184	25 (54,3%)
	>184	21 (45,7%)
Sorafenib dose modification	Yes	8 (17,3%)
	No	38 (82,7%)
Adverse events	Grade III	5 (10,8%)
	Grade IV	1 (2,2%)
OS (months), median (min,max)		10,20 (3,02-39,08)
OS (months)	≤10.2	24 (52,1%)
	>10.2	22 (47,9%)
Response to sorafenib	Yes	27 (58,6%)
	No	19 (41,4%)

ECOG PS: Eastern Cooperative Oncology Group Performance Score, TNM: Tumor Node Metastasis, WBC: White Blood Cell, SII: Systemic immune-inflammation index, dNLR: Derived neutrophil-lymphocyte ratio, PLR: platelet lymphocyte ratio, OS: Overall survival

Table 2. Univariable and multivariable analyses to predict overall survival in hepatocellular carcinoma patients

Variables	Univariable		Multivariable	
	HR(95%CI)	P value	HR(95%CI)	P value
Age greater than ≤65	1.419 (0.945-2.317)	0.117		
Sex (Female vs male)	1.434 (0.914-2.436)	0.145		
ECOG PS 0 vs 1	1.386 (0.748-2.187)	0.684		
Etiology HBV vs HCV	1.681 (0.581-2.168)	1.125		
TNM stage	2.214 (1.108-3.847)	0.024	0.912 (0.625-1.098)	0.242
Stage III inoperable vs Stage IV				
Tumor focus count Single vs multiple	1.194 (0.856-1.452)	0.047	1.069 (0.875-1.365)	0.358
Extrahepatic lesion Yes vs no	1.321 (0.682-2.654)	0.011	1.258 (1.068-1.785)	0.014
Albumin <3.5 g/Dl Yes vs no	1.654 (0.548-3.457)	1.187		
SII ≤355 vs >355	2.914 (1.425-5.129)	0.008	1.312 (1.057-1.456)	0.016
dNLR ≤1,8 vs >1,8	2.458 (1.015-3.587)	0.025	1.275 (1.014-1.502)	0.125
PLR ≤184 vs 184	2.147 (1.915-5.478)	0.038	1.354 (0.981-1.681)	0.087
Sorafenib dose modification Yes vs no	1.528 (0.756-2.112)	0.251		
Adverse events Yes vs no	1.451 (0.825-2.237)	0.148		
Response to sorafenib Yes vs no	2.328 (1.741-3.458)	0.032	1.181 (0.764-1.385)	0.343

Statistically significant p-values (<0.05). HR: Hazard ratio, CI: Confidence interval, ECOG PS: Eastern Cooperative Oncology Group Performance Score, TNM: Tumor Node Metastasis, SII: systemic immune-inflammation index, dNLR: derived neutrophil lymphocyte ratio, PLR: platelet lymphocyte ratio

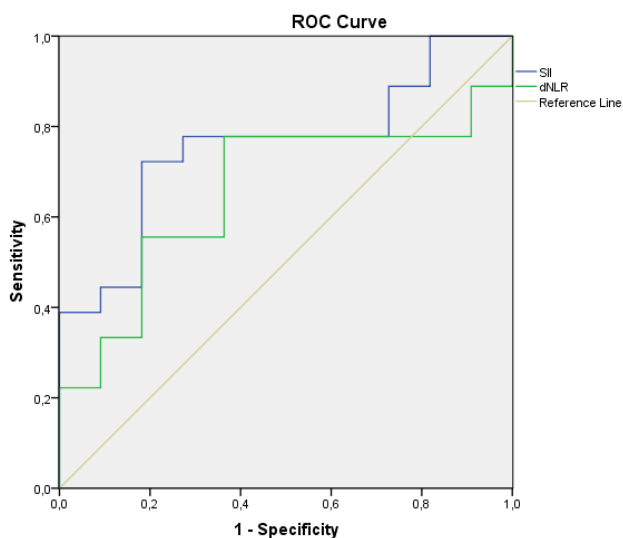


Fig. 1. ROC analysis and AUC for sensitivity and specificity of inflammatory parameters: SII: systemic immune-inflammation index, dNLR: derived neutrophil lymphocyte ratio. SII-AUC:0.758 and dNLR-AUC:0.657

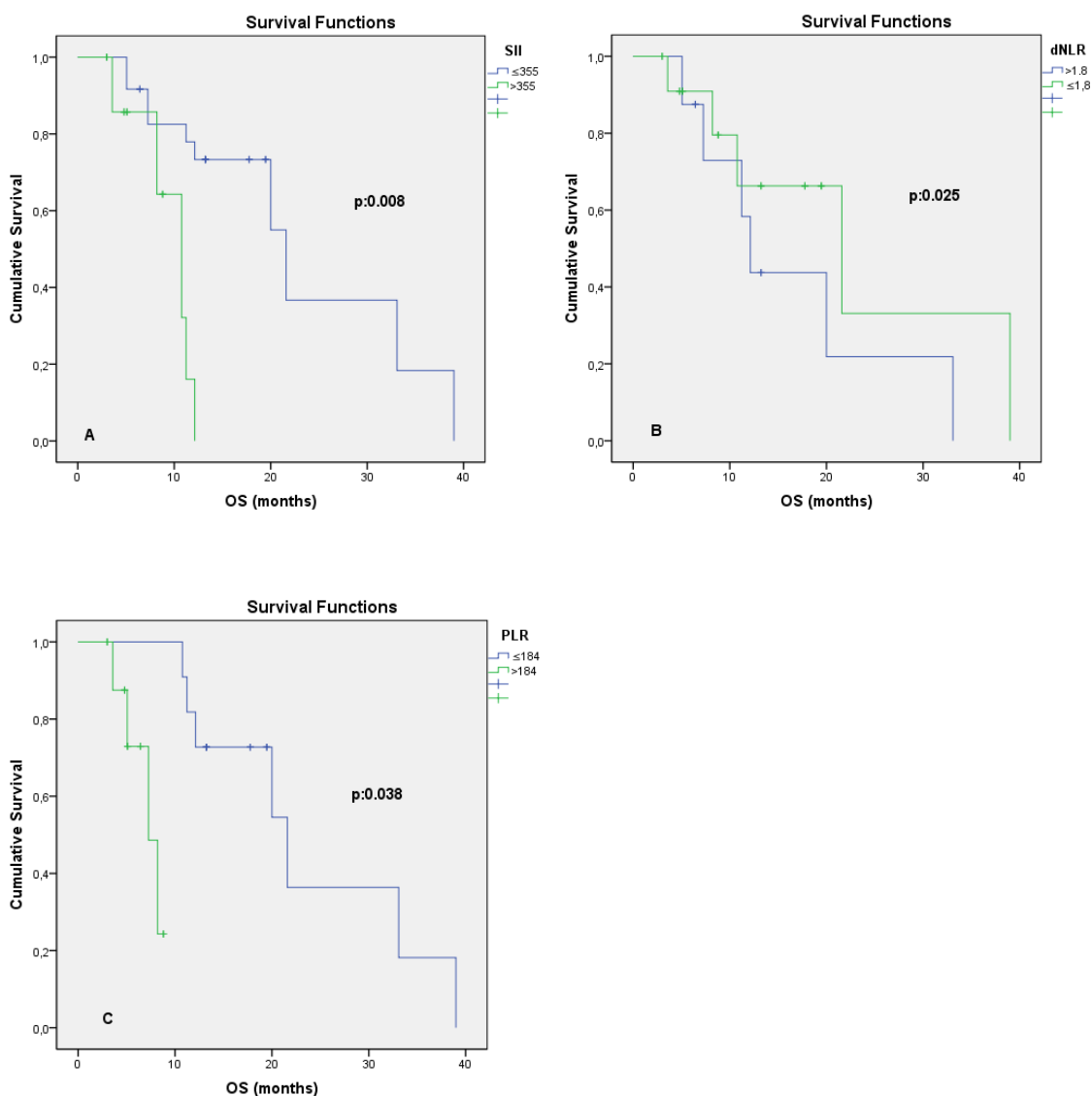


Fig. 2. Overall survival times according to inflammatory markers. SII: systemic immune-inflammation index (A), dNLR: neutrophil lymphocyte ratio (B), PLR: platelet lymphocyte ratio (C)

Discussion

CR is described as having a <5% BMPC ratio in addition to Hepatocellular cancer is a highly angiogenic tumor that develops in the setting of chronic inflammation and cirrhosis. The contributory role of inflammation in the development of cancer has long been studied, and recent studies focus on the effect of surrogate inflammatory markers on tumor dissemination and survival. Blood count parameter ratios have been used as markers predictive of tumor biology, aggressiveness, and other adverse outcomes associated with cancer (16). The vascular endothelial growth factor is released by platelets and neutrophils and plays an essential role in angiogenesis and tumor progression (17). Whereas the role of neutrophils in cancer pathogenesis is debated, they are known to take place in the microenvironment of various tumors such as HCC, renal cell carcinoma, and glioblastoma (18-20). On the other hand, lymphocytes release cytokines and prevent tumor progression by contributing to cytotoxic cell death (21). Sorafenib is an expensive anti-angiogenic multiple tyrosine kinase inhibitor that has been used in the treatment of HCC. In the present study, we aimed to evaluate the role of inflammatory indices, which are derived from complete blood count parameters, in predicting response to sorafenib treatment in patients with HCC. For this purpose, we investigated the predictive role of SII, dNLR, and PLR and found SII as an independent predictor of survival in these patients.

Inflammation is an essential step in the development of cancer and also a contributor to tumor progression. Inflammatory markers have been reported to be associated with poor survival and unresponsiveness to treatment in several solid organ cancers. In addition to thrombocytosis and neutrophilia, dNLR and PLR have been investigated in numerous studies in this regard (22). In 2012, Proctor et al. (23) reported that dNLR provided more prognostic information than NLR among more than ten thousand people with all cancer types (23). Li et al. (24) reported that a high dNLR was an independent prognostic factor in terms of survival and microvascular invasion in patients with HCC. In the present study, a high dNLR seemed to be associated with short survival time, but this association was not confirmed in the multivariate analysis.

Recently, the prognostic role of PLR has been investigated in patients with HCC who underwent hepatectomy or liver transplantation, and a high PLR before surgery has been found to be associated with HCC recurrence (25). To the best of our knowledge, the role of PLR in patients with HCC under sorafenib treatment has not been investigated in detail, and the findings of the present study may shed light on its role in this regard. Although it was not independently associated with survival in multivariate analysis, a high PLR was related to shorter survival in patients with HCC under sorafenib treatment in the present study.

It is not clear which physiological process affects SII. Neutrophils are associated with chemokines and proteases, which have a regulatory role in angiogenesis. These processes may affect blood circulation in tumors and tumor growth rate (26,27).

The platelets are able to release chemokines and cytokines. These cytokines may induce the proliferation of tumor cells (28). Lymphocytes play an important role in immune defense. A higher intensity of lymphocytes in the tumor microenvironment has been reported to be associated with better clinical outcomes and that these lymphocytes are related to circulating lymphocytes (29). A high lymphocyte ratio has also been reported to be associated with a better prognosis in several cancer types, and circulating lymphocytes may inhibit tumor metastasis and proliferation (30,31).

The systemic immune-inflammation index has been reported as an excellent prognostic index in patients with small-cell lung cancer, esophageal cancer, and renal cell carcinoma (13,32,33). In the present study, we investigated the prognostic value of SII in patients with HCC under sorafenib treatment, and our findings suggest that it is an independent predictor of survival.

The present study has several limitations. Firstly, it was a retrospective study with small sample size. Secondly, SII levels may be influenced by conditions such as acute infections and chronic viral infections. Nonetheless, it is not easy to determine an optimal cut-off for inflammatory markers because of the individual variation in the immune response. Therefore, the change in baseline SII level may be a better predictor than a constant cut-off. It may be rational to compare the prognostic value of the change in SII levels after treatment rather than a constant cut-off in further prospective studies.

Conclusion

The findings of the present study are important in terms of the independent association between SII levels and survival in patients with HCC under sorafenib treatment. We suggest that using SII to predict survival in HCC patients under sorafenib treatment may prove beneficial provided that our findings are confirmed in prospective studies.

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Conceptualization: Ali Ogul, Methodology: Mahmut Buyuksimsek; Formal analysis and investigation: Mahmut Buyuksimsek; Writing - original draft preparation: Ali Ogul; Writing - review and editing: Mahmut Buyuksimsek; Supervision: Mahmut Buyuksimsek.

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Ethical issues: Author declare, originality and ethical approval of research. The study was conducted under defined rules by the Local Ethics Commission guidelines and audits.

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