Cohort Study

Platelet-to-lymphocyte and neutrophil-to-lymphocyte ratios predict tumor size and survival in HCC patients: Retrospective study

Aslı Suner, Brian I. Carr *

ABSTRACT

Background: Inflammation is a recognized concomitant of hepatocellular carcinoma (HCC) and its indices are prognostically useful.
Aims: To evaluate two commonly used inflammatory indices, neutrophil-to-lymphocyte ratio (NLR) and the platelet-to-lymphocyte ratio (PLR), to examine their relationship to maximum tumor diameter (MTD) and to survival.
Methods: A database of 1024 prospectively-accrued HCC patients was examined, who had full baseline tumor parameter data, including CT scan information on HCC size and whose survival was known. Analyses of NLR and PLR were correlated to MDT and to survival. NLR and PLR cutoffs were calculated from receiver operator characteristic curves.
Results: Every MTD pair had significantly different PLR values, for MTD groups of groups <2/≥2, <3/≥3, <4/≥4, <5/≥5 cm. However there were few significant differences in NLR values. Logistic regression models of different MTD groups likewise showed significance for PLR. Patients with both low NLR and low PLR had the longest overall survival compared to all the other 3 combinations of NLR and PLR. In a Cox regression analysis, univariate models on NLR (≤3.02/>3.02) and PLR (≤6.82/>6.82) groups, showed significance for PLR, p = 0.034 and approaching significance for NLR, p = 0.057.
Conclusions: MTD pairs down to <2/≥2 cm showed significance for PLR, survival showed significance for PLR and almost for NLR.

1. Introduction

There has been much published evidence for a role of inflammation in many cancers, including hepatocellular carcinoma (HCC) [1,2]. Inflammation-based prognostic scores have been shown to be associated with survival [3] and with various parameters of tumor aggressiveness [4]. This may be related to the involvement in tumor growth of a variety of easily measurable indices of inflammation [5] in routine clinical blood tests, including levels of neutrophils, lymphocytes, monocytes, platelets, albumin, C-reactive protein (CRP), as well as marker ratios, such as albumin and CRP (Glasgow Index), neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) and monocyte-to-lymphocyte ratios, amongst others [6–26]. In the current study, NLR and PLR were evaluated with reference to maximum tumor diameter (MTD) and also to survival in a large Turkish HCC cohort. We found that PLR was useful in assessing MTD down to 2.0 cm and that

both PLR and NLR related to overall survival (OS).

2. Methods

2.1. Patients

A database of 1024 prospectively-accrued US HCC patients was examined, who had full baseline tumor parameter data, including CT scan information on HCC size and whose survival was known, as previously published [27]. This retrospective study was registered with ClinicalTrials.gov, with Identifier NCT04477720. Diagnosis was made either through tumor biopsy or according to international guidelines. The data and CT descriptors were prospectively recorded and entered into an HCC database intended for follow-up and analysis, as was survival information. Database management conformed to legislation on privacy and this study conforms to the ethical guidelines of the

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Declaration of Helsinki and the analysis was done by university IRB-approved protocol for the retrospective analysis of de-identified HCC patient records. This work has been reported in line with the STROCSS criteria [42].

2.2. Statistics

Descriptive statistics of two continuous variables, the neutrophil-to-lymphocyte ratio (NLR) and the platelet-to-lymphocyte ratio (PLR), for four different MTD groups with different cut-off values were calculated with mean, standard deviation, median, interquartile range, minimum and maximum values. Assumption of normality for the NLR level and PLR were assessed using the Shapiro-Wilk test. The Wilcoxon rank-sum (Mann-Whitney) test was performed to test the difference between two independent groups. Different cut-off values according to the NLR level and PLR to classify four different MTD groups for the total cohort of HCC patients were defined with ROC curve analysis to find the ideal cut-offs, as also shown previously [28]. A linear regression models were used to evaluate the associations between different MTD groups and NLR and PLR on single variables, while a final multiple logistic regression model in backward stepwise method on NLR and PLR variables included together in the model. Univariate logistic regression models of different MTD groups on NLR ($\leq3.02/>3.02$) or PLR ($\leq6.82/>6.82$) were obtained. A p-value of less than 0.05 was considered as statistically significant. All statistical analyses were performed using IBM SPSS version 21.0 (Chicago, IL, USA).

3. Results

3.1. Descriptive statistics of NLR and PLR for MTD groups

This investigation concerned 2 commonly used inflammatory indices, namely the plasma platelet-to-neutrophil ration (PLR) and the plasma neutrophil-to-lymphocyte ration (NLR) and their relationship to HCC tumor size or maximum tumor diameter (MTD) in each of the 1024 patients in the cohort that had PLR data recorded and the 1018 of these same patients who also had available NLR data. The patients were divided into MTD pairs, based on $<$ or ≥2, 3, 4 or 5 cm MTD and each MTD pair was examined for NLR (upper part) or PLR values (lower part) of Table 1. There were no significant differences between the NLR values for larger or smaller tumors, except for <2 vs. ≥2 cm MTD. By contrast, every MTD pair had significantly different PLR values, for higher vs. lower MTD pairs.

3.2. Receiver operating characteristic (ROC) curves for NLR and PLR

A receiver operating characteristic (ROC) curve analysis was next calculated (Table 2). The results of the ROC with 95% confidence intervals showed that the area under the curve (AUC) for PLR was statistically significant for high vs. low MTD for each MTD level that was considered.

3.3. Logistic regression models of different Maximum Tumor Diameter (MTD) groups

Logistic regression models were constructed of different Maximum Tumor Diameter (MTD) groups (Table 3). In Table 3A, we used only NLR or PLR alone in univariate logistic regression models on single variables. The results showed that only PLR alone was found to be statistically significant in univariate logistic regression models of the MTD groups ($<2/\geq2$, $<3/\geq3$, $<4/\geq4$, $<5/\geq5$ cm) (Table 3A; p < 0.05). In Table 3B, NLR and PLR variables were included together on the final multiple logistic regression models with the backward stepwise method. Although, only PLR was found to be statistically significant in multiple logistic regression models of the MTD groups of $<2/\geq2$ and $<3/\geq3$; both NLR and PLR were found to be statistically significant in multiple

Table 1
Comparisons of the neutrophil-to-lymphocyte ratio (NLR) and the platelet-to-lymphocyte ratio (PLR) for different Maximum Tumor Diameter (MTD) groups (cm).

Variable	MTD Group	N	Mean ± SD	Median (IQR)	Min-Max	p*
NLR	<2	71	8.44 ± 10.87	3.68 (7.51)	0.57–65.00	0.014*
	≥2	947	10.76 ± 13.34	6.00 (9.42)	0.12–98.00	
	<3	160	9.39 ± 10.35	5.75 (8.74)	0.43–65.00	0.194
	≥3	858	10.83 ± 13.65	5.93 (9.47)	0.12–98.00	
	<4	267	10.23 ± 12.88	6.17 (8.99)	0.21–98.00	0.371
	≥4	751	10.73 ± 13.30	5.86 (9.42)	0.12–98.00	
	<5	357	12.32 ± 29.90	2.08 (8.25)	0.10–180.00	0.488
	≥5	661	22.99 ± 38.93	6.95 (21.74)	0.10–192.00	
PLR	<2	71	15.73 ± 21.52	7.86 (17.02)	1.60–151.00	0.002*
	≥2	953	23.95 ± 34.06	13.04 (20.16)	0.60–306.00	
	<3	160	17.24 ± 21.38	10.19 (15.79)	1.36–151.00	0.001*
	≥3	864	24.51 ± 35.07	13.31 (20.72)	0.60–306.00	
	<4	270	17.32 ± 23.26	9.91 (15.98)	1.21–225.00	<0.001*
	≥4	754	25.55 ± 36.12	13.72 (21.31)	0.60–306.00	
	<5	360	17.29 ± 22.98	9.77 (15.98)	1.21–225.00	<0.001*
	≥5	664	26.67 ± 37.47	14.57 (22.38)	0.60–306.00	

Abbreviations: SD, Standard Deviation; IQR, Interquartile Range; Min, Minimum; Max, Maximum; MTD, maximum tumor diameter (cm); PLR, platelet lymphocyte ratio; NLR, neutrophil lymphocyte ratio; * Wilcoxon rank-sum (Mann-Whitney) test; *p-value<0.05 is significant.

logistic regression models of the MTD groups of $<4/\geq4$ and $<5/\geq5$ (Table 3B; p < 0.05). In Table 3C, results of univariate logistic regression models on NLR ($\leq3.02/>3.02$) groups showed that NLR groups alone were found to be statistically significant in univariate logistic regression models of the MTD groups of $<2/\geq2$ only (Table 3C; p < 0.05), and NLR>3.02 was 1.862 times more likely to have MTD of 2 cm. In Table 3D, results of univariate logistic regression models on PLR ($\leq6.82/>6.82$) groups showed that PLR groups alone were found to be statistically significant in univariate logistic regression models of the all MTD groups ($<2/\geq2$, $<3/\geq3$, $<4/\geq4$, $<5/\geq5$ cm) (Table 3D; p < 0.05).

3.4. Survival analyses

Survival times and overall survivals (OS) were then calculated, both the NLR ratio ($\leq3.02/>3.02$) and PLR ratio ($\leq6.82/>6.82$) groups, as well as for the total cohort of patients (Table 4). In the upper part of Table 4, patients with both low NLR ≤3.02 and low PLR ≤6.82 are seen to have the longest survival, compared to all the other 3 combinations of NLR and PLR. Patients with only NLR of ≤3.02 and only PLR of ≤6.82 each had significantly greater survival than those with only NLR >3.02 or only PLR >6.82.

A Cox regression analysis was then constructed of the NLR and PLR for overall survival (Table 5). In Table 5A, we used univariate models on single variables, and neither NLR nor PLR variables were statistically significant (Table 5A; p > 0.05). When a final model was constructed on

Table 2
Results of the area under the receiver operating characteristic (ROC) curve with 95% confidence intervals, and assessment of different cut-off values according to the neutrophil-to-lymphocyte ratio (NLR) and the platelet-to-lymphocyte ratio (PLR) to classify different Maximum Tumor Diameter (MTD) groups (cm).

		AUC	S.E.	p-value	95% C.I.	Cut-off	Sensitivity	Specificity	PPV	NPV	YI
NLR	MTD (<2/≥2)	0.587	0.036	0.014*	0.516–0.659	2.491	0.838	0.254	0.937	0.105	0.092
						3.023	0.774	0.352	0.941	0.105	0.126
						3.804	0.686	0.521	0.950	0.111	0.208
	MTD (<3/≥3)	0.532	0.026	0.194	0.482–0.582	2.491	0.838	0.200	0.849	0.187	0.038
						3.023	0.773	0.275	0.851	0.184	0.048
						4.108	0.659	0.431	0.861	0.191	0.090
	MTD (<4/≥4)	0.518	0.021	0.371	0.477–0.560	2.491	0.846	0.206	0.750	0.322	0.052
						3.023	0.776	0.266	0.748	0.297	0.042
						4.108	0.658	0.393	0.753	0.290	0.051
	MTD (<5/≥5)	0.513	0.019	0.488	0.475–0.551	2.491	0.850	0.202	0.664	0.421	0.052
						3.023	0.784	0.269	0.665	0.402	0.053
						3.718	0.702	0.359	0.670	0.394	0.061
PLR	MTD (<2/≥2)	0.611	0.036	0.002*	0.541–0.681	5.761	0.812	0.408	0.949	0.139	0.221
						6.820	0.757	0.465	0.950	0.125	0.221
						7.865	0.690	0.507	0.949	0.109	0.197
	MTD (<3/≥3)	0.580	0.025	0.001*	0.532–0.629	5.955	0.811	0.331	0.868	0.245	0.143
						6.820	0.765	0.388	0.871	0.234	0.153
						7.095	0.740	0.400	0.869	0.221	0.140
	MTD (<4/≥4)	0.598	0.020	<0.001*	0.558–0.638	5.854	0.832	0.315	0.772	0.401	0.146
						6.932	0.771	0.385	0.778	0.375	0.156
						7.385	0.740	0.404	0.776	0.357	0.144
	MTD (<5/≥5)	0.611	0.019	<0.001*	0.574–0.647	5.360	0.870	0.286	0.692	0.545	0.157
						6.932	0.789	0.381	0.701	0.495	0.170
						7.843	0.739	0.425	0.703	0.469	0.164

Abbreviations: AUC: Area under the ROC curve, S.E.: standard error, C.I.: confidence interval, PPV: Positive predictive value, NPV: Negative predictive value, YI: Youden's Index. MTD, maximum tumor diameter (cm); PLR, platelet lymphocyte ratio; NLR, neutrophil lymphocyte ratio; *p-value<0.05 is significant.

Table 3
Logistic regression models of different MTD groups. (**A**), Univariate logistic regression models on single variables. (**B**), Final multiple logistic regression model in backward stepwise method on NLR and PLR variables included together in the model. (**C**), Univariate logistic regression models on NLR (≤3.02/>3.02) groups. (**D**), Univariate logistic regression models on PLR (≤6.82/>6.82) groups.

	MTD group (<2/≥2 cm)			MTD group (<3/≥3 cm)			MTD group (<4/≥4 cm)			MTD group (<5/≥5 cm)		
Parameter	exp (β)	p-value	95% C.I.	exp (β)	p-value	95% C.I.	exp (β)	p-value	95% C.I.	exp (β)	p-value	95% C.I.
(**A**)												
NLR	1.018	0.154	0.993–1.044	1.010	0.208	0.995–1.025	1.003	0.595	0.992–1.014	1.004	0.455	0.994–1.014
PLR	1.014	0.046*	1.000–1.028	1.010	0.013*	1.002–1.019	1.011	0.001*	1.005–1.018	1.012	<0.001*	1.006–1.018
(**B**)												
NLR	–	–	–	–	–	–	0.963	<0.001*	0.946–0.981	0.958	<0.001*	0.941–0.976
PLR	1.014	0.045*	1.000–1.029	1.010	0.013*	1.002–1.019	1.026	<0.001*	1.015–1.037	1.029	<0.001*	1.019–1.040
(**C**)												
NLR												
≤3.02 [Ref]	1			1			1			1		
>3.02	1.862	0.017*	1.118–3.101	1.290	0.192	0.880–1.890	1.257	0.163	0.912–1.733	1.332	0.059	0.989–1.796
(**D**)												
PLR												
≤6.82 [Ref]	1			1			1			1		
>6.82	2.699	<0.001*	1.655–4.402	2.060	<0.001*	1.445–2.937	2.100	<0.001*	1.553–2.838	2.215	<0.001*	1.663–2.949

Abbreviations: C.I.: confidence interval. MTD, maximum tumor diameter (cm); PLR, platelet lymphocyte ratio; NLR, neutrophil lymphocyte ratio; *p-value<0.05 is significant.

NLR and PLR variables included together in the model (Table 5B), results showed that a continuous version of the NLR variable was found to be statistically significant (Table 5B; p < 0.05). The continuous NLR and PLR values were then grouped (with cut-offs of 3.02 and 6.82, respectively); results of univariate models on NLR (≤3.02/>3.02) and PLR (≤6.82/>6.82) groups indicated that although NLR was near to significance (p = 0.057), PLR was statistically significant (Table 5C; p = 0.034).

4. Discussion

HCC arises mostly in a liver that is chronically inflamed by viruses (hepatitis B or C), toxins (alcohol or free radicals from metabolic syndrome) or dietary carcinogens (Aflatoxin). The associated chronic up-regulation of pro-inflammatory factors either from the HCC cells or the tumor microenvironment [5,29] are thought to be important in driving HCC growth and invasiveness, and may in their own right be a logical target of therapeutic intervention by anti-inflammatory agents [30,31].

Although a large literature already exists on the use of various common blood tests that reflect systemic inflammation and prognosis, and to a lesser extent reflecting in turn the extent of the disease [6–26], the precise relationship of inflammatory markers to tumor extent has not been well defined. The current work attempts to do this by use of the commonly used PLR and NLR ratios, to assess their relationship to MTD and to try to find their ability to predict small tumor size (MTD). We found that for every MTD pair there were significantly different PLR values, for higher vs. lower MTD pairs. But not for NLR values. We also found that PLR alone was found to be statistically significant in univariate logistic regression models of all the MTD groups (<2/≥2,

Table 4
Means and medians for survival time and overall survival (OS) of the NLR ratio (≤3.02/>3.02) and the PLR ratio (≤6.82/>6.82) groups and total number of patients.

Variables		Mean				Median		
NLR	PLR	Estimate	S.E.	95% C.I.	Log-Rank[a]	Estimate	S.E.	95% C.I.
≤3.02	≤6.82	22.01	3.30	15.54–28.49	0.017*	11.00	1.27	8.50–13.49
≤3.02	>6.82	11.65	1.54	8.64–14.66		6.00	1.48	3.09–8.91
>3.02	≤6.82	13.64	2.60	8.55–18.74	0.747	6.00	1.33	3.39–8.61
>3.02	>6.82	14.21	0.79	12.66–15.75		8.00	0.69	6.64–9.36
OS		14.97	0.75	13.49–16.44		8.00	0.58	6.85–9.15
Only NLR		**Estimate**	**S.E.**	**95% C.I.**		**Estimate**	**S.E.**	**95% C.I.**
≤3.02		18.24	2.23	13.88–22.61		10.00	1.06	7.92–12.08
>3.02		14.14	0.76	12.67–15.63	0.048*	8.00	0.59	6.85–9.15
OS		14.95	0.75	13.48–16.42		8.00	0.59	6.85–9.15
Only PLR		**Estimate**	**S.E.**	**95% C.I.**		**Estimate**	**S.E.**	**95% C.I.**
≤6.82		18.60	2.17	14.36–22.84		10.00	1.14	7.77–12.23
>6.82		14.03	0.73	12.59–15.46	0.027*	8.00	0.60	6.83–9.17
Overall		15.05	0.74	13.58–16.52		8.00	0.58	6.86–9.14

Abbreviation: NLR, Neutrophil-to-lymphocyte ratio. PLR, Platelet-to-lymphocyte ratio; overall survival (OS); C.I.: confidence interval. S.E.: standard error. [a] Adjusted for NLR, comparing PLR groups. *p-value<0.05 is significant.

Table 5
Cox regression analysis of the NLR and PLR for overall survival. (**A**), Univariate models on single variables. (**B**), Final model on NLR and PLR variables included together in the model. (**C**), Univariate models on NLR (≤3.02/>3.02) and PLR (≤6.82/>6.82) groups.

Variables	exp (β)	p-value	95% C.I.
(A)			
NLR	1.005	0.095	0.999–1.010
PLR	1.001	0.479	0.999–1.003
(B)			
NLR	1.010	0.039*	1.000–1.019
PLR	0.998	0.209	0.995–1.001
(C)			
NLR(≤3.02/>3.02)	1.201	0.057	0.994–1.450
PLR(≤6.82/>6.82)	1.216	0.034*	1.015–1.457

Abbreviations: NLR, Neutrophil-to-lymphocyte ratio; PLR, Platelet-to-lymphocyte ratio; C.I, confidence interval.
*p-value<0.05 is significant.

<3/≥3, <4/≥4, <5/≥5 cm). An assessment of NLR and PLR cut-off values by ROC curves was made, to classify different MTD groups (cm).

Survival times and overall survivals (OS) were then calculated and patients with only NLR of ≤3.02 and only PLR of ≤6.82 each had significantly greater survival than those with only NLR >3.02 or only PLR >6.82. Thus, PLR showed statistically significant results for both MTD and for survival.

What might be the mechanisms by which high NLR and PLR are associated with poorer HCC prognosis and tumor size? There are likely to be several. Clearly there is a 2-way interaction between tumor and inflammatory microenvironment [1,2,5]. In addition to immune cell infiltration of tumors, inflammatory cell involvement of the peri-tumorous microenvironment is increasingly seen to be important in driving tumor growth, including activated macrophages, stellate and mast cells, together with prognostic molecular signatures that were not found in the tumors themselves [32,33]. The peritumor infiltration by neutrophils drives in part both the inflammatory response that involves free radicals and the angiogenic response [34–36]. Furthermore, platelets are thought to be important in driving HCC growth through participating in immune mechanisms as well as through their release of multiple growth factors [30], [37–41]. Thus platelets, as reflected in elevated PLR, seem to be important in HCC growth and even in drug resistance and may be a future druggable target.

Ethical approval

The study was approved by the IRB of the university of Pittsburgh for the retrospective analysis of dead, de-identified patients with HCC.

Consent

NA, as the study was on data from dead, de-identified patients.

Author contribution

Study concept or design: Brian Carr.
Data collection: Brian Carr.
Data analysis or interpretation: Aslı Suner.
Writing the paper: Brian Carr and Aslı Suner.

Registration of research studies

Name of the registry: ClinicalTrials.gov.
Unique Identifying number or registration ID: NCT04477720.
Hyperlink to your specific registration (must be publicly accessible and will be checked): ClinicalTrials.gov Identifier: NCT04477720.
Carr, Brian Protocol Record BCarr.
Retrospective Analysis of De-identified Deceased HCC Patients, is registered and will be posted on the ClinicalTrials.gov public website.
RECORDS USUALLY APPEAR ON ClinicalTrials.gov WITHIN 2 BUSINESS DAYS of the receipt of this message.

Guarantor

Brian Carr.

Declaration of competing interest

The authors declare no conflict of interest. All authors have read and agree with this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.amsu.2020.08.042.

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