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Are the Neutrophil-to-Lymphocyte and Platelet-to-Lymphocyte Ratios Reliable Predictive Factors of Response and Overall Survival in Egyptian Hepatocellular Cancer Patients Treated with Transarterial Chemoembolization?

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Abstract

Background: Transarterial chemoembolization is approved treatment for hepatocellular carcinoma. It is difficult to anticipate how a tumor will respond to therapy so finding a baseline biomarker may help tailor treatment and identify patients who need frequent follow-up or more aggressive treatment.

Inflammatory ratios such as neutrophil-to-lymphocyte (NLR) and platelet-to-lymphocyte (PLR), may be used as quantitative biomarkers for the assessment of individual tumors.

Aim of Study: The aim of this study is to analyze the predictive relevance of pretreatment NLR and PLR in patients with HCC undergoing trans-arterial chemoembolization. This is one of few studies that evaluates these factors in an Egyptian population with HCC.

Patients and Methods: This is a retrospective study on 57 patients with HCC from Kasr Al-Ainy Hospital, Cairo University, Egypt who underwent TACE from 2020 till 2023.

Data included laboratory reports such as CBC, liver functions, coagulation profile and alpha fetoprotein as well as demographic data.

Multiphasic imaging was done to assess response using mRECIST criteria. From patients' initial visits to the HCC clinic until their death or end of study, overall survival was determined.

Results: Demographic criteria showed an average age of 60.51 years with male predominance. NLR and PLR showed a median of 1.97 and 95.08 respectively.

Predictors of response to therapy and survival showed that only poor performance status was a predictor of no response to TACE. However, NLR and PLR were not shown to have a direct association with either response nor survival. In addition, ROC curves were plotted to detect an estimate cut off for both ratios for prediction of response and survival and the maximum scores obtained for prediction of mortality were 0.536 and 0.533 for NLR and PLR respectively while area under curve for prediction of response was 0.535 and 0.506 for NLR and PLR respectively.

Conclusion: The current study shows no value for NLR and PLR in prediction of survival or response to TACE in patients with HCC.

Key Words: *HCC – TACE – NLR – PLR.*

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Introduction

INTRA-ARTERIAL therapies, like transarterial chemoembolization (TACE), are guideline-approved treatments for hepatocellular carcinoma (HCC), the sixth most common cancer with steadily rising incidence rates worldwide **[1,2],** most of whom are diagnosed at intermediate to advanced disease stages and therefore no longer responsive to curative therapies **[3,4].**

Because some patients need several treatment sessions to achieve a treatment response and others continue to advance despite therapy, it is difficult to anticipate how a tumor will respond to intra-arterial therapy in the future. Finding baseline blood or imaging biomarkers may help tailor treatment and identify a subset of HCC patients who need more frequent follow-up or more aggressive treatment **[5].**

Apart from imaging characteristics, HCC's dynamic and adaptive nature and its interaction with the tumor microenvironment (TME) result in a high degree of tumor heterogeneity and may be crucial in determining how susceptible cancer cells are to nonsurgical treatments like TACE **[6].**

In particular, it is thought that chronic liver illnesses create an environment that is conducive to inflammation, which facilitates the development and spread of hepatic tumors [7].

Although the anti-tumoral inflammatory response includes tumor-infiltrating lymphocytes, neutrophils and a high platelet count inhibit the activity of anti-tumoral immune cells and encourage neoangiogenesis through the release of vascular endothelial growth factor (VEGF) [8].

Therefore, inflammatory ratios that have been connected to tumor angiogenesis, immune evasion, and metastatic illness, such as neutrophil-to-lymphocyte (NLR) and platelet-to-lymphocyte (PLR), may be used as quantitative biomarkers for the assessment of individual tumors [9].

It is still unknown what the ideal NLR and PLR are for predicting how well HCC treatment would work. More knowledge of the possible predictive significance of NLR and PLR may help interventional radiologists choose the kind of therapy and follow-up, as intra-arterial therapies are frequently used in this patient population. In this study, the predictive relevance of pretreatment NLR and PLR in patients with HCC undergoing trans-arterial chemoembolization will be analyzed and compared. This is one of few studies that evaluates these factors in an Egyptian population with HCC.

Patients and Methods

This is a retrospective cross-sectional study on 57 Adult Egyptian patients (>18 years of age) from both genders, diagnosed with HCC who underwent TACE therapy in the period from January 2020 till January 2023.

This study was conducted with the Declaration of Helsinki.

Inclusion and exclusion criteria were as follows:

Inclusion criteria:

- Age from 18-70 years.
- Patients diagnosed with HCC and were fit for receiving treatment via TACE after MDT decision, and for whom both clinical and laboratory data are complete.
- HCC was diagnosed according to the criteria in the guidelines of the American Association for the study of Liver Diseases (AASLD), using multiphasic computerized tomography (CT) or magnetic resonance imaging (MRI) techniques and alpha-fetoprotein (AFP) [10], and is categorized according to BCLC staging system into very early, early, intermediate, advanced or terminal stages [11].

Exclusion criteria:

- Missing Laboratory or clinical data.

Data gathered included laboratory reports such as complete blood count, liver function tests, coagulation profile and alpha fetoprotein as well as clinical and medication histories, and demographic data. NLR and PLR were computed using the neutrophil, platelet and lymphocyte counts.

Triphasic CT abdomen or Dynamic MRI abdomen was done at intervals of 3 months in the 1st year following TACE then every 6 months thereafter to assess the response.

An expert radiologist assessed the response to treatment using the mRECIST criteria [12]. The absence of intratumoral arterial contrast enhancement in every lesion was considered a complete response (CR) based on the mRECIST criteria.

Likewise, a reduction of greater than 30% in the total diameters of viable lesions with arterial phase enhancement was considered a partial response (PR). If the total diameters of viable lesions with arterial phase enhancement increased by more than 20%, progressive disease (PD) was taken into consideration. Patients were deemed to have stable disease (SD) if they did not fall into any of these categories.

From the time of the patients' initial visits to the multidisciplinary HCC clinic until their death or the end of the study, the overall survival was determined. The log-rank test was used to compare the survival curves that were plotted using the Kaplan-Meier method.

Statistical analysis:

Data were coded and entered using the statistical package for the Social Sciences (SPSS) version 28 (IBM Corp., Armonk, NY, USA). Data was summarized using mean, standard deviation, median, minimum and maximum in quantitative data and using frequency (count) and relative frequency (percentage) for categorical data. Comparisons between quantitative variables were done using the non-parametric Mann-Whitney tests [13]. For comparing categorical data, Chi square ($\chi 2$) test was performed. Exact test was used instead when the expected frequency is less than 5 [14]. Correlations between quantitative variables were done using Spearman correlation coefficient [15]. ROC curve was constructed with area under curve analysis performed to detect best cutoff value of PLR and NLR for detection of response and mortality. Logistic regression was done to detect independent predictors of mortality [16]. Survival curves were plotted by the Kaplan-Meier method and compared using the log-rank test [17]. *p*-values less than 0.05 were considered as statistically significant.

Results

Demographic criteria of the studied population is shown in Table (1) showing an average age of 60.51 years with male predominance. Almost all patients had an underlying cirrhotic liver apart from only 1 patient who developed HCC on top of normal liver.

The majority of the studied population were shown to have a compensated or mildly decompensated liver status as shown through Child score where 93% of patients were classified as Child A, in addition, alpha fetoprotein levels were less than 400 in 78.9% of patients reflecting the fact that TACE is usually indicated in this group of patients. The main etiology of liver disease in the studied population were shown to be due to hepatitis C virus in 81.8% while hepatitis B contributed to the underlying liver disease in 3.6% of patients and the remaining patients were shown to have non viral HCC (18.2%).

Neutrophil to lymphocyte and Platelet to lymphocyte ratios showed a median of 1.97 and 95.08 respectively (Table 1).

Table (1): Deomgraphic and laboratory profile of studied population.

	Mean	Standard Deviation	Median	Minimum	Maximum
Age (years)	60.51	8.69	62.00	30.00	75.00
Hemoglobin (gm/dl)	12.59	2.03	12.50	7.30	17.30
White blood cells ($x10^3/\mu l$)	5.85	2.41	5.40	2.20	11.00
Neutrophil count %	58.61	14.66	59.00	15.00	93.00
Absolute Neutrophil Count	3.53	1.93	3.22	0.51	7.59
Lymphocytes count %	29.15	11.47	28.00	6.00	55.00
Absolute Lymphocyte Count	1.66	0.84	1.57	0.27	3.76
Platelets ($x10^3/\mu l$)	165.16	83.69	150.00	40.00	357.00
NLR	2.65	2.15	1.97	0.34	13.68
PLR	135.41	159.59	95.08	24.42	1103.70
Total bilirubin (mg/dl)	1.03	0.60	0.90	0.20	3.60
Alanine Transferase (ALT) (U/L)	41.35	31.82	31.00	5.00	195.00
Aspartate Transferase (AST) (U/L)	51.08	45.32	37.00	15.00	275.00
Albumin (gm/dl)	3.84	0.61	3.80	2.70	5.73
Creatinine (mg/dl)	0.93	0.23	0.90	0.20	1.60
International Normalized Ratio	1.15	0.16	1.10	0.95	1.70
Focal lesion size or size of largest lesion if 2 or multiple	4.40	2.01	4.00	1.40	12.00

		Count	%
Gender	Male	45	78.9%
	Female	12	21.1%
Smoker	Yes	19	33.3%
	No	38	66.7%
Diabetes Mellitus	Yes	21	36.8%
	N0	36	63.2%
Performance status	0	31	54.4%
	1	23	40.4%
	2	3	5.3%
Liver	Cirrhotic	56	98.2%
	Not cirrhotic	1	1.8%
NLR	<1.97	29	50.9%
	>1.97	28	49.1%
PLR	<95.08	28	49.1%
	>95.08	29	50.9%
Etiology of liver disease	Hepatitis C	45	81.8%
	Hepatitis B	2	3.6%
	Non Viral HCC	10	18.2%
Alpha Fetoprotein (U/L)	<400	45	78.9%
	>400	12	21.1%
Number of tumor lesions	Single	28	49.1%
	Two	8	14.0%
	Multiple	21	36.8%
CHILD Score	A	52	91.2%
	B	4	7.0%
	Not cirrhotic	1	1.8%

Response rate after TACE was assessed using the modified RECIST criteria where almost three quarters of patients showed positive response whether complete in 52.63% of patients or partial in 26.32% while around 21% failed to respond to therapy showing progressive disease pattern (Fig. 1). The median overall survival in the studied group was 25 months (Fig. 2).

Predictors of response to therapy and survival were analyzed using the available data and it was shown that only poor performance status was a predictor of no response to TACE and higher ALT and lower albumin levels were associated with poor survival rates. However, NLR and PLR were not shown to have a direct association with either response nor survival in the studied population (Tables 2,3). In addition, ROC curves were plotted to detect an estimate cut off for both ratios for prediction of response and survival and the maximum scores obtained for prediciton of mortality were area under curve of 0.536 and 0.533 for NLR and PLR respectively while area under curve for prediciton of response was 0.535 and 0.506 for NLR and PLR respectively (Figs. 3,4).

Neutrophil to lymphocyte and platelet to lymphocyte ratios were compared to different laboratory parameters and it was shown that PLR was significantly higher in those with better liver functions in the form of higher albumin, lower bilirubin and INR levels. On the other hand, there was no significant difference between NLR and all parameters studied (Table 4).

Table (2): Correlation between demographics and laboratory profile with response.

	Response										*p*-value
	Yes					No					
	Mean	SD	Median	Minimum	Maximum	Mean	SD	Median	Minimum	Maximum	
- Age (years)	60.89	8.61	62.00	30.00	75.00	59.08	9.24	59.00	45.00	73.00	0.462
- Hemoglobin (gm/dl)	12.32	1.93	12.40	7.30	17.00	13.58	2.16	13.85	10.60	17.30	0.098
- White blood cells ($x10^3/_1$,l)	5.98	2.51	6.00	2.20	11.00	5.34	2.03	4.68	3.20	8.60	0.570
- Neutrophil count %	58.71	13.76	58.70	16.40	93.00	58.25	18.32	66.50	15.00	80.00	0.761
- Absolute Neutrophil Count	3.60	1.96	3.34	1.05	7.59	3.26	1.89	2.72	0.51	6.48	0.639
- Lymphocytes count %	29.66	11.16	30.00	6.00	55.00	27.25	12.91	22.00	12.00	52.00	0.347
- Absolute Lymphocyte Count	1.73	0.86	1.60	0.27	3.76	1.39	0.69	1.34	0.41	2.65	0.225
- Platelets ($x10^3/_1$,l)	171.80	86.03	152.00	40.00	357.00	140.25	72.10	132.00	45.00	315.00	0.282
- NLR	2.66	2.29	1.88	0.34	13.68	2.63	1.58	2.80	0.71	6.15	0.710
- PLR	138.09	174.35	95.42	24.42	1103.70	125.33	89.06	86.49	35.07	342.70	0.953
- Total bilirubin (mg/dl)	1.00	0.58	0.80	0.20	3.60	1.13	0.72	1.00	0.20	2.60	0.524
- Alanine Transferase (ALT) (U/L)	41.75	34.79	31.00	5.00	195.00	39.83	17.55	32.50	20.00	78.00	0.550
- Aspartate Transferase (AST) (U/L)	51.77	49.50	37.00	15.00	275.00	48.50	25.41	45.50	21.00	98.00	0.537
- Albumin (gm/dl)	3.90	0.64	4.00	2.70	5.73	3.63	0.48	3.60	3.00	4.70	0.131
- Creatinine (mg/dl)	0.94	0.22	0.90	0.20	1.60	0.89	0.24	0.95	0.50	1.30	0.767
- International Normalized Ratio	1.13	0.15	1.10	0.95	1.70	1.20	0.17	1.19	1.00	1.40	0.255
- Focal lesion size or size of largest lesion if 2 or multiple	4.28	1.88	4.00	1.40	12.00	4.86	2.46	4.50	2.00	10.80	0.522

Table (2): Count.

	Response				*p*-value
	Yes		No		
	Count	%	Count	%	
Gender:					
Male	35	77.8%	10	83.3%	1
Female	10	22.2%	2	16.7%	
Smoker:					
Yes	15	33.3%	4	33.3%	1
No	30	66.7%	8	66.7%	
Diabetes Mellitus:					
Yes	18	40.0%	3	25.0%	0.504
No	27	60.0%	9	75.0%	
Performance status:					
0	23	51.1%	8	66.7%	0.039
1	21	46.7%	2	16.7%	
2	1	2.2%	2	16.7%	
Liver:					
Cirrhotic	44	97.8%	12	100.0%	1
Not cirrhotic	1	2.2%	0	0.0%	
NLR:					
<1.97	24	53.3%	5	41.7%	0.473
>1.97	21	46.7%	7	58.3%	
PLR:					
<95.08	21	46.7%	7	58.3%	0.473
>95.08	24	53.3%	5	41.7%	
Hepatitis B:					
Positive	0	0.0%	2	16.7%	0.041
Negative	45	100.0%	10	83.3%	
Hepatitis C:					
Positive	36	80.0%	9	75.0%	0.702
Negative	9	20.0%	3	25.0%	
Alpha Fetoprotein (U/L):					
<400	36	80.0%	9	75.0%	0.702
>400	9	20.0%	3	25.0%	
Number of Tumor Lesions:					
Single	23	51.1%	5	41.7%	0.495
Two	5	11.1%	3	25.0%	
Multiple	17	37.8%	4	33.3%	
CHILD Score:					
A	42	93.3%	11	91.7%	0.623
B	2	4.4%	1	8.3%	
Not cirrhotic	1	2.3%	0	0.0%	

Table (3): Correlation between demographics and laboratory profile with survival.

	Survival										*p*-value
	Alive					Dead					
	Mean	SD	Median	Minimum	Maximum	Mean	SD	Median	Minimum	Maximum	
- Age (years)	60.96	7.39	62.00	48.00	72.00	60.07	9.90	60.00	30.00	75.00	0.873
- Hemoglobin (gm/dl)	12.56	1.88	12.35	7.60	17.00	12.62	2.19	13.00	7.30	17.30	0.886
- White blood cells ($x10^3$/µl)	5.78	2.53	5.10	2.20	11.00	5.92	2.34	6.00	2.90	10.50	0.798
- Neutrophil count %	57.31	15.66	58.00	16.40	93.00	59.87	13.78	61.00	15.00	80.00	0.384
- Absolute Neutrophil Count	3.42	2.05	2.56	1.05	7.59	3.64	1.84	3.36	0.51	7.35	0.544
- Lymphocytes count %	29.79	12.08	29.00	6.00	55.00	28.54	11.02	27.00	12.00	52.00	0.544
- Absolute Lymphocyte Count	1.68	0.88	1.58	0.27	3.42	1.64	0.81	1.52	0.41	3.76	0.873
- Platelets ($x10^3$/µl)	158.04	73.13	150.00	40.00	298.00	172.03	93.55	146.00	45.00	357.00	0.731
- NLR	2.78	2.73	2.03	0.34	13.68	2.53	1.41	1.97	0.71	6.15	0.638
- PLR	143.93	210.29	95.25	24.42	1103.70	127.17	90.29	92.17	26.41	418.06	0.666
- Total bilirubin (mg/dl)	0.98	0.44	0.95	0.20	2.23	1.08	0.73	0.90	0.20	3.60	0.767
- Alanine Transferase (ALT) (U/L)	32.31	22.17	29.00	5.00	112.00	50.07	37.29	38.00	13.00	195.00	0.017
- Aspartate Transferase (AST) (U/L)	43.91	37.45	35.00	15.00	187.00	58.00	51.51	44.00	21.00	275.00	0.080
- Albumin (gm/dl)	4.03	0.61	4.05	2.90	5.73	3.66	0.57	3.60	2.70	5.10	0.026
- Creatinine (mg/dl)	0.94	0.14	0.90	0.67	1.23	0.92	0.29	0.90	0.20	1.60	0.670
- International Normalized Ratio	1.14	0.18	1.09	0.95	1.70	1.15	0.14	1.12	1.00	1.40	0.675
- Focal lesion size or size of largest lesion if 2 or multiple	3.96	1.70	4.00	1.40	8.80	4.83	2.21	4.50	2.00	12.00	0.127

Table (3): Count.

	Survival				*p*-value
	Alive		Dead		
	Count	%	Count	%	
Gender:					
Male	23	82.1%	22	75.9%	0.561
Female	5	17.9%	7	24.1%	
Smoker:					
Yes	8	28.6%	11	37.9%	0.454
No	20	71.4%	18	62.1%	
Diabetes Mellitus:					
Yes	12	42.9%	9	31.0%	0.355
No	16	57.1%	20	69.0%	
Performance status:					
0	18	64.3%	13	44.8%	0.139
1	10	35.7%	13	44.8%	
2	0	0.0%	3	10.3%	
Liver:					
Cirrhotic	28	100.0%	28	96.6%	1
Not cirrhotic	0	0.0%	1	3.4%	

Table (3): Count.

	Survival				p-value
	Alive		Dead		
	Count	%	Count	%	
NLR:					
<1.97	14	50.0%	15	51.7%	0.896
>1.97	14	50.0%	14	48.3%	
PLR:					
<95.08	13	46.4%	15	51.7%	0.689
>95.08	15	53.6%	14	48.3%	
Hepatitis B:					
Positive	0	0.0%	2	6.9%	0.491
Negative	28	100.0%	27	93.1%	
Hepatitis C:					
Positive	23	82.1%	22	75.9%	0.561
Negative	5	17.9%	7	24.1%	
Alpha Fetoprotein (U/L):					
<400	24	85.7%	21	72.4%	0.218
>400	4	14.3%	8	27.6%	
Number of Tumor Lesions:					
Single	15	53.6%	13	44.8%	0.769
Two	3	10.7%	5	17.2%	
Multiple	10	35.7%	11	37.9%	
CHILD Score:					
A	26	92.8%	27	93.1%	1
B	1	3.6%	2	6.9%	
Not cirrhotic	1	3.6%	0	0.0%	

Table (4): Correlation between NLR and PLR with patient's characteristics.

	NLR		PLR	
	Correlation Coefficient	p-value	Correlation Coefficient	p-value
Survival in Months	-0.154-	0.253	-0.028-	0.837
Age (years)	-0.121-	0.369	0.123	0.363
Hemoglobin (gm/dl)	-0.053-	0.696	-0.121-	0.371
White blood cells ($x10^3/\mu l$)	0.217	0.105	-0.118-	0.383
Platelets	0.163	0.225	0.569	<0.001
Total bilirubin (mg/dl)	-0.142-	0.294	-0.420-	0.001
Alanine Transferase (ALT) (U/L)	-0.232-	0.082	-0.217-	0.105
Aspartate Transferase (AST) (U/L)	-0.235-	0.078	-0.203-	0.130
Albumin (gm/dl)	0.113	0.404	0.267	0.045
Creatinine (mg/dl)	0.102	0.451	0.218	0.103
International Normalized Ratio	0.017	0.902	-0.338-	0.010
Focal Lesion size or size of largest lesion if 2 or multiple	0.081	0.549	0.088	0.515

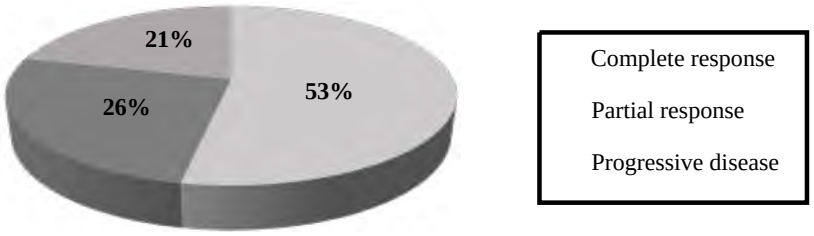
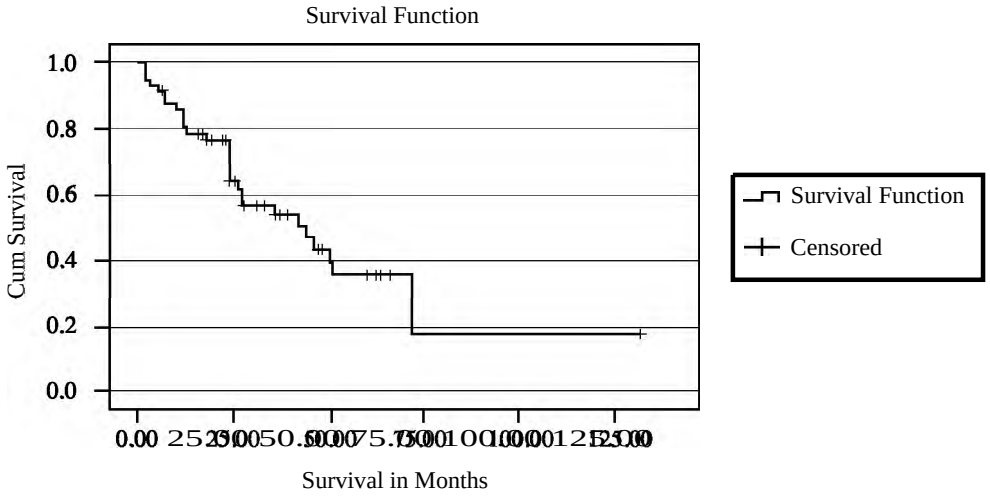


Fig. (1): Response to TACE according to mRECIST criteria.

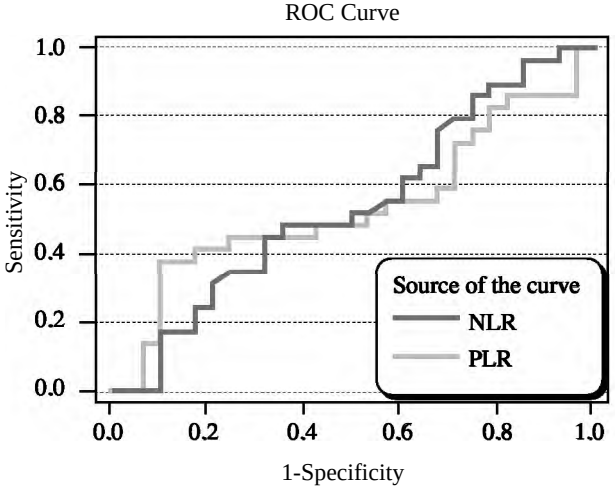


Means and Medians for Survival Time

Meana				Median			
95% Confidence interval				95% Confidence interval			
Estimate	Std. error		Upper bound	Estimate	Std. error	Lower bound	Upper bound
52.890	9.706	33.867	71.913	44.000	11.485	21.489	66.511

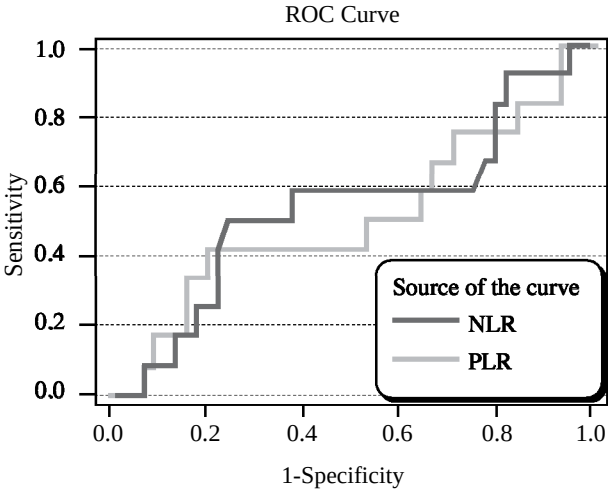
a. Estimation is limited to the largest survival time if it is censored.

Fig. (2): Kaplan Meier for mortality.



	Area under the curve	*p*-value	95% Confidence interval	
			Lower bound	Upper bound
NLR	0.536	0.639	0.384	0.688
PLR	0.533	0.673	0.379	0.688

Fig. (3): ROC curve for detection of mortality using NLR, PLR.



	Area under the curve	*p*-value	95% Confidence interval	
			Lower bound	Upper bound
NLR	0.535	0.728	0.337	0.733
PLR	0.506	0.957	0.305	0.706

Fig. (4): ROC curve for detection of responders using NLR, PLR.

Discussion

A growing body of research indicates that a poor prognosis for a variety of cancer types is linked to the systemic inflammatory response [18,19,20]. Lymphocyte immune cells and circulating neutrophils in addition to platelets play contradictory roles as essential opposing regulators in the inflammatory processes associated with cancer development [21]. On one side, a key component of the leukocyte population, neutrophils provide pro-angiogenic substances including vascular endothelial growth factors (VEGFs), therefore promoting tumor formation and progression [18].The inhibition of an anticancer adaptive immune response or the over-expression of cyclooxygenase-2 are two possible explanations for such an occurrence [22,23,24]. Similarly, the process of tumor angiogenesis is also significantly influenced by platelets. The impact of platelets and the cytokines they secrete on tumor progression is not yet completely comprehended; however, elevated platelet counts are linked to adverse outcomes in a variety of solid cancers [25,26]. Platelets have the capacity to release significant quantities of proangiogenic cytokines, including platelet-derived growth factor (PDGF) [27] and VEGF [28]. In addition, activated platelets promote tumor spread by dramatically enhancing the adhesion between tumor cells and endothelial cells [29]. Furthermore, a higher platelet count can inhibit NK cells' anti-tumor immunological responses [30]. Conversely, lymphocytes can inhibit tumor development and are crucial elements of cancer immune surveillance [31]. A diminished lymphocyte count correlates with an inadequate immune response to tumors, hence facilitating tumor development and metastasis [32]. Moreover, numerous studies indicate that through tumor cell lysis, adaptive immune cells, including B-lymphocytes, CD8+ cytotoxic T-lymphocytes, and CD4+ helper T-lymphocytes, play rather significant roles in the control of cancer progression [21,33].

In this context, to predict survival and recurrence in several malignancies, including HCC, a number of inflammatory and immune-based prognostic scores, including platelet to lymphocyte ratio (PLR) and neutrophil-lymphocyte ratio (NLR), have been created.

In the current study, NLR and PLR were assessed as markers to predict overall survival (OR) and response to TACE (as assessed by mRECIST criteria) in a cohort of Egyptian patients with HCC, however, both markers were not shown to have a significant relationship with neither survival nor response to treatment.

In contrast to our findings, other studies indicated that the neutrophiltolymphocyte ratio (NLR) was strongly correlated with overall and disease-free survival following various therapies, including TACE, radio-frequency ablation (RFA), and surgical resection[34, 35, 36]. In patients with intermediate to advancedstage unresectable HCC undergoing TACE, a higher NLR predicted poor survival [35,37,38,39]. Wang et al., for instance, proposed that in patients with HCC receiving TACE, an elevated NLR (NLR >2.4) independently indicated a poor survival rate [40]. In a similar manner, Sandow et al., demonstrated that a higher pretreatment absolute lymphocyte count and a lower pretreatment NLR correlated with improved overall survival in 93 HCC patients undergoing TACE using doxorubicin-eluting microspheres [41]. In addition, several studies concluded that the PLR was a useful prognostic biomarker for overall survival

and/or response in patients with HCC **[42-46]**. For example, in a study conducted by Xue et al. on 291 patients with unresectable HCC receiving TACE, an elevated baseline PLR was found to be an independent negative predictor for OS (p=0.002) **[47].** Moreover, He et al., assessed the prognostic significance regarding overall survival of the NLR–PLR combination (neutrophil/platelet-to-lymphocyte ratio) in 216 patients with HCC undergoing TACE therapy, revealing that the AUROC values for the NLR–PLR score were consistently superior to those of NLR and PLR individually **[48].**

Nonetheless, consistent with our findings, a number of studies reported no significant correlation between response rates and different prognostic parameters including OS, with respect to both ratios in patients with HCC. Sullivan et al., corroborated with our study's findings, concluding that their research does not endorse the prognostic significance of NLR for guiding therapy in HCC in a Western center, while MELD and Child-Pugh scores proved to be more predictive **[49]**. Following TACE, 189 HBV related-HCC patients' overall survival was found to be negatively predicted by the aspartate aminotransferase-lymphocyte ratio (ALRI) and the systemic immune-inflammation index (SII) (HR = 2.181, p = 0.003 and HR = 2.453, p = 0.003; respectively) rather than NLR or PLR-which showed no significant correlation with OS on multivariate regression analysis **[50]**. Similarly, in a retrospective study conducted on 652 HCC patients undergoing surgical resection, Yang et al. concluded that the lymphocyte-to-monocyte ratio (LMR) was an independent risk factor for OS (p= 0.002) on multivariate analysis, but not the NLR or PLR **[51].** In addition, according to Shindoh et al., NLR was less effective than AFP or des-gamma-carboxyprothrombin (DCP) at predicting overall survival and showed no prognostic significance **[52]**. In three hundred twenty-four patients with early-stage HCC undergoing surgical resection, Chan et al., examined the roles of the prognostic nutritional index (PNI), PLR, and NLR. They found that neither PLR nor increased NLR (≥5) were meaningful predictive markers for overall survival **[53].** Additionally, in their study, Zhou et al., showed that the GPS is a better indicator of survival for HBV-HCC patients following TACE than other inflammation-based prognostic scores, such as NLR **[54].**

Our findings can be attributed to a number of different factors. Numerous parameters, such as tumor stage, degree of fibrosis, ethnicity, and liver disease etiology, have been found to influence NLR and PLR prognostic values **[55]**. Chronic liver disease linked to HCV was the primary underlying etiology of HCC in the majority of patients included in our study (81.8%). A meta-analysis by Li et al., encompassing 21 studies with 8,779 patients, revealed through subgroup analysis that a high PLRwas significantly correlated with poor OSin the cohort comprised entirely of HBV patients (100%) (HR: 1.46, 95% CI: 1.22–1.73, p<0.0001) and in the high proportion cohort (80–100%) (HR: 1.31, 95% CI: 1.03–1.65, p=0.02), but not in the low proportion cohort (≤80%) (HR: 1.21, 95% CI: 0.94–1.56, p=0.14) **[56]**. These findings indicate that the correlation between PLR and OS was more pronounced in studies involving HBV-related HCC patients. Notably, regional subgroup analysis also showed that high PLR levels were linked to worse OS in the Chinese group (HR: 1.43, 95% CI: 1.26–1.62, p<0.00001), but not in other countries (HR: 1.04, 95% CI: 0.81–1.33, p=0.77), according to the same study. In a similar fashion, in their subgroup analysis, Lin et al., determined that the NLR exhibited superior prognostic value in HCC patients from mainland China (DOR, 7; AUC, 0.79) compared to those from Korea (DOR, 3; AUC, 0.64) and Taiwan (DOR, 2; AUC, 0.63). Furthermore, NLR demonstrated enhanced prognostic performance as a predictor of outcome in HCC patients from the North (DOR, 8; AUC, 0.80) relative to those from the South (DOR, 3; AUC, 0.69) **[57]**. To the best of our knowledge, only two other Egyptian studies evaluated the prognostic role of NLR and PLR in patients with HCC. In agreement with our findings, Elgindy et al. determined that NLR and PLR were not effective as early prognostic indicators for HCC in a study involving 114 HCV-related HCC patients **[58]**. Conversely, Lehleh et al., revealed a significant correlation between NLR and post-TACE ablation rates in 40 HCC patients, although they did not provide survival data **[59].** This disparity in findings implies that more research is required to ascertain whether Egyptian ethnicity has a detrimental impact on the prognostic performance of NLR and PLR in patients with HCC. On a different angle, the fact that 98.2% of our research sample had liver cirrhosis is another factor that may help to explain our findings. In their study of 234 HBV-HCC patients, Wang et al., examined the impacts of three inflammatory markers (NLR, PLR, and PNI). They discovered that NLR was the only meaningful predictive factor, and that its influence was more pronounced in patients in Ishak stages 0–5 than in those in Ishak stages 6 **[60]**. The subsequent result was validated by another study that evaluated 108 Serbian patients and found that NLR had a predictive value in non-cirrhotic HCC patients with low fibrosis scores, but the significance was not verified in cirrhotic patients **[61]**. Furthermore, because liver cirrhosis is frequently accompanied

with hypersplenism and a corresponding decrease in platelets, it has been hypothesized that PLR will be impacted by liver cirrhosis as a predictive biomarker in cirrhosis-related HCC **[49]**. In a similar context, Qin et al., examined 1452 HCC patients and discovered that, in contrast to patients without clinically significant portal hypertension (CSFH), neither NLR nor PLR demonstrated any predictive power in HCC patients with CSPH **[62].**

Our study acknowledges several limitations. Initially, this retrospective analysis was based on a singular institutional database of TACE-treated HCC patients, and our work lacked external validation. In addition, alternative justifiable cutoff values for variables may exist based on other studies. To substantiate these findings, a comprehensive prospective validation research is therefore required.

Conclusion:

The current study unlike others done show no value for NLR and PLR in prediction of survival or response to TACE in patients with HCC. These contradictory findings show that more research is needed to determine how well NLR and PLR predict HCC outcomes in certain populations, such as HCV-related HCC in Egyptian patients.

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هل تعتبر نسب العدلات إلى الخلايا الليمفاوية والصفائح الدموية إلى الخلايا الليمفاوية عوامل تنبؤية موثوقة للاستجابة والبقاء على قيد الحياة بشكل عام لدى مرضى سرطان الخلايا الكبدية المصريين الذين عولجوا باستخدام العلاج الكيميائي عبر الشرايين؟

يُعدّ الحقن الكيميائى عبر الشرايين علاجًا معتمدًا لسرطان الخلايا الكبدية. من الصعب توقع كيفية استجابة الورم للعلاج، لذا قد يُساعد إيجاد مؤشر حيوى أساسى فى تصميم العلاج وتحديد المرضى الذين يحتاجون إلى متابعة دورية أو علاج أكثر فعالية.

يمكن استخدام نسب الالتهاب، مثل نسبة العدلات إلى الخلايا الليمفاوية (NLR) ونسبة الصفائح الدموية إلى الخلايا الليمفاوية (PLR)، كمؤشرات حيوية كمية لتقييم الاورام الفردية.

هذه دراسة استعادية أجريت على ٥٧ مريضًا مصابًا بسرطان الخلايا الكبدية من مستشفى قصر العيني، جامعة القاهرة، مصر، والذين خضعوا لعملية حقن كيميائى للشرايين المغذية لاورام الكبد بين عامى ٢٠٢٠ و ٢٠٢٣. تضمنت البيانات تقارير مخبرية مثل تعداد الدم الكامل ، ووظائف الكبد، و دلالات الاورام، بالإضافة إلى بيانات ديموغرافية. أُجرى التصوير متعدد المراحل لتقييم الاستجابة باستخدام معايير mRECIST.

تم تحديد معدل البقاء على قيد الحياة بشكل عام، بدءًا من زيارات المرضى الأولى لعيادة سرطان الخلايا الكبدية وحتى وفاتهم أو انتهاء الدراسة.

تظهر الدراسة الحالية عدم وجود قيمة لنسبة العدلات إلى الخلايا الليمفاوية ونسبة الصفائح الدموية إلى الخلايا الليمفاوية فى التنبؤ بالبقاء على قيد الحياة أو الاستجابة للحقن الكيماوى للشرايين فى المرضى المصابين بسرطان الخلايا الكبدية.