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Role of Pre-Operative of Neutrophil/Lymphocyte and Platelet/Lymphocyte Ratio in Prognosis of Hepatocellular Carcinoma

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Abstract

Introduction: Hepatocellular carcinoma (HCC) has a poor prognosis and is ranked in the top 2 leading causes of death in Taiwan. The clinical features which affect survival rate should be noticed for alarming. We tried to study the neutrophil-lymphocyte ratio (NLR) and platelet-lymphocyte ratio (PLR) for the predictor of prognosis of HCC. **Patients and Methods:** A total of 525 patients with HCC were undergone surgical or non-surgical treatment registered in Cancer Registry Center of our hospital. The clinical features included patient's basic profiles, and neutrophil, lymphocyte and platelet count in the peripheral blood at the time of diagnosis. The ratio of neutrophil/lymphocyte and platelate/lymphocyte was measured and their survival rates were analyzed based on their ratio scales. **Results:** Three scales of NLR and PLR were ≤1.62, 1.63 - 2.57, ≥2.58 and ≤224, 225 - 253, ≥254 respectively. Either higher NLR ≥ 2.58 or higher PLR ≥ 254 was found mostly in the male and TMN stage III and IV with a significant difference ($P < 0.01$). The 5-year survival rates of NLR ≤ 1.62, 1.63 - 2.57, ≥2.58 were 33.9%, 33.7%, and 16.7% respectively ($P < 0.001$). The mean survival times were 34.1 ± 1.4, 29.3 ± 8.1, and 14.2 ± 2.1 months for the scales of PLR ≤ 224, 225 - 253, and ≥ 254 respectively. The 5-year survival rates were 25.5%, 36.4%, and 7.7% for the groups of the PLR ≤ 224, 225 - 253, and ≥254 respectively ($p < 0.001$). **Conclusion:** Neutrophil, lymphocyte and platelet are players in cancer growth and have a potential role as predictors of survival in our HCC patients. Therefore, we should pay more attention to the higher NLR or PLR which will result in a poorer prognosis in our patients.

Keywords

Neutrophil, Lymphocyte, Platelet, Liver Cancer, Prognosis

1. Introduction

HCC had been ranked as the 2nd leading cause of cancer death in Taiwan for several years [1]. Most oncologists try to get a good survival due to the improvement of care program in the world [2] [3]. Pretreatment imaging and assessment remain the main methods used to evaluate prognosis in liver cancer patients after treatments [4] [5] [6]. The relationship of the prognosis of HCC patients and inflammation was noted in recent decade [4] [7] [8].

Inflammation is an important component of tumor progression which had been mentioned for decades. It is well known that major liver cancer develops during inflammatory reaction of hepatitis B or C virus infection [9] [10]. Tumor micro-environment regulated by inflammatory cells clearly plays a basic role in the neoplastic process, stimulation of proliferation and migration and survival [11] [12] [13]. The inflammatory reaction usually responds to tumors persistence. Tumor cells produce various cytokines and chemokines that attract leukocytes. The inflammatory component of a developing neoplasm may include a diverse leukocyte population such as neutrophils, macrophages, and lymphocytes [12] [14].

Platelets can release granules containing a variety of contents that can both inhibit and stimulate plasmatic coagulation, angiogenesis immune-surveillance, or neoplasm growth through the releasing growth factors such as platelet derived growth factor, platelet factor IV and thrombospondin [15] [16]. Therefore, platelets can play important roles in tumor pathophysiology, including immune escape in hematogenous tumor spread and leading to tumor cell adhesion, invasion and tumor progression. In the previous reports, good or poor predictor of survival with neutrophil-lymphocyte ratio (NLR) or platelet-lymphocyte ratio (PLR) was demonstrated in some solid tumors such as liver, colo-rectum, breast, lung, and cervical cancers [17] [18] [19] [20] [21]. The prognostic potential of a novel inflammation-based system, the combination of the NLR and PLR, for predicting the survival time of 287 patients with HCC who had an elevated NLR (>2.58) and an elevated PLR (>131.78) were allocated an important prognostic score [22]. In addition to clinical grading scales of HCC, NLR or PLR could be used for demonstrating that patients with HCC have a significantly high risk of progressive disease following initial treatments [23] [24]. Therefore, we try to study the roll of NLR and PLR scales in the predictor of prognosis of HCC patients.

2. Patients and Methods

There were a total of 653 HCC patients registered in Cancer Registry Center of

our hospital from 2010 to 2014. Among them, 525 patients with complete data were enrolled in this study and there were 371 (70.7%) male and 154 (29.3%) female. All patients were confirmed diagnosis based on the cancer treatment guideline from our Cancer Registration Center. There were 131 (24.9%) and 394 (75.1%) patients initially underwent surgical and non-surgical treatments in our series. The non-surgical treatment included trans-arterial chemo-embolization (TACE), hepatic artery chemo-infusion (HAI), percutanous ethanol injection (PEI) or radio-frequency ablation (RFA) based on our hospital treatment guideline. The clinical features include patient's basic profiles, and neutophil, lymphocyte and platelet count in the peripheral blood at the time of diagnosis. The optimal cut-off from normal range of leukocyte, neutrophil & lymphocyte, and platelet were 4000 - 10,000/dl, 43% - 71% & 16.7% - 43.4%, and 150,000 - 440,000/dl respectively, the scale of NLR and PLR were derived from the lower normal range and higher normal range in cell number for neutrophil, lymphocyte and platelet. The 3 scales of NLR and PLR were ≤1.62, 1.63 - 2.57, ≥2.58 and ≤224, 225 - 253, ≥254 respectively. The 1-, 3-, and 5-year survival rates were analyzed.

These results are presented as mean ± SD and Kaplan-Meier analysis for their survival rates. Statistical analysis was performed with an unpaired Student's t-test after ANOVA for more than the other two groups in liver cancer patients. The P-values less than 0.05 were considered to be significant.

3. Results

1) General profiles of the patients of three scales of NLR

Three scales of NLR of HCC patients and their basic profiles were listed in Table 1. Relatively poor survival was found to be in the scale of higher NLR. Higher NLR was found mostly in the male (248, 74.5%) and TMN stage III and IV with a significant difference ($P < 0.01$). Surgical treatment was underwent more in the patients of low NLR (n = 26, 36.6% vs n = 299, 79.9%, $P < 0.002$).

The number of death was 262 (78.7%) in the higher NLR ≥ 2.58 with poor prognosis compared to other scales as shown in Table 1 & Table 2. The survival curves demonstrated poorer prognosis of HCC patients in Figure 1. The mean survival times were 44.3 ± 3.2, 40.4 ± 2.6, and 24.1 ± 1.4 months for the scales of the NLR ≤ 1.62, 1.63 - 2.57, and ≥2.58 respectively. The 5-year survival rates were 33.9%, 33.7%, and 16.7% respectively ($P < 0.001$). If NLR was more than 2.58, the 5-year survival rate was shorter than that of the other two groups ($P = 0.001$).

2) General profiles of the patients of three scales of PLR

Basic profiles of three scales of PLR of liver cancer patients were listed in Table 3. Relative poor survival was found in the scale of higher PLR. Higher PLR ≥ 254 were found mostly in the male (62, 69.7%) and TMN stage III and IV (n = 68, 77.3%) with a significant difference ($P < 0.01$). Surgical treatment was performed in the patients of PLR ≤ 224 (n = 113, 26.6%) and PLR ≥ 254 (n = 15, 16.9%) without significant difference ($P = 0.153$).

Table 1. Basic profiles of patients divided by three scales of NLR.

variant	stratum	≤1.62		1.63 - 2.57		≥2.58		P-value
		N = 71		N = 121		N = 333		
Age (M ± SD)		59.5 ± 11.0		64.7 ± 11		61.8 ± 12.4		0.01*
Gender (n, %)	Male	47	66.2%	76	62.8%	248	74.5%	0.037*
	Female	24	33.8%	45	37.2%	85	25.5%	
TMN Stage	I	35	49.3%	54	44.6%	85	25.7%	0.001*
	II	19	26.8%	27	22.3%	50	15.1%	
	III	13	18.3%	34	28.1%	138	41.7%	
	IV	4	5.6%	6	5.0%	58	17.5%	
Differentiation (Diff) (n, %)	well	3	4.2%	6	5.0%	9	2.7%	0.061
	moderately	20	28.2%	28	23.1%	50	15.0%	
	poorly	0	0.0%	7	5.8%	15	4.5%	
	Un-Diff	0	0.0%	0	0.0%	1	0.3%	
	unknown	48	67.6%	80	66.1%	258	77.5%	
Hepatitis B/C (n, %)	Non B/C	8	11.3%	16	13.2%	72	21.7%	0.175
	HBV	31	43.7%	54	44.6%	149	44.9%	
	HCV	29	40.8%	46	38.0%	100	30.1%	
	HBV + HCV	3	4.2%	5	4.1%	11	3.3%	
GOT (M ± SD)		82.4 ± 71.6		63.3 ± 40.9		87.8 ± 91.5		0.016*
GPT (M ± SD)		76.3 ± 52.2		57.3 ± 37.7		60.1 ± 68.7		0.084
GOT/GPT (M ± SD)		1.19 ± 0.67		1.24 ± 0.61		1.73 ± 1.43		0.001*
Albumin (M ± SD)		3.7 ± 0.5		3.7 ± 0.6		3.5 ± 0.6		0.085
WBC × 10^3 (M ± SD)		5 ± 1.7		5.9 ± 4.2		8.5 ± 5.0		0.001*
Platalate × 10^3 (M ± SD)		139.5 ± 67.1		148 ± 82.7		183.5 ± 101.8		0.001*
Lymphocyte (M ± SD)		1952.7 ± 716.4		1659.3 ± 1130.2		1086.0 ± 556.3		0.001*
Treat. method	Non-surgical	45		63.4%		83		68.6%
	Surgical	26	36.6%	38	31.4%	266	79.9%	0.002*
Survival	Death	39	54.9%	71	58.7%	262	20.1%	
	Alive	32	45.1%	50	41.3%	71	78.7%	0.001*

*P ≤ 0.05.

Table 2. Survival rate based on the scale of N/L ratio of liver cancer.

N/L	n	Death	Survival (Month)		Survival (%)		
			Mean	SD	1 yr	3 yr	5 yr
≤1.62	71	39 (54.9%)	44.3	3.2	80.3	60.3	33.9
1.63 - 2.57	121	71 (58.6%)	40.4	2.5	76.9	49.4	33.7
≥2.58	333	262 (78.7%)*	24.1	1.4	50.8	25.8	16.7

*P < 0.001.

Table 3. Basic profiles of patients divided by three scales of PLR.

variant	stratum	≤224		225 - 253		≥254		P-value
		N = 425		N = 11		N = 89		
Age (M ± SD)		61.9 ± 0.6		64.7 ± 2.2		63.1 ± 12.9		0.529
Gender (n, %)	Male	229	70.4%	10	90.9%	62	69.7%	0.327
	Female	126	29.6%	1	9.1%	27	30.3%	
TMN Stage	I	158	37.3%	3	27.3%	13	14.8%	0.001*
	II	89	21.0%	0	0.0%	7	8.0%	
	III	127	30.0%	7	63.6%	51	58.0%	
	IV	50	11.8%	1	9.1%	17	19.3%	
Differentiation (Diff) (n, %)	well	15	3.5%	0	0.0%	3	3.4%	0.001*
	moderately	84	19.8%	2	18.2%	12	13.5%	
	poorly	19	4.5%	0	0.0%	3	3.4%	
	Un-Diff	0	0.0%	1	9.1%	0	0.0%	
	unknown	307	72.2%	8	72.7%	71	79.8%	
Hepatitis B/C (n, %)	Non B/C	68	16.0%	2	20.0%	26	29.2%	0.121
	HBV	194	45.6%	4	40.0%	36	40.4%	
	HCV	147	34.6%	3	30.0%	25	28.1%	
	HBV + HCV	16	3.8%	1	10.0%	2	2.2%	
GOT (M ± SD)		77.8 ± 3.8		55 ± 10.5		101.8 ± 9.3		0.021*
GPT (M ± SD)		63 ± 3.1		46.2 ± 13.3		56.9 ± 5.3		0.482
GOT/GPT (M ± SD)		1.40 ± 0.05		1.65 ± 0.62		2.25 ± 0.20		0.001*
Albumin (M ± SD		3.6 ± 0.0		3.8 ± 0.2		3.3 ± 0.1		0.001*
WBC × 10^3 (M ± SD)		7.0 ± 0.2		7.8 ± 1.2		9.5 ± 0.6		0.001*
Platalate × 10^3 (M ± SD)		143.9 ± 3.3		221.9 ± 32.9		280.1 ± 12.4		0.001*
Neutrophi (M ± SD)		4697.1 ± 181		6131.1 ± 1107		7972.6 ± 543.2		0.001*
Lymphocyte (M ± SD)		1474.5 ± 40.3		903.6 ± 129.8		713 ± 41.2		0.001*
Treat. method	Non-surgical	312	73.4%	8	72.7%	74	83.1%	0.153
	Surgical	113	26.6%	3	27.3%	15	16.9%	
Survive	Death	286	67.3%	7	63.6%	80	89.9%	0.001*
	Alive	139	32.7%	4	36.4%	9	10.1%	

*P ≤ 0.05.

In the period of 5 years follow-up study, the number of death was 80 (89.9%) patients in the scale of PLR ≥ 254 with poorer prognosis compared to other scales as shown in Table 3 & Table 4. The survival curves demonstrated poorer prognosis of HCC patients with PLR ≥ 254 shown in Figure 2. The mean survival times were 34.1 ± 1.4, 29.3 ± 8.1, and 14.2 ± 2.1 months for the groups of the PLR ≤ 224, 225 - 253, and ≥254 respectively. The 5-year survival rates were 25.5%, 36.4%, and 7.7% for the groups of the PLR ≤ 224, 225 - 253, and

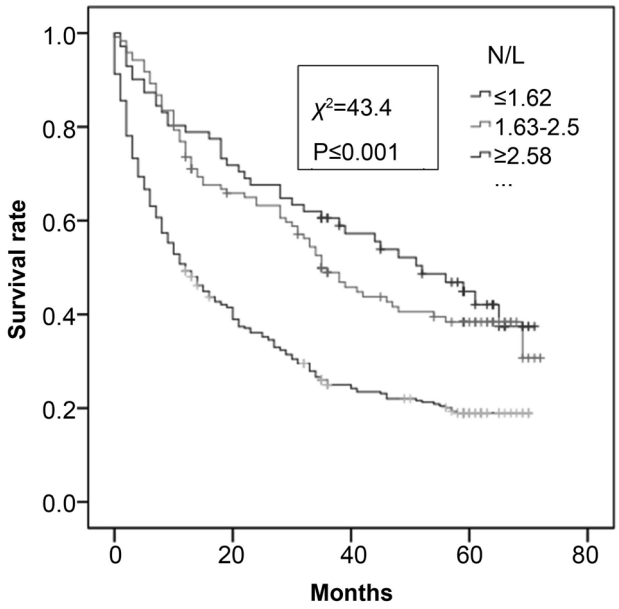

Figure 1. Survival cure of liver cancer patients based on the scale of N/L ratio and high ratio had a poor prognosis (χ^2 = 43.4, P ≤ 0.001).

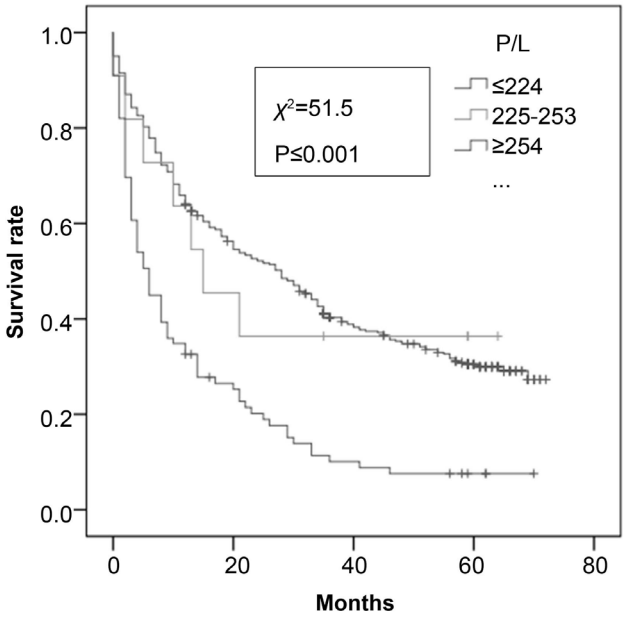

Figure 2. Survival cure of liver cancer patients based on the scale of P/L ratio and high ratio had a poor prognosis (χ^2 = 51.5, P ≤ 0.001).

Table 4. Survival rate based on the scale of P/L ratio of liver cancer

P/L	n	Death n	Survival (Month)		Survival (%)		
			Mean	SD	1 yr	3 yr	5 yr
≤224	425	286	34.1	1.4	65.9	40.5	25.5
225 - 253	11	7	29.3	8.1	63.6	36.4	36.4
≥254	89	80	14.2	2.1	34.8	11.6	7.7

≥254 respectively ($P < 0.001$). The results of higher PLR ≥ 254 could reflect poorer survival more solitary than that of higher NLR ≥ 2.58 as shown in **Table 1** & **Table 3**, and **Figure 1** & **Figure 2**.

4. Discussion

Clinical features and molecular pathology of HCC are the main determinants of current treatment strategies and prognosis factors. The relationship between the inflammatory cells and cancer has been demonstrated by accumulating studies [11]. The counts of peripheral inflammatory cells, including neutrophil, lymphocyte and platelet, have demonstrated the strong link between the inflammatory system and prognosis in cancer patients [6] [10]. In particular, NLR and PLR have recently been reported to be prognostic factors in several types of solid cancers [17] [18] [19] [20] [21].

Early in the neoplastic process, these inflammatory cells are powerful tumor promoters, facilitating genomic instability and promoting angiogenesis. The inflammatory cells produced chemokines and cytokines that influenced the whole tumor mass, regulating the growth, migration and differentiation of all cell types in the tumor micro-environment [11] [14]. In addition, these inflammatory cells will release growth factors, promoting angiogenesis and lymphangiogenesis, stimulating DNA damage, remodelling the extra-cellular metaprotease to facilitate invasion, coating tumour cells to make available receptors for disseminating cells via lymphatics and capillaries, and evading host defense mechanisms. In fact, excess inflammatory cells in the tumor microenvironment which harbor risk for developing cancer or are indicators of prognosis in a fully developed malignancy [11] [13] [25].

The role of neutrophils in cancer usually reflects a state of host inflammation, which is a hallmark of cancer. They can participate in different stages of the oncogenic process including tumor initiation, growth, proliferation or metastasis [13] [26] [27]. In patients with solid cancers, neutrophils expand both locally at the tumor microenvironment and systemically, the expansion of neutrophil is generally associated with poor prognosis because neutrophils are key regulators of intra-luminal survival of cancer cell line and extravasation through their cross-talk with host cells and disseminating cancer cells [28]. Lymphocyte is a non-specific but commonly used as a marker of host immunity [29] [30]. Liver cancer cells could evade the immune surveillance via modulating the key immune cells such as lymphocytes by alpha feto-protein [31] which will affect the prognosis of cancer patients. In recent years, numerous evidences had demonstrated that the lymphocyte count is an independent prognostic marker in various cancers, such as liver, breast, colorectal, lung and others cancers [32] [33] [34] [35] [36]. Besides, lymphocyte count and lymphocyte-white blood cell ratio were also associated with overall survival in advanced cancer patients reported by Zhao [29]. Taken together, these results suggested that a low level of lymphocytes may reflect a poor health status and poor prognosis in advanced cancer

patients.

NLR is calculated from existing routine blood examination for our patients. An elevated NLR is associated with worse outcomes in many solid tumors, both in early and advanced stage of cancer [37] [38]. By using NLR acting as a biomarker, there is a potential for the identification of early responders and prognostic relevance associated with clinical outcome [8] [39]. We should note that the excessive presence of inflammation and neutrophil which were an indirect risk and can be varied among cancer cell types has the worse impact on the outcome. In our series, three scales of NLR were ≤1.62, 1.63 - 2.57, and ≥2.58 for comparison in our HCC patients. Patients with lower baseline of NLR ≤ 1.62 were associated with better overall survival. In addition, in other reports, patients with baseline NLR < 5 had a better median survival of 20.7 months compared to a median overall survival of 7.9 months in patients with baseline NLR ≥ 5 specifically in advance cancer patients [37], Cancer patients of poor prognosis were reported if NLR ≥ 5 in patients with advanced solid tumors treated with PD-1/PD-L1 inhibitors reported by Ameratunga *et al.* [40]. Concerning base line, there was a statistically significant association between baseline NLR ≥ 3.5 and immediate progression on 2-month follow-up imaging after TACE patients with progressive disease had a mean of NLR 4.10 compared to stable disease, partial, and complete response had a mean of 2.76, 2.72, and 2.48 respectively in their follow-up results [23]. In our series, the mean survival times were 44.3 ± 3.2 and 24.1 ± 1.4 months if the NLR ≤ 1.62, and ≥2.58 ($P < 0.001$). Moreover, in another report by using the Cox proportional hazards model showed that NLR > 2.81 was significantly associated with poor overall survival and tumor recurrence in the total or subgroups of patients grading with Barcelona Clinic Liver Cancer (BCLC) stages [41]. Taking together, it is true to demonstrate that a higher NLR resulted in a poorer prognosis reported in similar observations in liver cancer patients [18] [19]. From above studies, the base line of NLR was variable due to their study population included patients in general or specific focus on a specific clinical stage of HCC patients.

It is clear that higher platelet level will result in poorer prognosis because platelet granules contain the greatest abundance of cancer-related factors including, adhesion molecules, growth factors, angiogenic factors, tissue metalloproteinases, chemokines, and immunologic molecules [42] [43] [44]. Even circulating tumor cells may encounter platelet-derived microparticles which may serve to activate the platelets and lead to metastasis [43] [45]. This process is facilitated by adhesion of tumor emboli to the vascular endothelium as well as stimulation of immune cells cytokine and growth factor production among the cellular responses. Therefore, platelets are well suited to serve as facilitators in cancer progression and metastasis which will clearly affect the prognosis of cancer patients [43] [46] [47]. Increased platelet will create an elevated PLR which was associated with reduced overall survival in patients with advanced cancer [48] in addition to HCC [49] [50]. Mean survival was shorter if PLR ≥ 254 in our series. It is an evidence that either higher NLR or PLR were significantly asso-

ciated with lymph node metastasis, and poor overall survival in most studies [6] [38] [51]. Taken together, either increased neutrophil and platelet, or decreased lymphocyte will elevate either NLR or PLR. This can be a predictor for the poor prognosis of cancer patients by routine clinical tests. There are some limitations including the applying treatment methods in the patients who follow the treatment guide-line of our hospital cancer registry center. Therefore, there is still a work to be done before using NLR and PLR as validated prognostic markers in clinical settings.

In conclusion, the neutrophil, lymphocyte and platelet are players in cancer growth and have a potential role as predictors of survival in our HCC patients. NLR and PLR are easily obtained in our clinical practice and we should pay more attention to reach a lower ratio for getting a better survival in our patients where possible.

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Contribution of Authors

Study Design: Ker CG.

Data collection: Tong HI, Yang MY, Tseng IT, Chang DM, Chen HY, Ko CM, Chao CY.

Biostastic: Wang BW, Chen YF.

Interpretation and Manuscript: Ker CG.

Conflicts of Interest

There are no any conflicts of interest of all authors listed in this manuscript or institution or product that is mentioned in the manuscript.

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