Comparison of Inflammatory Indexes in Patients Treated with Sorafenib in Advanced Hepatocellular Carcinoma: A Single-Center Observational Study

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ABSTRACT

Objective: Sorafenib has limited survival benefits with lower tumor response rates in hepatocellular carcinoma (HCC). Many researchers have attempted to identify predictors for sorafenib. In this study, we compared the role of lymphocyte/monocyte ratio (LMR), neutrophil/monocyte ratio (NMR), platelet/neutrophil ratio (PNR), systemic inflammation response index (SIRI) and systemic immune inflammation (SII) in patients with HCC received sorafenib treatment.

Materials and Methods: In this study, we retrospectively enrolled 80 patients who used Sorafenib in advanced stage HCC between January 2011 and December 2018. Baseline neutrophil, lymphocyte, monocyte and platelet counts were recorded. Cut-off points of LMR, NMR, PNR, SIRI and SII were calculated by the receiver operating characteristic (ROC) curve analysis. Overall survival (OS) and progression-free survival (PFS) were demonstrated by Kaplan-Meier analysis, and the log-rank test was used for comparing the curves

Results: Median OS was 29 weeks (95% CI 20.41–37.58), and PFS was 16 weeks (95% CI: 12.04–19.95). We found that only low SIRI value was associated with increased survival. OS were 19 weeks for SIRI ≥2.2 and 38 weeks (95% CI: 30.96–45.03 for patients with SIRI <2.2 (p=0.005). PFS was 12 weeks for SIRI ≥2.2 and 20 weeks for SIRI <2.2 (p=0.098). The life expectancy of patients with SIRI values less than 2.2 was 2.02 times higher than the other group.

Conclusion: To our knowledge, NMR and PNR indexes were evaluated for the first time in our study in HCC patients. Low SIRI value was related to increased survival in patients receiving sorafenib with HCC.

Keywords: Hepatocellular carcinoma, inflammation, sorafenib

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INTRODUCTION

Hepatocellular carcinoma (HCC) is the most common primary malignancy of the liver. Although surveillance programs are used more frequently, the majority of HCC patients are diagnosed at an advanced stage (1). In addition, some patients with early-to-moderate HCC progress to advanced stage disease during follow-up. Only palliative treatment options are available for this group of patients.

Sorafenib is a tyrosine kinase inhibitor with effects on tumor angiogenesis and proliferation, and two placebo-controlled randomized trials have shown that this drug prolongs survival in advanced HCC patients (2, 3). However, due to the primary and acquired drug resistance mechanisms developed when taking sorafenib treatment, the drug has limited survival benefits with lower tumor response rates than expected (4). Many researchers have attempted to identify baseline or pretreatment predictors for sorafenib because the same effect was not seen in all HCC patients and response rates were not satisfactory (2). Recently, systemic inflammation was reported to be closely related to malignancy (5). Inflammation plays a significant role in the development and progression of the tumor. Immune and inflammatory cells, such as neutrophils, monocytes and lymphocytes in the systemic circulation, may contribute to tumor cell invasion and metastasis (6). Different inflammation-based scores have been proposed and are considered useful in this respect (7).

We compared the role of lymphocyte/monocyte ratio (LMR), neutrophil/monocyte ratio (NMR), platelet/neutrophil ratio (PNR), systemic inflammation response index (SIRI) and systemic immune inflammation (SII) in patients with HCC received sorafenib treatment in this study.

MATERIALS and METHODS

Study Populations and Design

We retrospectively recorded the patients who were followed up with the diagnosis of HCC at Gaziantep University School of Medicine between January 2011 and December 2018. The number of patients who were prescribed sorafenib treatment was 98. However, 80 patients who had used sorafenib treatment for at least four weeks

were analyzed. This study was approved by the Ethics Committee of Gaziantep University (Decision no: 2019/02, 09.01.2019). This was a retrospective study. Thus, patients were not consented before being included in this study. The inclusion criteria were as follows: HCC diagnosis based on histologically proven or dynamic imaging and underlying chronic liver disease, good performance status (ECOG level <2) and liver function tests consistent with Child-Pugh class A or B-7. Exclusion criteria were as follows: Another history of malignant disease in the past five years, renal and/or hepatic insufficiency, acute coronary syndrome, autoimmune diseases, or systemic inflammatory diseases. The following variables were collected for analysis: age and gender; date of HCC diagnosis; treatment history; date of death or last follow-up; blood test results (baseline neutrophil, lymphocyte, monocyte and platelet counts) were recorded. Prognostic indexes were calculated according to the following formula:

LMR: Peripheral lymphocyte count/Peripheral monocyte count

NMR: Peripheral neutrophil count/Peripheral monocyte count

PNR: Peripheral platelet count/Peripheral neutrophil count

SIRI: Peripheral neutrophil count x Monocyte count/ Lymphocyte count,

SII: Peripheral platelet count x Neutrophil count/ Lymphocyte count

Statistical Analysis

Frequency and percentage distribution values were used for demographic variables. Cut-off points of LMR, NMR, PNR, SIRI and SII were calculated by the receiver operating characteristic (ROC) curve analysis (Youden statistic). For the comparison of them and demographic variables, one-sample t-test and analysis of variance were used. Overall survival (OS) was defined as the time interval between the onset of treatment and death or final follow-up. Progression-free survival (PFS) was defined as the time between the onset of treatment and disease progression or death or last follow-up. OS and PFS were demonstrated by Kaplan-Meier analysis, and the log-rank test was used for comparing the curves. The survival durations were presented as weeks. Cox regression method was used in univariate analysis to determine important variables in OS and PFS durations. A p-value of <0.05 was accepted for statistical significance. SPSS 22.0 software (SPSS, Chicago, IL, USA) was used for statistical analysis.

RESULTS

Patient Characteristics

The mean age was 69 (range 29–83) years and 83.8% were male gender. Etiology of HCC were infection of heatitis B (n=49, 61%), infection of hepatitis C (n=8, 10%), non-alcoholic fatty liver disease (n=10, 12.5%), alcoholic liver disease (n=4, 5%) and cryptogenic (n=9, 11.25%). 15% of patients had extra-hepatic metastases.

Median follow up time was 31.5 weeks (range 5–155 weeks). There were 72 (90%) deaths in total. At the time of analysis, eight (10%) patients were actively receiving sorafenib. A summary of the distribution of clinical variables is outlined in Table 1.

Table 1. Distribution of the clinical variables

Variables	n	R or %
Age (years), Mean±SD	61.94±11.7 (29–83)	
Gender		
Female	13	16.25
Male	67	83.75
Etiology		
Hepatitis B	49	61
Hepatitis C	8	10
Non-alcoholic fatty liver disease	10	12.5
Alcohol	4	5
Cryptogenic	9	11.25
Metastatic sites		
Liver-multifocal	60	75
Extra-hepatic	20	25
Previously applied treatments		
Transplantation	2	2.5
TACE	11	13.75
TARE	1	1.25
None	66	82.5
Neutrophil count, Mean±SD (x10⁶/l)	4918±1835 (880–11210)	
Monocyte count, Mean±SD (x10⁶/l)	717±285 (250–1980)	
Lymphocyte count, Mean±SD (x10⁶/l)	1395±488 (470–3300)	
Platelet count, Mean±SD (x10⁹/l)	202±82 (56–427)	

R: Range; TACE: Transarterial chemoembolization; TARE: Transarterial radioembolization; SD: Standard deviation

In our study, the OS of patients according to HCC diagnosis was 34 weeks (95% CI: 29.22–38.77); OS based on the use of sorafenib treatment was 29 weeks (95% CI: 20.41–37.58); the PFS value was 16 weeks (95% CI: 12.04–19.95).

LMR, NMR, PNR, SIRI, SII and Clinical Outcome

Median PFS and OS, according to LMR, NMR, PNR, SIRI and SII, are shown in Table 2, Figure 1 and Figure 2.

The cut-off point of LMR was determined by the ROC analysis. The cut-off point was 1.4 for LMR [p=0.737; AUC=0.535; sensitivity=29.17% (95% CI: 19.0–41.1); specifity=100.0% (95% CI: 63.1–100.0)]. The PFS value for both LMR ≤1.4 and >1.4 was 16 weeks and there was no statistically significant difference (p=0.601). Median OS were 31 weeks (95% CI: 24.61–37.38) for LMR >1.4 and 18 weeks (95% CI: 20.41–37.58) for LMR ≤1.4 (p=0.155).

The cut-off point for NMR was 5.2 [p=0.005; AUC=0.805; sensitivity=81.94% (95% CI: 71.1–90); specifity=87.5% (95% CI: 47.3–99.7)]. Median PFS were 19 weeks (95% CI: 11.31–26.68) for NMR <5.2 and 14 weeks (95% CI: 8.53–19.46) for NMR ≥5.2 (p=0.126). Median OS were 31 weeks (95% CI 17.86–44.13) for patients with NMR <5.2 and 26 weeks (95% CI: 15.47–36.52) for ≥5.2 (p=0.150).
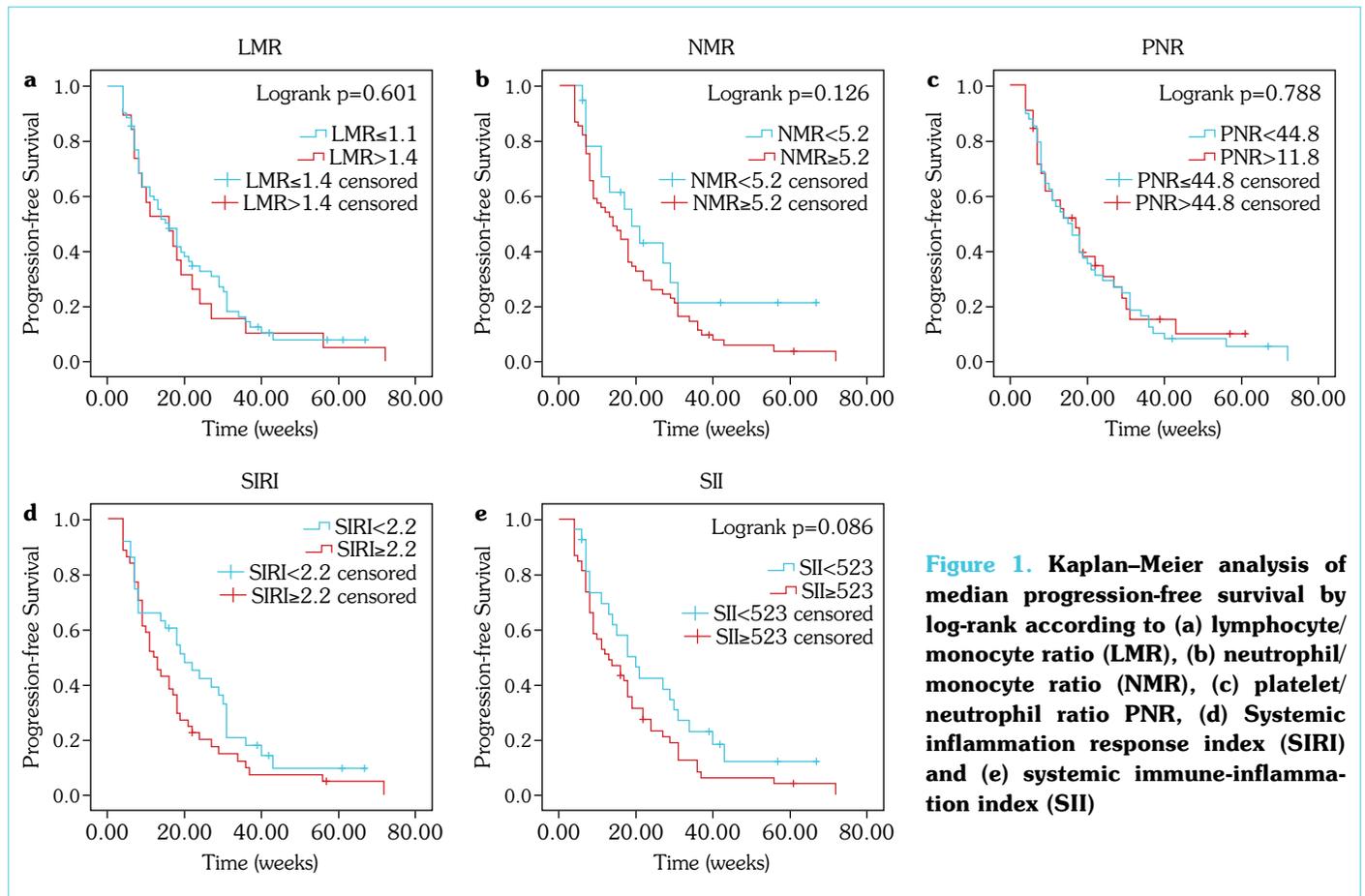
Figure 1. Kaplan–Meier analysis of median progression-free survival by log-rank according to (a) lymphocyte/monocyte ratio (LMR), (b) neutrophil/monocyte ratio (NMR), (c) platelet/neutrophil ratio PNR, (d) Systemic inflammation response index (SIRI) and (e) systemic immune-inflammation index (SII)

Table 2. Kaplan–Meier analysis of median progression-free and overall survival according to LMR, NMR, PNR, SIRI and SII

	PFS		OS	
	Median (95% CI)	**Log-rank P**	**Median (95% CI)**	**Log-rank P**
LMR		0.601		0.155
≤1.4	16 (6.04–25.95)		18 (20.41–37.58)	
>1.4	16 (11.35–20.64		31 (24.61–37.38)	
NMR		0.126		0.150
≥5.2	14 (8.53–19.46)		26 (15.47–36.52)	
<5.2	19 (11.31–26.68)		31 (17.86–44.13)	
PNR		0.788		0.055
≤44.8	15 (9.90–20.09)		20 (7.55–32.44)	
>44.8	17 (10.52–23.48)		33 (25.10–40.89)	
SIRI		0.098		**0.005**
≥2.2	12 (8.28–15.71)		19 (15.76–22.23)	
<2.2	20 (11.68–28.31)		38 (30.96–45.03)	
SII		0.086		0.209
≥523	13 (6.88–19.11)		20 (16.52–23.47)	
<523	20 (12.54–27.45)		31 (26.00–35.99)	

LMR: Lymphocyte/monocyte ratio; NMR: Neutrophil/monocyte ratio; PNR: Platelet/neutrophil ratio; SIRI: Systemic inflammation response index; SII: Systemic immune-inflammation index; PFS: Progression-free survival; OS: Overall survival; HR: Hazard ratio; CI: Confidence interval

For PNR, the determined cut-off point was 44.8 (p=0.127; AUC=0.630; sensitivity=63.89% (95% CI: 51.7–74.9); specifity=75.0% (95% CI: 34.9–96.8). Median PFS were 15 weeks (95% CI: 9.90–20.09) for ≤44.8 and 17 weeks (95% CI: 10.52–23.48) for PNR >44.8 (p=0.788). Median OS were 20 weeks (95% CI: 7.55–32.44) for PNR ≤44.8 and 33 weeks (95% CI: 25.10–40.89) for PNR >44.8 (p=0.055).

The cut-off point for SIRI was 2.2 (p=0.127; AUC=0.630; sensitivity=63.89% (95% CI 51.7–74.9); specifity=75.0% (95% CI: 34.9–96.8). Median OS were 19 weeks (95% CI: 15.76–22.23) for SIRI ≥2.2 and 38 weeks (95% CI: 30.96–45.03) for patients with SIRI <2.2 (p=0.005). Median PFS was 12 weeks (95% CI: 8.28–15.71) for SIRI ≥2.2 and 20 weeks (95% CI: 11.68–28.31) for SIRI <2.2 (p=0.098).

For SII, the cut-off point was 523 [p=0.002; AUC=0.740; sensitivity=69.44% (95% CI: 57.5–79.8); specifity=75.00% (95% CI: 34.9–96.8)]. Median PFS were 13 weeks (95% CI: 6.88–19.11) for SII ≥523 and 20 weeks (95% CI: 12.54–27.45) for SII <523 (p=0.086). Median OS were 20 weeks (95% CI: 16.52–23.47) for SII ≥523 and 31 weeks (95% CI: 26.00–35.99) for patients with SII <523 (p=0.209).

According to the univariate Cox regression analysis for OS, a statistically significant difference was found in the SIRI variable (p=0.005). Life expectancy was 2.02 times higher for SIRI <2.2 (Table 3).
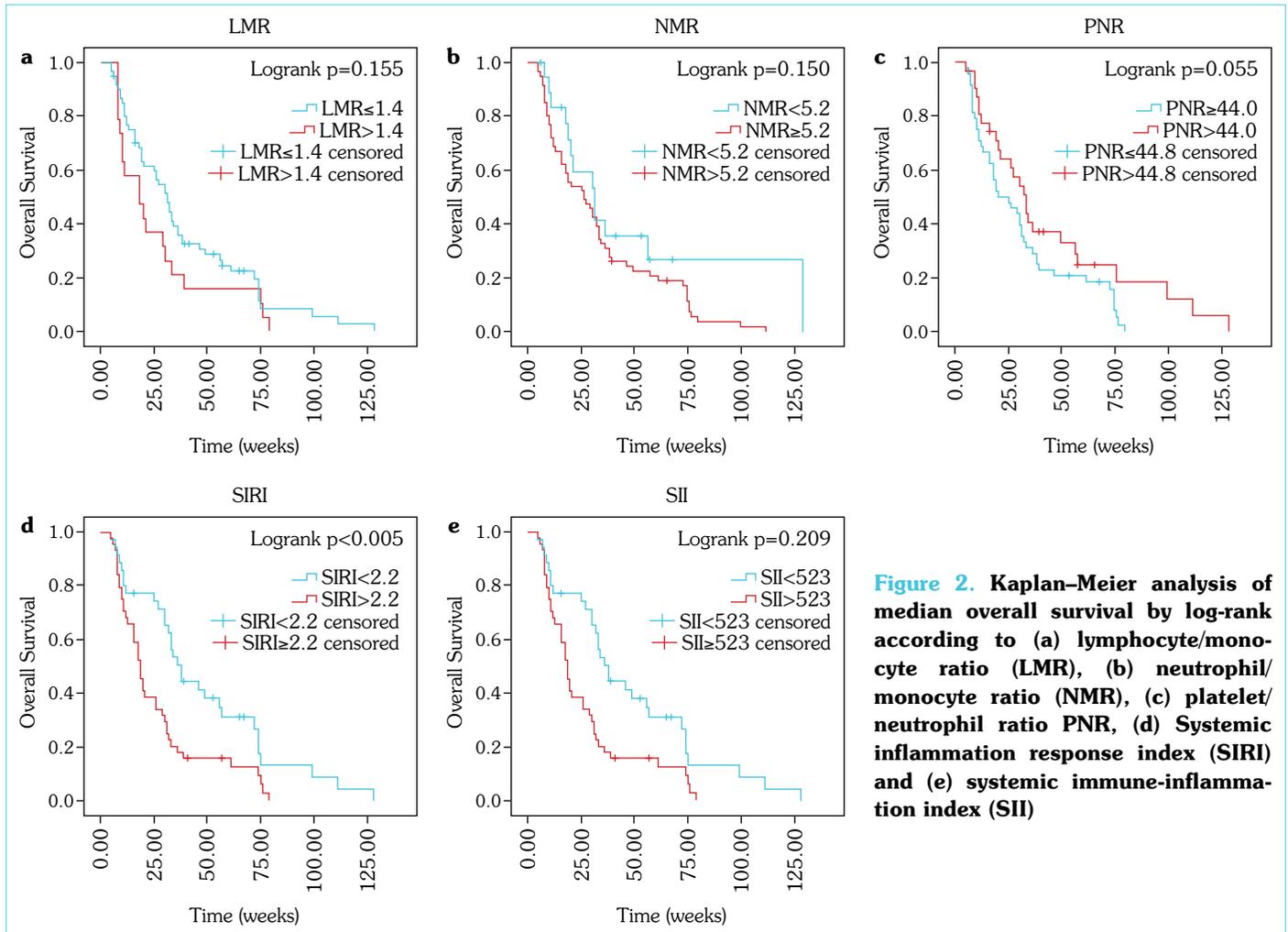
Figure 2. Kaplan–Meier analysis of median overall survival by log-rank according to (a) lymphocyte/monocyte ratio (LMR), (b) neutrophil/monocyte ratio (NMR), (c) platelet/neutrophil ratio PNR, (d) Systemic inflammation response index (SIRI) and (e) systemic immune-inflammation index (SII)

Table 3. Univariate analyses of hepatocellular carcinoma patients for overall survival

Variables	Univariate analysis	
	P	**HR (95% CI)**
Gender (Female–Male)	0.743	0.89 (0.47–1.71)
Etiology	0.252	0.43 (0.10–1.81)
LMR group: ≤1.4 vs >1.4	0.167	1.45 (0.85–2.49)
NMR group: <5.2 vs ≥5.2	0.160	0.63 (0.34–1.19)
PNR group: ≤44.8 vs >44.8	0.063	1.61 (0.97–2.67)
SIRI group: <2.2 vs ≥2.2	0.005	2.02 (1.24–3.31)
SII group: <523 vs ≥523	0.219	1.38 (0.82–2.31)

LMR: Lymphocyte/monocyte ratio; NMR: Neutrophil/monocyte ratio; PNR: Platelet/neutrophil ratio; SIRI: Systemic inflammation response index; SII: Systemic immune-inflammation index; HR: Hazard ratio; CI: Confidence interval

DISCUSSION

Although HCC is important among cancer-related deaths, few markers have been identified for predicting survival. Therefore, it is very significant to find inexpensive, appropriate and reliable markers to predict prognosis in HCC patients. As a prognostic marker in cancer patients worldwide, interest for systemic inflammation is increasing. In our study, only low SIRI value was found to be associated with increased survival in patients receiving sorafenib with HCC.

Activated monocytes secrete a large number of proinflammatory cytokines that cause tumor growth and progression of the tumor. Lymphocytes mediate the progression of cancer by the cell-mediated immune response. A high lymphocyte value and a low monocyte value have a positive effect on the immune-related response to the tumor. In a meta-analysis, it was shown that LMR had a good prognostic effect (8). In our study, there was no statistically significant difference for PFS and OS with values of 1.4 for LMR. However, when the LMR ≤1.4 and >1.4 group were compared, a positive 13-week difference in OS value was observed in favor of 1.4.

The neutrophil is the most common cell among the white blood cells and has the shortest half-life. It is the first cell to respond to trauma or attack. Therefore, it is involved in the formation of the immune response by contacting the tumor cells in the first order (9). In previous studies, NMR was examined in breast and prostate cancer patients in addition to other inflammation-related parameters in cancer (10, 11). To our knowledge, NMR was investigated first time with HCC in our study. The cut-off value was 5.2 and

there was a numerical difference in PFS and OS values in favor of <5.2, but there was no statistically significant difference. In the light of previous studies, low levels of neutrophil and monocyte were known as good parameters. Neutrophil secretes vascular endothelial growth factor (VEGF) and proteases, such as matrix metalloproteinase and elastase enzymes, causing cancer cells to invade and metastasize. Monocytes also increase cancer cell migration and inhibit immunity to the tumor cell (12). Although there was no statistically significant difference in our study, it was thought that the high level of monocyte value might be important for the response to the tumor.

As seen in NMR, low levels of neutrophils in PNR can cause better results in response to the tumor. Platelet-derived growth factor and VEGF, which are act as main factors on cell proliferation, angiogenesis and tumor metastasis, are secreted from platelets (13). These cells contain proinflammatory molecules and cytokines. Thus, they are involved in inflammatory and immune responses (14). In our study, when compared to PNR ≤44.8 to >44.8, OS benefit was observed in favor of >44.8 (33 versus 20 weeks, p=0.055).

SIRI is another simple, noninvasive prognostic marker and more comprehensive than other markers. In the study of Xu et al. (6), the relationship between survival and HCC was investigated. According to this study, the median OS was longer with low SIRI in patients receiving local treatment or sorafenib treatment. In our study, we have shown that there was a relationship with a low SIRI value (<2.2) and OS in the unresectable or metastatic patients (18 versus 38 weeks, p=0.005). There was also a difference between a low value of SIRI (<2.2) and PFS, but not statistically significant (12 versus 20 weeks, p=0.098).

SII is another comprehensive marker. Gardini et al. (15) reported a prognostic effect in 56 HCC patients receiving sorafenib treatment. It had been shown that high SII values had a negative effect on survival. In our study, PFS (13 versus 20 weeks) and OS (20 versus 31 weeks) values were found to be decreased in patients with cut-off value ≥523, but there was no statistically difference (p=0.086, p=0.209, respectively).

In our study, we have shown that LMR, SIRI and SII values have a prognostic effect in accordance with the literature. NMR and PNR values were first studied in patients with HCC in our study. According to the results of these two markers, we have shown that the low neutrophil value is more effective on prognosis than low monocyte and platelet values. Although the parameters calculated using two parameters were more practical, as shown in SIRI and SII, the results may be more effective with the use of more parameters. We found numerical differences between the groups. However, statistically significant difference was not observed.

In recent years, a considerable improvement has been made in immunotherapies for all of the cancer types. There is a need for biomarkers to predict the clinical efficacy of immune checkpoint inhibitors. In patients with lung cancer receiving immunotherapy, high neutrophil/lymphocyte ratio has been shown to be associated with poor prognosis (16). In another study, the pretreatment inflammation marker was reported to be associated with decreased survival and poor treatment response (17). Chronic inflammatory status has been shown to be associated with an increase in reg-

ulatory T-cell numbers, changes in control point expression and dendritic cell function (18). In view of chronic necro-inflammatory conditions and increased expression of the programmed cell death-1 (PD-1) and the programmed cell death-ligand1 (PD-L1) in HCC tumor formation, immunotherapeutic agents have been involved in HCC treatment management (19). Increased expression and upregulation of PD-1 was shown to be associated with the progression of HBV-associated cirrhosis to HCC and recurrence of the primary tumor after surgical resection (20, 21). Validation of PD-L1 expression and inflammatory markers may be important because they are an option as a viable test to help assess the patient's prognosis.

Our study had a few limitations, including its retrospective design and the comparatively small sample size. However, regardless of these restrictions, our results were the source of the importance of inflammatory markers. The use of these simply available and noninvasive markers in combination with others could help clinicians to predict the results.

CONCLUSION

Few markers have been identified for predicting survival. To our knowledge, NMR and PNR values were first studied in patients with HCC in our study. We found that only low SIRI value was associated with increased survival in patients receiving sorafenib with HCC. Our results showed that a simple, readily available and inexpensive biochemical marker might be useful in refining the prognosis. However, large prospective studies should be performed to verify whether inflammatory indexes have predictive and prognostic in HCC patients.

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