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Original article

Impact of Immuno-Nutritional Status (Prognostic Nutritional Index, Neutrophil/Lymphocyte Ratio, Platelet/Lymphocyte Ratio) on Response to Transarterial Chemoembolization in Patients with Hepatocellular Carcinoma

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Abstract:

Background: Hepatocellular carcinoma (HCC) ranks as the fifth most common cancer worldwide. For individuals with intermediate-stage HCC, Transarterial chemoembolization (TACE) is a viable therapy option. So it is crucial to select patients to improve clinical outcomes in HCC patients after TACE. For patients with various cancers, immune health, including nutritional status and inflammatory state is essential. The prognostic nutritional index (PNI) is a multiparametric indicator that has been shown to accurately reflect patients' immune-inflammatory and nutritional status. The levels of neutrophil/lymphocyte ratio (NLR), and platelet-to-lymphocyte ratio (PLR) have been well-documented as systemic inflammation biomarkers that predict the prognosis of multiple neoplasms. **Aim:** This Study aimed to detect the impact of immuno-nutritional status in HCC patients treated with TACE. **Patients and methods:** Sixty patients with HCC who underwent TACE were enrolled and followed up in the Tropical Medicine Department, Tanta University. We excluded patients with prior locoregional therapy, systemic therapy and/or surgical intervention. At baseline and at 1& 3months post-procedure, laboratory criteria, tumor criteria were recorded, PNI, NLR PLR were calculated before TACE. Univariate and multivariate analyses were performed to identify factors affecting response to TACE. **Results:** Univariate analysis showed that high PNI, low NLR and low PLR were associated with a better response after TACE while multivariate analysis showed that only high PNI was an independent predictor of good response. **Conclusion:** Prognostic nutritional index can be used as baseline predictor of response before TACE.

Keywords: Hepatocellular carcinoma; prognostic nutritional index; neutrophil/lymphocyte ratio; platelet /lymphocyte ratio; TACE.

Introduction

Hepatocellular carcinoma is the fourth most prevalent cancer in Egypt [(1)] and the fifth most frequent cancer overall [(2)]. The number of patients in Egypt was more than doubled over a ten-year period, and health officials viewed HCC as one of the most challenging medical issues [(3).]

Over the past ten years, HCC management has undergone a substantial improvement. The optimum course of treatment is chosen based on the stage of the tumor and the potential benefits of different medications using the Barcelona Clinic Liver Cancer (BCLC) staging system [(4)].

Trans- arterial chemoembolization has been demonstrated to be the preferred approach for intermediate stage HCC, with overall survival ranging from 16 months without intervention to 20 months with TACE [(5)].

Multiple scores have been published as a result of the need to construct a predictive score for TACE overall survival; however, they have yet to be validated in various populations to determine their significance.

A variety of factors have been associated to the prognosis of HCC, including tumor diameter, disease stage, alpha fetoprotein (AFP), vascular invasion, presence of cirrhosis, and platelet count [(6, 7)]. There is considerable debate over the best criteria for predicting the course of HCC patients. There is accumulating evidence that preoperative nutritional and immunological conditions might predict outcome in several malignant tumors, including HCC.

The nutritional status of individuals with various solid tumors is closely connected with their clinical outcomes. Recent studies have found that nutritional factors can assist in predicting the prognosis of several malignancies, including colorectal [(8)], esophageal [(9)], and other kinds. To assess the risk of gastrointestinal surgery, Buzby et al. initially introduced the idea of the prognostic nutritional index (PNI). The PNI, based on the circulating peripheral blood lymphocyte count and serum albumin, has been used to assess the immune nutritional status of cancer patients. Albumin is regarded as an important component of liver function in HCC patients [(10)].

Inflammation is another well-known component that promotes the development, progression, and metastasis of cancer [(11)]. Chronic inflammation and cirrhosis are the two key factors that lead to the development of HCC [(12)]. Survival and recurrence after treatment for HCC are influenced by the inflammatory responses and immunological state of the patients [(13)].

The worst prognosis for cancer patients has been linked to systemic inflammation, according to studies [(14)].

An increased level of inflammation, including the neutrophil to lymphocyte ratio (NLR) and platelet to lymphocyte ratio (PLR), has been associated with poor survival in HCC patients [(15)].

According to previous research, pretreatment NLRs in HCC patients can predict tumor recurrence and survival [(16, 17)].

However, there is disagreement over the precise function of NLR in HCC patients across studies due to many factors, as varying sample numbers, study methodology, and regional differences [(18)]. In some studies, there is a strong correlation between higher NLR and a worse prognosis, but not in others [(19)].

A poor prognosis has been associated with elevated PLR (platelet to lymphocyte ratio) in a number of cancers, including colorectal cancer [20], breast cancer [21], and gastric cancer [22]. Investigations examining the predictive value of PLR in HCC have also been carried out [23-25].

So, this study aimed to detect the role of immune nutritional status including prognostic nutritional index, neutrophil/lymphocyte ratio, and platelet/lymphocyte ratio among hepatocellular cancer patients who underwent trans-arterial chemoembolization.

Patients and Methods:

This study was a prospective study that included 60 patients with hepatocellular carcinoma From November 2021 to November 2022 who underwent trans-arterial chemoembolization and were followed in Tropical Medicine Department, Tanta University.

Patients with Child-Pugh class A or B (≤7) [26]; an ECOG (Eastern Cooperative Oncology Group) performance status score ≤1 [27], had no venous invasion or extra hepatic metastasis; and had not received any treatment for HCC before, underwent TACE and were included in this study while patients with prior locoregional therapy, systemic therapy and/or surgical intervention were excluded from the study.

The response to treatment was evaluated by a single professionally trained radiologist using mRECIST criteria (modified Response Evaluation Criteria in Solid Tumours). In all lesions, a complete response (CR) was characterized as the absence of intra-tumoral arterial contrast enhancement. When there was an evident reduction of more than 30% in the overall diameter of viable lesions by arterial phase enhancement, this was referred to as a partial response (PR). The two of them were collectively known as the "responders" group. The occurrence of a total diameter increases of more than 20% in viable lesions due to arterial phase enhancement was referred to as progressive disease (PD). Patients were considered to have a stable disease (SD) if they could not be divided into any of these groups. These two were referred to as non-responders [28].

All patients were subjected to full history taking, thorough clinical examination, laboratory investigations (before and 1&3 month after TACE) including: Liver function tests, including: ALT, AST, bilirubin level, albumin level, prothrombin time and activity, CBC, alpha fetoprotein (AFP) and Triphasic CT with contrast before and 1,3 months after TACE.

Prognostic nutritional index was calculated before TACE according to the following formula: 10 × serum albumin (g/dl) + 0.005 × total lymphocyte count (per mm3) [29]. Neutrophil /lymphocyte ratio and platelet /lymphocyte ratio were calculated before and 1 month after TACE.

An informed consent was obtained from all individual participants included in the study.

The study was approved by the Ethical Committee of Faculty of Medicine Tanta University by approval code 36086/11/22.

Statistical analysis

Data was fed to the computer and analyzed using IBM SPSS software package version 20.0. (Armonk, NY: IBM Corp). Continuous variables were presented as means ± standard deviations or median with range. Categorical variables were presented as numbers and percentages. Differences between groups were analyzed using independent samples t-tests for

continuous variables and Chi-squared tests for categorical variables. Roc curve and Logistic Regression tests were used to estimate the odds ratios (OR) and 95% confidence intervals (CI) for tumor response. The significance of the obtained results was judged at the 5% level.

Results

This study included 60 patients with HCC who underwent TACE for the first time [male/female34/26; age, 61.3±5.8 (48-70) years]; the etiology for cirrhosis was HCV in 43 patients and HBV in17 patients, as shown in table (1).

The study included 48 patients with child A (80%) and 12 patient with child B 7 (20%), the number of focal lesions were single in 31 patients (51.7%) ,2 in 14 patients (23.3%) and multiple in 15 patients (25%).Size of focal lesions was <5 cm in 34 patients (56.67%) and ≥5cm in 26 patients(43.33%).

As regard to biochemical data few days before and 1 month after TACE, there was no significant difference except for HB level which was higher before TACE than after (mean 12.994, 12.690 g/dl), respectively, *p* value <0.001. Also, bilirubin was significantly higher before TACE than after (1.039, 0.916), respectively, *p* value 0.011.

Prognostic nutritional index was calculated before TACE and the results were 46.986±9.914 with significant positive correlation between PNI and male gender, Child-Pugh class A, HB level, WBCs, platelet count and albumin level. On the contrary, low PNI was observed in patients with higher AFP (p<0.001), high total bilirubin, high NLR and PLR as shown in table 2.

There was a significant difference in PNI between patients who achieved response than non-responders (51.856, and 41.420 respectively) with *p* value <0.001 and cut off level of >42.83, sensitivity (93.75) specificity (64.29), PPV (positive predictive value):٧٥.٠ , NPV (negative predictive value):٩٠.٠ , AUC (area under curve): 0.815 (Figure, 1).

As regards NLR there was no significant difference in its level before and after TACE. Median NLR of the baseline data was 2.16. We took it as a threshold for preoperative NLR to distinguish between high (NLR >2.16) and low (NLR ≤2.16) NLR.

Of the 60 patients, 31 had NLR value ≤2.16. Clinical and treatment data in the low (≤2.16) NLR and high (>2.16) NLR groups were compared in table 3. Compared with the patients in low NLR group, those with high NLR had a lower HB level, platelet and total bilirubin and higher AFP level (p<0.05) (Table, 3).

Table 1: Baseline characteristics of the patients.

Variable		N	%
Age(years)	**Range**	48-70	
	Mean ±SD	61.283±5.770	
Etiology	**HBV**	17	28.33
	HCV	43	71.67
Sex	**Female**	26	43.33
	Male	34	56.67
No of focal	**Single**	31	51.67
	Two	14	23.33
	Multiple	15	25.00
Size of tumor (cm)	**Range**	1.5-12	
	Mean ±SD	4.555±2.370	
Child score	**A**	48	80.00
	B7	12	20.00
Tumor response	**No**	28	46.67
	Yes	32	53.33

HBV: hepatitis B virus; HCV: hepatitis C virus; SD: standard deviation

Table 2: PNI and different parameters.

			PNI			T-Test	
		N	**Mean**	**±**	**SD**	**t**	**P-value**
Age(years)	**<60 Years**	18	49.374	±	13.050	1.227	0.225
	>=60 Years	42	45.962	±	8.200		
Sex	**Female**	26	42.576	±	6.581	-3.248	0.002*
	Male	34	50.358	±	10.764		
Size(cm)	**<5 cm**	34	47.484	±	9.387	0.442	0.660
	>=5 cm	26	46.335	±	10.717		
Child	**A**	48	49.072	±	8.800	3.570	0.001*
	B	12	38.640	±	10.061		
Etiology	**HBV**	17	45.214	±	9.673	-0.869	0.388
	HCV	43	47.687	±	10.032		
		ANOVA				**F**	**P-value**
No of focal	**Single**	31	47.650	±	6.492	0.424	0.656
	Two	14	47.724	±	12.421		
	Multiple	15	44.925	±	13.211		

Correlations

	PNI	
	R	**P-value**
HB (g/dl)	0.461	<0.001*
WBC / µL of blood	0.297	0.021*
PLT / µL of blood	0.292	0.023*
Albumin (g/dl)	0.782	<0.001*
Bilirubin (mg/dl)	-0.064	0.627
PLR	-0.402	0.001*
NLR	-0.572	<0.001*
AFP (ng/mL)	-0.443	<0.001*

HBV: hepatitis B virus; HCV: hepatitis C virus; HB :hemoglobin level; WBC :white blood cells; PLT: platelets; PLR :platelet/ lymphocyte ratio; NLR: neutrophile/ lymphocyte ratio; AFP: alpha-feto protein; statistical test used: T test and Anova; *r*= pearson correlation* $p<0.05$: statistically significant.

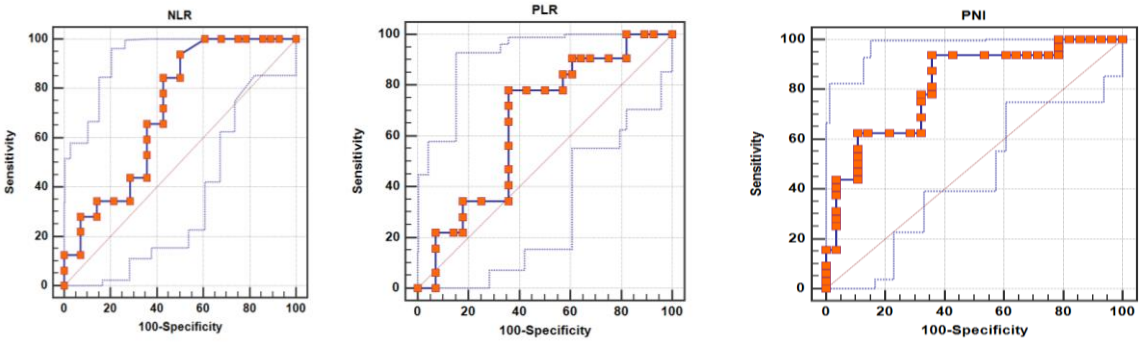

Figure 1: ROC curve of PNI, NLR and PNI tumor response.

Table 3: Baseline NLR and different baseline parameters.

		Baseline NLR				
		Low (≤2.16)		High (>2.16)		
		N	%	N	%	*p*-value
Age(years)	**<60 Years**	10	32.26	8	27.59	0.693
	>=60 Years	21	67.74	21	72.41	
Sex	**Female**	8	25.81	18	62.07	0.005*
	Male	23	74.19	11	37.93	
Etiology	**HBV**	9	29.03	8	27.59	0.901
	HCV	22	70.97	21	72.41	
No of focal	**Single**	19	61.29	12	41.38	0.203
	Two	7	22.58	7	24.14	
	Multiple	5	16.13	10	34.48	
Size of tumor (cm)	**<5 cm**	14	45.16	20	68.97	0.063
	>=5 cm	17	54.84	9	31.03	
Tumor response	**No**	10	32.26	18	62.07	0.021*
	Yes	21	67.74	11	37.93	
Child	**A**	25	80.65	23	79.31	0.897
	B	6	19.35	6	20.69	
	Mean ±SD			**Mean ±SD**		
HB(g/dl)	13.733	±	1.293	12.205	± 1.307	<0.001*
WBC / µL of blood	5376.548	±	2434.935	5076.517	± 2837.502	0.661
PLT / µL of blood	190967.742	±	82577.432	136137.931	± 96774.304	0.021*
Albumin (g/dl)	3.916	±	0.641	3.664	± 0.717	0.156
Bilirubin (mg/dl)	1.202	±	0.621	0.866	± 0.429	0.018*
AFP (ng/mL)	47.096	±	157.937	823.591	± 1307.098	0.002*

HB: hemoglobin level; WBC: white blood cells; PLT: platelets; PLR: platelet/ lymphocyte ratio; NLR: neutrophil/ lymphocyte ratio; AFP: alpha-feto protein; * $p \leq 0.001$: statistically significant; SD: Standard deviation; Statistical test used: Chi-Square and T test.

As regard to tumor response, patients with low NLR were associated with good response than patients with high N/L ratio, p value 0.021. And cut off level of ≤2.77, sensitivity (93.75) specificity (50), PPV: 68.2, NPV: 87.5, AUC: 0.713 (Figure, 1; table, 5).

On the other hand, as regard to PLR there was no significant difference in its level before and after TACE. Median PLR of the baseline data was 86.11. Patients with PLR ≤ 86.11 were assigned to the low PLR group, while patients with PLR> 86.11 were assigned to the high PLR group.

Of the 60 patients, 31 had PLR value ≤86.11. Clinical and treatment data in the low (≤86.11) PLR and high (>86.11) PLR

groups were compared in table 4. Compared with the patients in low PLR group, those with high PLR had a lower HB level (p<0.05).

Patients with low P/L ratio were associated with better response than patients with high P/L ratio, p value 0.021. And cut off level of ≤97.58, sensitivity (78.12) specificity (64.29), PPV: 71.4, NPV: 72.0, AUC: 0.655 (Figure, 1; table, 5).

Table 6, shows that five predictors in the univariate analysis were significantly associated with objective response to TACE: size of focal lesion, AFP, PNI, PLR, NLR while in the multivariate analysis, there were only two independent predictors of response: low AFP and high PNI.

Table 4: Baseline PLR and different baseline parameters.

		Baseline PLR				
		Low (≤86.11)		High (>86.11)		
		N	%	N	%	*p*-value
Age(years)	<60 Years	6	19.35	12	41.38	0.063
	>=60 Years	25	80.65	17	58.62	
Sex	Female	10	32.26	16	55.17	0.073
	Male	21	67.74	13	44.83	
Etiology	HBV	8	25.81	9	31.03	0.653
	HCV	23	74.19	20	68.97	
No of focal	Single	17	54.84	14	48.28	0.865
	Two	7	22.58	7	24.14	
	Multiple	7	22.58	8	27.59	
Size of tumor(cm)	<5 cm	19	61.29	15	51.72	0.455
	>=5 cm	12	38.71	14	48.28	
Tumor response	No	10	32.26	18	62.07	0.021*
	Yes	21	67.74	11	37.93	
Child	A	26	83.87	22	75.86	0.438
	B	5	16.13	7	24.14	
HB (g/dl)	13.469	± 1.383	12.487	± 1.478		<0.001*
WBC/ µL of blood	5748.74	± 2951.829	4678.655	± 2122.159		0.661
PLT / µL of blood	190967.742	± 82577.432	136137.931	± 96774.304		0.062
Albumin (g/dl)	3.884	± 0.566	3.698	± 0.792		0.298
Bilirubin (mg/dl)	1.159	± 0.629	0.912	± 0.449		0.087
AFP (ng/ml)	261.182	± 873.677	594.740	± 1086.511		0.194

HB: hemoglobin level; WBC: white blood cells; PLT:platelets;PLR:platelet/ lymphocyte ratio; NLR:neutrophile/ lymphocyte ratio; AFP:alpha-feto protein ; * p≤0.05: statistically significant; SD: Standared deviation; Statistical test used: Chi-Square and T test.

Table 5: ROC curve of PNI, NLR, PLR and tumor response.

	ROC curve between responders and non-responders					
	Cutoff	**Sens.**	**Spec.**	**PPV**	**NPV**	**Accuracy**
NLR	≤2.77	93.75	50.0	68.2	87.5	**71.3%**
PLR	≤97.58	78.12	64.29	71.4	72.0	**65.5%**
PNI	>42.83	93.75	64.29	75.0	90.0	81.5%

NLR: neutrophil/ lymphocyte ratio ; PLR:platelet/ lymphocyte ratio;PNI:prognostic nutritional index;ROC: receiver operating characteristic curve;AUC:area under curve.

Table 6: Univariate and multivariate analysis of variables associated with good response.

	Univariate analysis		**multivariate analysis**	
	95%CI	**P value**	**95%CI**	***p* value**
Age (years)	0.005	0.967	0.006	0.51
Size of tumor(cm)	-0.3278	0.01*	-0.113	4.02
No of tumors	-0.219	0.09276	0.096	0.221
Child score	-0.1719	0.1892	0.058	0.427
AFP(ng/ml)	-0.442	< 0.001*	-0.0002	0.008*
PNI	0.5296	< 0.001*	0.027	< 0.001*
NLR	-0.4202	< 0.001*	-0.036	0.576
PLR	-0.2634	0.042*	0.0009	0.059

PLR: platelet/ lymphocyte ratio; NLR: neutrophil/ lymphocyte ratio; AFP: alpha-feto protein ;PNI: prognostic nutritional index; statistically significant (p value < 0.05), CI = confidence interval; statistical test: multivariate regression analysis

Discussion:

HCC is one of the most common malignant tumors in the world, accounting for the fourth most common cause of cancer-related death [(1)]. Only 20% of HCC patients are eligible for intervention with a liver transplant or surgery because most patients are discovered late [(2)]. Making predictive biomarkers is therefore essential for enhancing patient care for this condition.

Using indicators of systemic inflammation, such as CRP levels, neutrophil/lymphocyte ratios, lymphocyte-to-monocyte ratios, and platelet-to-lymphocyte ratios, one can predict the prognosis of neoplastic disorders including lung carcinoma [(30)], gastric carcinoma [(31)], and liver carcinoma [(32)].

The prognosis of tumor patients also depends on the host condition, such as the patient's nutritional status, in addition to tumor condition and immunological factors [(33)].

The immune-inflammatory and nutritional status of patients have been shown to be reflected by the prognostic nutritional index (PNI), a multiparametric indicator based on peripheral lymphocyte count and serum albumin, even though in HCC it more specifically reflects the liver dysfunction that underlies this cancer [(34)].

This study aimed to evaluate the role of PNI as an immune-nutritional indicator, and neutrophil/lymphocyte ratio (NLR) and platelet lymphocyte ratio (PLR) which reflects the inflammatory status, both of which are of high accuracy, low cost, as predictors of response for TACE.

The study included 60 patients with HCC who underwent TACE for the first time [male/female34/26; age, 61.3±5.8 (48-70) years]. , the etiology for cirrhosis was HCV in 43 patients and HBV in17 patients, 48 patients with child A (80%) and 12 patient with child B 7 (20%), the number of focal lesions were single in 31 patients (51.7%) ,2 in 14 patients (23.3%)and multiple in 15 patients (25%).Size of focal lesions was <5 cm in 34 patients (56.67%) and ≥5cm in 26 patients(43.33%).

The response after TACE was described according to MRECIST criteria. Based on their tumor response 3 months after TACE, 32 patients (53.33%) were responders while 28(46.67%) patients were non responders.

PNI was found to be higher among patients with tumor response according to MRECIST criteria; these results were in consistence with Müller, et al (2021) who showed that PNI had highly predictive and prognostic factors [(35)]. Also, Man, et al

(2018) showed that patients with a lower preoperative PNI had a worse prognosis [36].

In this study, high PNI was associated with child A and low AFP. This is in consistence with Li, et al (2021) who found that high PNI (>45) was more frequent in patients with Child-Pugh class A (p<0.001), ALT and AST<40 IU/L (p=0.001 and p<0.001, respectively), TBIL<21μmol/L (p=0.012), no vascular invasion (p<0.001) and AFP <200 [37]. Other studies showed also that low PNI group has a higher serum AFP than high PNI group [29, 38, ,39].

According to univariate analysis, low NLR and low PLR were linked to a good response in terms of inflammatory indicators. This finding was in consistence with Cruz, et al (2019) who found that higher baseline NLR is linked to higher rates of HCC tumor progression at 2-month follow-up imaging following TACE [40]. Also, Schobert, et al (2020) showed that high NLR was independently associated with worse tumor response after DEB-TACE (Drug-eluting bead transarterial chemoembolization) [41]. Other studies showed also that high NLR was a predictor of poor survival in patients with unresectable intermediate- or advanced-stage HCC who received TACE [42-46].

But, multivariate analysis showed that they were not independent predictors of response, Shayegan et al, (2023) found that baseline NLR did not show significant results while NLR level more than 2.6 after treatment is believed to be able to discriminate non-responders [46]. The increase in NLR after treatment, not pretreatment NLR indicated favorable outcomes in some studies and poor outcomes in other studies [47, 48].

Furthermore, elevated NLR is associated with elevated AFP, this was in consistent with Min et al, (2017) who found that elevated NLR is associated with unfavorable tumor characteristics including the presence of multiple tumors, vascular invasion, elevated AFP, cirrhosis, and presence of hepatitis B surface antigen [49]. Also, it was consistent with other studies as Wong et al, (2019) [50].

Univariate analysis in the study showed also that low PLR was associated with better response. Schobert et al, (2020) reported that PLR is a tumor response predictor in patients with HCC having undergone DEB-TACE [41]. Wang et al, (2019) suggest that in HCC patients undergoing TACE, the pretreatment platelet count is a useful biomarker for predicting the prognostic outcomes [50].While multivariate analysis showed that PLR was not an independent predictor of response this was consistent with Wang TC, et al(2021) who concluded that, in the univariate study, TACE response was associated with NLR, PLR, and SIRI (Systemic Inflammation Response Index); in the multivariate analysis, TACE response was significantly correlated with SIRI alone. [51].

Tumor response was found to be significantly correlated with male gender, size of focal lesion <5 cm, baseline albumin, and lower AFP level. Jeong, et al (2017) found that in patients who received TACE as a first-line therapy, tumor size (≤ 5 cm) and single nodularity were predictive factors for CR, while increased levels of AFP (> 20 ng/mL) were prognostic of recurrence after CR[52]. A high probability of HCC recurrence after complete ablation was significantly related to male sex, AFP level (> 10 mg/mL), and multiple tumors, according to a second

analysis of 357 patients with HCC who received radiofrequency ablation for primary HCC [(53)].

So the results showed that only baseline PNI and not NLR and PLR was independent predictor of tumor response by multivariate regression analysis as high PNI was associated with better response after TACE ,($p<0.001$), with cut off level of >42.83 .

Conclusion

In conclusion, TACE is now an essential component of treating HCC. To prevent undesirable results and choose the best-responding patients during pre-operative sessions, efforts should be made in clinical and scientific communities to better understand the tumoral behavior and associated factors. PNI can be used as an independent predictor of response before TACE. Predictive results from larger studies and multiple centers with follow-up information and confounding factor adjustments may be more reliable.

Abbreviations:

HCC: Hepatocellular carcinoma.
TACE: trans arterial chemoembolization.
AFP: alpha feto protein.
HB: haemoglobin.
WBCs: white blood cells
BCLC: Barcelona clinic liver cancer
HBV infection: hepatitis B virus infection
HCV infection: hepatitis C virus infection
PNI: prognostic nutritional index
NLR: neutrophil/lymphocyte ratio
PLR: platelet /lymphocyte ration
mRECIST: modified Response Evaluation Criteria in Solid Tumours.
ECOG: Eastern Cooperative Oncology Group performance status.
AUC: area under curve.
ROC curve: receiver operating characteristic curve.

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