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Original Article

Can platelet lymphocyte ratio and neutrophil to lymphocyte ratio be used as prognostic predictors for hepatocellular carcinoma?

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Abstract

Aim: To investigate the predictive value of platelet to lymphocyte and neutrophil to lymphocyte ratios for hepatocellular carcinoma outcomes

Material and Methods: 37 hepatocellular carcinoma patients were retrospectively collected. All of the hepatocellular carcinoma patients were treated with conventional methods; transarterial chemoembolization, radiofrequency ablation or both. The patient and tumor characteristics, platelet to lymphocyte ratio and neutrophil to lymphocyte ratio were recorded. The association between platelet to lymphocyte ratio and neutrophil to lymphocyte ratio and tumor free survival rates, recurence rates, need of repeated conventional therapy were analyzed.

Results: The mean MELD (model for end stage liver disease) score of 37 hepatocellular carcinoma patients was 10.75±4.484 (mean age 59.59±17.23 years). High platelet to lymphocyte ratio and neutrophil to lymphocyte ratio were found to be associated with hepatocellular carcinoma recurrence ($p<0.01$). However platelet to lymphocyte ratio and neutrophil to lymphocyte ratio were irrevelant with tumor size and number ($p>0.05$). Platelet to lymphocyte ratio and neutrophil to lymphocyte ratios were significantly high in patients who had repated transarterial chemoembolisation, radiofrequency ablation or both ($p<0.01$). The disease free survival of these patients who need repeated procedures was 6.5 months and it was significantly lower than the other patients ($p<0.05$)

Conclusion: Platelet to lymphocyte ratio and neutrophil to lymphocyte ratio were found to be predictive for aggressive cancer behavior, so they can be used as markers for hepatocellular carcinoma

Keywords: Hepatocellular Carcinoma; Platelet To Lymphocyte Ratio; Neutrophil To Lymphocyte Ratio; Treatment Response; Recurrence.

INTRODUCTION

Hepatocellular carcinoma (HCC) is one of the most frequent (the fifth) malignity. It also has high mortality rates as being the third malignancy causing death (1). HCC management is challenging and requires a multidisciplinary approach. At the time of diagnosis most of the patients have advanced HCC with distant metastasis (2). Morbidity and mortality of HCC is frequent due to short disease free survivals. It is obvious that new predictive biomarkers are needed to improve prognosis and select the optimum treatment strategy. In recently published articles, systemic inflammation is reported to influence cancer progression (3). Here in this study, our aim is to evaluate the predictive value of platelet to lymphocyte ratio (PLR) and neutrophil to lymphocyte ratio (NLR) for HCC outcomes in patients who were treated with radiofrequency ablation (RF) and/or transarterial chemoembolization (TACE).

MATERIAL and METHODS

We retrospectively evaluated HCC patients who were diagnosed between April 2014 and April 2018. The clinical data of 37 HCC patients was analysed . All of the HCC patients were treated with conventional methods; transarterial chemoembolization, radiofrequency ablation or both (TACE, RF or both). The European Association for the study of the liver (EASL) guidelines are used for HCC diagnosis (4). To stage HCC, computed tomography (CT) or magnetic resonance imaging (MRI) was performed. The demographical data, etiology of liver disease, Child-Pugh scores, total tumor diameter, tumor number, pathologic evaluation, therapeutic tools, and tumor free survival rates,

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recurence rates, need of repeated conventional therapy were all recorded for each patient. The ratio of neutrophils and lymphocytes counts (NLR) and the ratio between the absolute blood count of platelets and lymphocytes (PLR) are calculated and recorded. According to our protocol,we prefer RF for tumors ≤2cm. We mostly prefer TACE+RF, especially for tumor diameter between 3 and 5cm. If the tumor is localised near to major vascular structures, portal hilus, diaphragma or other organs than we also prefer TACE+RF. For tumors>5cm, we performed TACE alone. After the treatment we followed up patients with MRI or CT for residual viable tumor screening. The viable tumor is defined as the area of enhancement during arterial phase as stated in EASL guidelines. If we diagnosed viability or recurence of HCC, we repeated the treatment. Follow up CTor MRI is performed at the first month of the treatment. The follow ups are repeated for every three month. Statistical analysis were performed with Chi-square test, Kaplan-Meier methods and data were given with Standard deviation (SD). The statistically significant p value was accepted as <0,05.

RESULTS

Between April 2016-April 2018; 37 patients were diagnosed and treated for HCC (mean age 59.5 years). Twenty-nine (78%) of them were ChildA, eight (22%) of them were ChildB (the mean MELD score was 10.7±4.4 (Table1). Among of these, 17 patients (43%) had liver disease due to hepatitis B (HBV). We followed up patients for 15.4 months. Radiologically 24 (64%) patients were within Milan criteria, 13 (36%) patients were beyond Milan criteria. All patients had TACE, RF or TACE+RF as conventional therapy. High PLR (70.1 ± 22.3 vs 162.9 ± 50.3; p<0.01) and NLR (2.68 ± 0.65 vs 4.88 ± 1.76; p<0.01) ratios were found to be associated with HCC recurrence (p<0.01) (Table1).

However, PLR and NLR ratios were irrevelant with tumor size and number (p>0.05). PLR and NLR ratios were significantly high in patients who had repeated TACE, RF or both (p<0.01). The disease free survival of these patients who need repeated procedures was 6.5 months and it was significantly lower than the other patients (p<0.05) (Table2). The disease free survival of the patients with high PLR (>125) and NLR (>4) were significantly worse than the others (Figure1-2). In addition to that; the disease free survival of the patients who need repeated procedures was significantly lower than the other patients.

Table 1. Demographic findings and tumor characteristics comparison of high and low PLR and NLR values

	High PLR and NLR		Low PLR and NLR		P
	PLR >125	NLR > 4	PLR < 125	NLR < 4	
Age (mean years)	60.14	58	57.88	60.10	> 0.05
Gender					
male	7	8	23	22	
female	2	1	5	6	
MELD score (mean)	11		10.6		> 0.05
Child score					> 0.05
Child A	7	8	22	21	
Child B	2	1	6	7	
Etiology of liver disease					> 0.05
HBV	4	5	13	12	
HCV	1	1	2	2	
Steatohepatitis	0	0	1	1	
cryptogenic	4	3	5	7	
others	0	0	7	7	
Type of the treatment					>0.05
RF	1	2	4	3	
TACE	6	5	19	20	
RF+TACE	2	2	5	5	
Repeated treatment	9	9	3	3	< 0.01
Tumor number					> 0.05
> 3	8	2	6	5	
1-3	1	7	22	23	
Tumor diameter					> 0.05
≤ 3 cm	1	3	7	6	
> 3 cm	8	6	21	23	
Recurrence	9	9	3	3	< 0.01
HCC Free survival					< 0.05
≤ 6 month	8	8	7	8	
> 6 month	1	1	21	20	
Total	9	9	28	28	

Table 2. The association of tumor related factors and treatment with HCC free survival

Tumor related characteristics	HCC free survival		p
	≤ 6 months	> 6 months	
Tumor number			> 0.05
> 3	12	18	
≤ 3	3	4	
Tumor diameter			> 0.05
>3 cm	11	18	
≤ 3 cm	4	4	
Therapy			> 0.05
Single	6	19	
Multiple	9	3	
Differentiation			< 0.01
Poor	9	4	
Moderate	4	3	
Well	2	8	

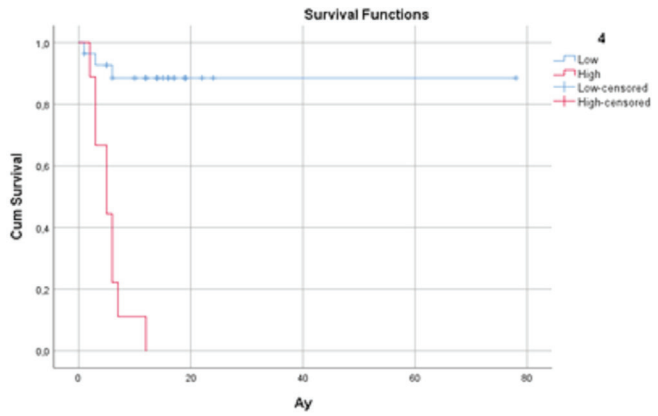

Figure 1. The disease free survival of the patients with high NLR (>4)

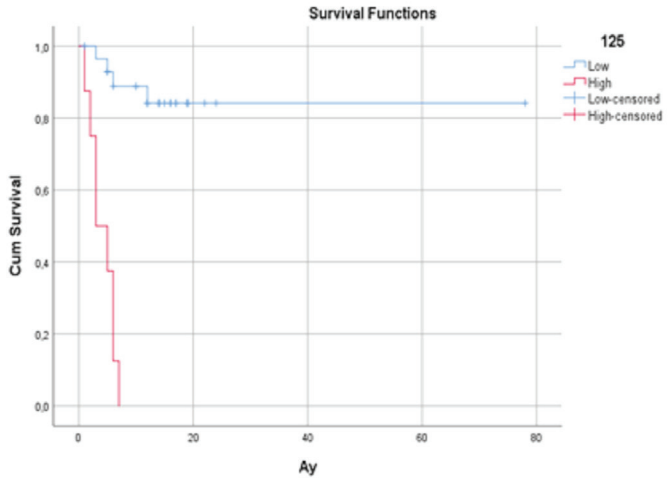

Figure 2. The disease free survival of the patients with high PLR (>125)

DISCUSSION

The treatment of HCC is challenging and requires multidisciplinary approach. At the time of diagnosis most of the patients have advanced HCC with distant metastasis (2). In HCC management; surgical resection (SR), radiofrequency ablation (RF), transarterial embolization (TACE) and liver transplantation (LT) can be applied. Liver transplantation is the only treatment option in which both tumor and the underlying cirrhotic liver disease are removed (5). Due to frequent recurrence and metastasis, HCC morbidity and mortality is high. Milan criteria were introduced in 1996 for optimal HCC outcome. Than it was realised that HCC patients beyond Milan criteria has the chance to be cured, Milan criteria were expanded to others to be used in management (6-8). These expanded current criteria are based on radiological imaging; HCC size, number and macrovascular invasion. However, radiologic evaluation is not enough for HCC behavior and recurrence following therapy (9). Therefore, it is obvious that new predictive biomarkers are needed to improve prognosis and select the optimum treatment strategy. In recently published articles, systemic inflammation is shown to promote cancer progression (3). Malignancy can trigger inflammation and cytokine activation. Inflammation markers like C-reactive protein, serum ferritin, neutrophil to lymphocyte ratio (NLR), lymphocyte to monocyte ratio (LMR), platelet to lymphocyte ratio (PLR) are shown to be prognostic indicators in various cancers (10-12). The correlation of HCC recurrence and these markers were reported in many studies. However, the results are conflicting due to heterogeneity in samples and treatment protocols. It is reported in many malignancies that high platelet to lymphocyte ratio (PLR) is reported to be associated with poor prognosis since platelets influence cancer progression and lymphocyte count declines in late stages of cancer. In addition to this, PLR is reported to correlate with HCC overall and disease free survival. Many studies reported that increased lymphocyte count indicates better cancer outcome. So, it is seen that neutrophils, platelets and lymphocytes can influence tumor outcome. A high NLR and PLR may show an inadequate immune response (13-14). Here in this study, we evaluated the predictive value of PLR and NLR for HCC outcomes in patients who were treated with TACE, RF or both. We found association between PLR and NLR ratios and HCC recurrence ($p<0.01$). As a consequence of that, PLR and NLR ratios were significantly high in patients who had repeated TACE, RF or both ($p<0.01$). The disease free survival of the patients with high PLR (>125) and NLR (>4) were significantly worse than the others. In addition to that; who the disease free survival of the patients need repeated procedures was 6.5 months and it was significantly lower than the other patients.

CONCLUSION

Our study revealed that NLR and PLR can predict HCC recurrence and survival. Although further studies involving larger patient series are required, it should be kept in mind

that; these two easy applicable tests can also provide information about prognosis of HCC.

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