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Significances of Peripheral Inflammatory Cells and Neutrophil/Platelet-Lymphocyte Ratio in Breast Cancer after Resection

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Abstract

Introduction: Breast cancer had become top leading cause of death in Taiwan and endangered women's health worldwide. Therefore, we try to invest the peripheral inflammatory cell counts and neutrophil-lymphocyte ratio (NLR) and platelet-lymphocyte ratio (PLR) from our routine practice for the predictor of prognosis of breast cancer after resection. **Patients and Methods:** There were 574 breast cancer patients accepted surgical resection and registered in Cancer Registry Center of our hospital. Patient's basic profiles, peripheral neutophil, lymphocyte and platelet count were measured for study. The scales of NLR and PLR were derived from the lower and higher normal range in cell count from neutrophil, lymphocyte and platelet respectively. Therefore, the scales for NLR and PLR were ≤1.62, 1.63 - 2.57, ≥2.58 and ≤224, 225 - 253, ≥254 respectively for analysis. **Results:** Poor 5-yr survival rate was found if higher cell counts of neutrophil and platelet ($p \leq 0.05$). Three scales of NLR were ≤1.62, 1.63 - 2.57, ≥2.58, and their 5-year survival rates were 94%, 91% and 84% respectively ($p = 0.019$). In the subgroup of HER-2 (negative), and 3-Negative breast patients had a higher NLR of poor prognosis. But higher PLR was found less in 3-Negative and non in 3-Positive patients ($p = 0.039$). The PLR was ≤224, 225 - 253, ≥254 and their 5-year survival rates were 92%, 87%, and 64% respectively ($p = 0.001$); Multivariate Cox regression model for predictor of breast cancer patients who have 3.39 (PLR ≥ 254) and 2.45 (NLR ≥ 2.58) times risk ($p = 0.02$ and $p = 0.002$) of poor prognosis respectively. **Conclusion:** Peripheral inflammatory cell counts are easily to take in our clinical practice and have a potential role as predictors of

prognosis. We have to pay attention to the trends of peripheral inflammatory cell count and their ratio in our clinical practice where possible.

Keywords

Inflammatory Cell, Neutrophil-Lymphocyte Ratio, Platelet-Lymphocyte Ratio, Cancer Prognosis, Survival Rate

1. Introduction

Breast cancer had endangered women's health worldwide and had been as the first causes of death of women in Taiwan for several years [1]. Pretreatment imaging, laboratory tests and surgical procedures remain the main methods used for evaluation of the prognosis [2] [3]. Theoretically, the inflammatory cells role as one of the important parts of tumor progression which had been mentioned for decades [4] [5]. Tumor micro-environment regulated by inflammatory cells clearly plays a basic influence on the neoplastic process, stimulation of proliferation, migration and survival [5] [6]. The inflammatory component of a developing neoplasm may include a diverse leukocyte population such as neutrophils, macrophages, and lymphocytes [6] [7].

Platelets can release a variety of contents that can both inhibit and stimulate angiogenesis, immune-surveillance, or neoplasm growth through the releasing some growth factors such as platelet derived growth factor, platelet factor IV and thrombospondin [8] [9]. In addition, platelets can play important roles in immune escape in hematogenous tumor spread and lead to tumor cell adhesion, invasion and tumor progression [10]. In the previous reports, predictor of better or poor survive with neutrophil/lymphocyte ratio (NLR) or platelate/lymphocyte ration (PLR) was demonstrated in breast cancer or even other solid tumors [11] [12] [13] [14] [15]. The measurement of the systemic inflammatory response had been refined using modified Glasgow Prognostic Score including the NLR or PLR to have prognostic value and independently association with survival in all cancers [16]. In univariate analysis by Ramos [17], an NLR > 3 was associated with poor overall survive ($p < 0.001$) and PLR > 250 was associated with worse overall survive ($p < 0.001$). However, after adjustment for potential confounders, only the PLR was more independently associated with worse outcomes. In the study of Fujii [18], they demonstrated that the finding of either a high FDG uptake in PET-CT scanning in breast tumor or a high NLR may be predictive of aggressive features and a reflection of poor prognosis among breast cancer patients. Prognostic significance for NLR PLR, and lymphocyte was simple predictors that might be useful for identifying patients who have high recurrence risk, and those that are candidates for additional treatments [19]. Therefore, we conduct this study to invest the inflammatory cells counts including the neutrophil, lymphocyte, platelet, NLR and PLR in the prognosis of breast cancer patients.

2. Patients and Methods

Breast cancer patients who were accepted surgical resection were 574 registered in Cancer Registry Center of our hospital from 2006 to 2011 and follow-up at least for 5 years in this study. All patients were confirmed diagnosis based on the cancer treatment guideline, and registered under the surveillance care program in our Cancer Registration Center. The clinical features include patient's basic profiles, and neutophil, lymphocyte and platelet cell count in the peripheral blood at the time of diagnosis were measured. The optimal cut-off from normal range of neutrophil, lymphocyte, and platelet were 43% - 71% (1720 - 2840/dl), 16.7% - 43.4% (668 - 1736/dl), and 150,000 - 440,000/dl in cell count respectively in our hospital, Therefore, the scales of NLR and PLR were derived from the lower normal range and higher normal range of cell count for neutrophil, lymphocyte and platelet respectively. Three scales of NLR were ≤1.62, 1.63 - 2.57, ≥2.58, and of PLR were ≤224, 225 - 253, ≥254 respectively of breast cancer. The 1-yr, 3-yr, and 5-year survival rates and their recurrent rates were analyzed according to the scales and variable factors including age, TMN stage, grading, vessel infiltration, lymph-node metastasis, positive rate of ER, PR, and HER2, and subtype (3-positive and 3-negative).

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

3. Results

1) Netrophil, Lymphocyte, and Platelet Counts in Breast Cancer Patients.

Mean survive time effected by peripheral neutrophil, lymphocyte, and platelet cell were listed in Table 1. Survival rate divided by scale of neutrophil, lymphocyte, and platelet were shown in Figures 1(a)-(c). Poor 5-yr survival rates were found if higher cell counts of neutrophil and platelet with a significant difference ($p \leq 0.05$). On the contrary, the 5-year survival rate was poor if lymphocyte cell counts was less than 16.6% as Table 1 and Figure 1(b).

2) N/L Ratio in Breast Cancer Patients.

NLR and the variable factors of breast cancer were shown in Table 2. The higher NLR were found in the group of HER-2 (negative), and 3-Negative breast cancer patients. There was none high NLR in 3-Positive breast cancer ($p < 0.01$). The NLR of breast cancers and their survival times and rates were listed in Table 2, The NLR was ≥2.58, the 5-year survival rates was poor prognosis than that of other two groups ($p = 0.019$). There were 11 (5.9%), 16 (9.2%), and 19 (15.4%) death within 5 years after operation found in the patients with PLR ≤ 224, 225 - 253, and ≥254 respectively. Their mean survival times were shorter in the patients of high score of NLR ≥ 2.58. The 1-yr, 3-yr, and 5-yr survival rates and curves demonstrated poor prognosis with higher NLR in Table 3 and Figure 2. Multivariate Cox regression model for predictor of prognosis were found poor

Table 1. Survival rates according to the scale of neutrophil, lymphocyte, and platelet.

Neutrophil (%)	N	Death	Survival months		Survival rate (%)		
			Mean	SE	1 yr	3 yr	5 yr
≤42	136	3	77.9	0.66	99	98	98
43 - 71	386	31	123.5	1.47	97	93	90
≥72	46	13	83.1	5.92	85	73	69
Lymphocyte (%)	N	Death	Survival months		Survival rate (%)		
			Mean	SE	1 yr	3 yr	5 yr
≤16.6	31	10	54.5	4.54	81	71	64
16.7 - 43.4	516	35	124.8	1.18	97	94	92
≥43.5	27	2	76	2.16	100	96	89
Platelet (10^3)	N	Death	Survival months		Survival rate (%)		
			Mean	SE	1 yr	3 yr	5 yr
≤149	21	4	77.9	4.95	95	85	76
150 - 440	561	43	123.7	1.22	96	93	91
≥441	11	3	62.8	6.6	91	81	63

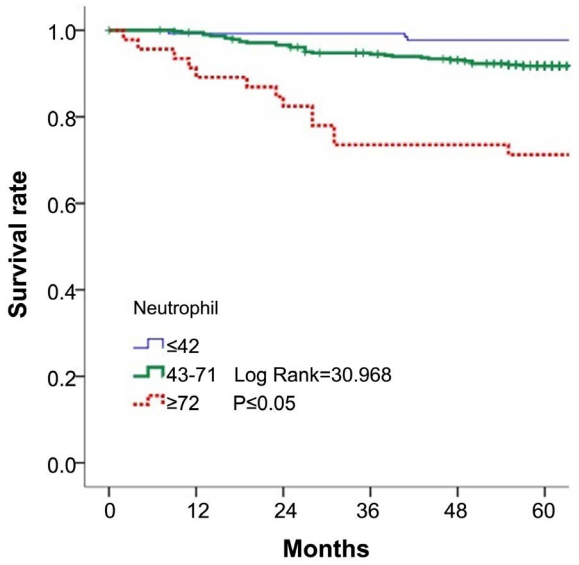
Table 2. Descriptive information of breast cancer patients divided into three scales according to the N/L ratio and variates.

Variate	Stratification	N/L ≤ 1.62		N/L 1.63 - 2.57		N/L ≥ 2.58		P value
		N = 187		N = 174		N = 123		
Age	(M ± SD)	54.3 ± 10.6		52.4 ± 11.6		51.7 ± 10.7		0.094
Stage	I	78	41.7	59	33.9	43	35	0.173
	II	72	38.5	78	44.8	46	37.4	
	III	28	15	31	17.8	22	17.9	
	IV	9	4.8	6	3.4	12	9.8	
Grade	well	37	19.8	38	21.8	32	26.0	0.205
	moderately	105	56.1	85	48.9	51	41.5	
	poorly	32	17.1	34	19.5	23	18.7	
	unknown	13	7	17	9.8	17	13.8	
Vessel (+)	No	123	65.8	118	67.8	79	64.2	0.048
	Yes	56	29.9	51	29.3	37	30.1	
	unknown	8	4.2	5	2.8	7	5.7	
LN (+) count.	(M ± SD)	12.5 ± 8.0		13.7 ± 7.3		11.8 ± 7.0		0.082
LN (+)	No	110	58.8	98	56.3	70	56.9	0.759
	Yes	72	38.5	73	42	48	39	
	unknown	5	2.7	3	1.7	5	4.1	
ER	Positive	133	72.7	114	65.9	91	75.8	0.149
	Negative	50	27.3	59	34.1	29	24.2	
PR	Positive	118	64.8	104	60.1	80	66.1	0.509
	Negative	64	35.2	69	39.9	41	33.9	
Her-2	Positive	52	28.4	54	31.4	19	15.7	0.008*
	Negative	131	71.6	118	68.6	102	84.3	
Subtype	3-Positive	11	9.9	0	0	0	0	<0.001*

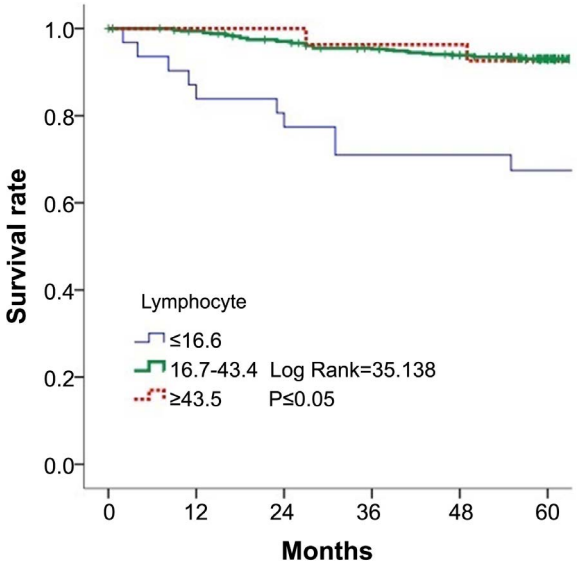
Continued

	3-Negative	21	18.9	30	56.6	21	77.8	
	Others	79	71.2	23	43.4	6	22.2	
WBC × 10^3	(M ± SD)	6.6 ± 2.0		7.1 ± 1.5		7.7 ± 2.3		<0.001*
Platalate × 10^3	(M ± SD)	241.6 ± 75.3		267.2 ± 61.5		269.4 ± 86.5		0.001*
Neutrophil	(M ± SD)	3780 ± 1701.3		4311 ± 983.8		5458.0 ± 1901.1		<0.001*
Lymphocyte	(M ± SD)	2218.1 ± 700.7		2122.8 ± 489.0		1529.8 ± 426.6		<0.001*
Recurrent	Yes	18	9.6	23	13.2	14	11.4	0.561
	No	169	90.4	151	86.8	109	88.6	
Status	Death	11	5.9	16	9.2	19	15.4	0.019*
	Alive	176	94.4	158	90.8	104	84.6	

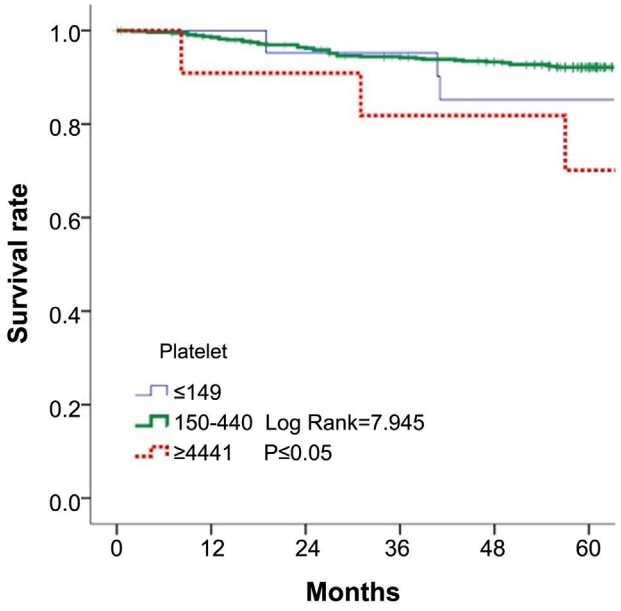
*P < 0.05.



(a)



(b)



(c)

Figure 1. Analysis of 5-year survival rate with Kaplan-Meier method in breast cancer patients divided into three scales of neutrophil (a), lymphocyte (b), and palatelet (c) and revealed a significant difference of survival rate of (a) $X^2 = 30.968$, $P \leq 0.05$, (b) $X^2 = 35.138$, $P \leq 0.05$ and (c) $X^2 = 7.945$, $P \leq 0.05$ in each group.

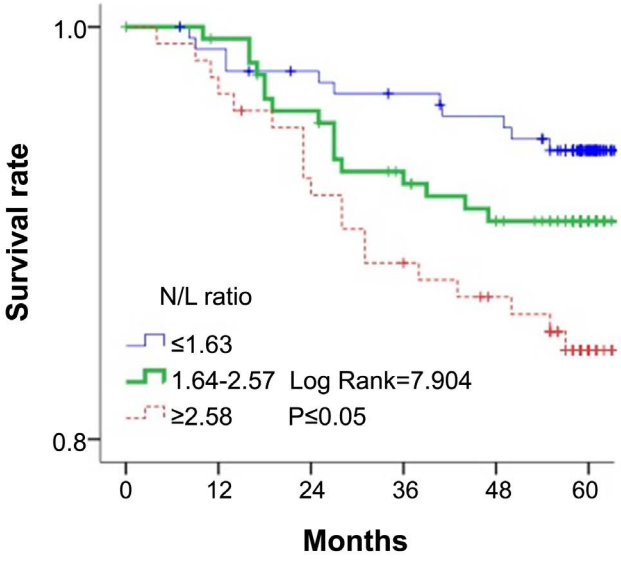


Figure 2. Analysis of five-year survival rate of Kaplan-Meier method in breast cancer patients divided into three scales according N/L ratio ($P \leq 0.019$) with Log-rant test.

in the TMN stage IV having Hazard ratio of 28.56 ($p = 0.001$), and NLR > 2.58 to having 2.45 times risk of poor prognosis ($p = 0.021$) than other groups as shown in Table 4. There was no different prognosis concerning operative method.

3) P/L Ratio in Breast Cancer Patients

The descriptive information variable factors and PLR of breast cancer patients were shown in Table 5. The lower PLR were found in the group of low lymph

Table 3. Analysis of five-year survival rate of Kaplan-Meier method in breast cancer patients divided into three groups according N/L ratio.

N/L	N	Death	Survival months		Survival rate (%)		
			Mean	SE	1 yr	3 yr	5 yr
≤1.62	187	11	76.1	0.9	99	97	94
1.63 to 2.57	174	16	122	2.4	99	93	91
≥2.58	123	19	95.4	2.7	98	89	84

Table 4. Multivariate Cox regression model for predictor of prognosis of breast cancer.

Variate	β	Hazard ratio	95% CI of HR		P value
			Lower	Upper	
Age	0.048	1.049	1.021	1.077	<0.001*
Stage					
I (ref.)		1			
II	1.25	3.489	1.134	10.741	0.029*
III	1.932	6.905	2.175	21.929	0.001*
IV	3.352	28.565	8.849	92.209	0.001*
N/L ratio					
≤1.62 (ref.)		1			
1.63 to 2.57	0.624	1.866	0.857	4.063	0.116
≥2.58	0.897	2.453	1.142	5.269	0.021*
OP type					
BCS (ref.)		1			
MRM	0.03	1.030	0.300	3.531	0.962

*P < 0.05. BCS: breast conservative surgery. MRM: modified radical mastectomy.

Table 5. Descriptive information of breast cancer patients divided into three scales according P/L ratio and variates.

Variate	Stratification	P/L ≤ 224		P/L 225 - 253		P/L ≥ 254		P value
		N = 440		N = 16		N = 28		
Age	(M ± SD)	53.1 ± 11.0		52.3 ± 12.3		52 ± 11.3		0.796
Stage	I	170	38.6	4	25	6	21.4	0.001*
	II	180	40.9	9	56.3	7	25	
	III	71	16.1	3	18.8	7	25	
	IV	19	4.3	0	0	8	28.6	
Grade	well	100	22.7	4	25	3	10.7	0.94
	moderately	222	50.5	8	50	11	39.3	
	poorly	80	18.2	2	12.5	7	25	
	unknown	38	8.6	2	12.5	7	25	

Continued

Vessel (+)	No	300	68.2	8	50	12	42.9	0.02*
	Yes	124	28.2	8	50	12	42.9	
	unknown	16	3.7	0	0	4	14.2	
LN (+) count	(M ± SD)	13 ± 7.5		12.0 ± 4.5		10.5 ± 6.9		0.203
LN (+)	No	256	58.2	9	56.3	13	46.4	0.464
	Yes	173	39.3	7	43.8	13	46.4	
	unknown	11	2.5	0	0	2	7.1	
ER	Positive	314	72.2	9	56.3	15	60	0.178
	Negative	121	27.8	7	43.8	10	40	
PR	Positive	276	63.6	9	56.3	17	65.4	0.817
	Negative	158	36.4	7	43.8	9	34.6	
Her-2	Positive	117	26.9	4	25	4	16	0.481
	Negative	318	73.1	12	75	21	84	
Subtype	3-Positive	10	5.7	1	14.3	0	0	0.039*
	3-Negative	62	35.6	6	85.7	4	40	
	Others	102	58.6	0	0	6	60	
WBC × 10^3	(M ± SD)	7.0 ± 1.8		7.1 ± 1.7		7.3 ± 3.7		0.847
Platalate × 10^3	(M ± SD)	248.37 ± 59.7		322.4 ± 94		340 ± 142.8		0.001*
Neutrophil	(M ± SD)	4299.9 ± 1484		5120.4 ± 1492.1		5519 ± 3385.4		0.001*
Lymphocyte	(M ± SD)	2088 ± 598.4		1358.0 ± 373.4		1139.7 ± 364.8		0.001*
Recurrent	Yes	49	11.1	3	18.8	3	10.7	0.637
	No	391	88.9	13	81.3	25	89.3	
Status	Death	34	7.7	2	12.5	10	35.7	0.001*
	Alive	406	92.3	14	87.5	18	64.3	

*P < 0.05, BCS: breast conservative surgery. MRM: modified radical mastectomy.

vessel involvement and low positive lymph-node metastasis, Higher PLR was found less in 3-Negative breast cancer and none in 3-Positive breast cancer (p = 0.039). The PLR of breast cancers and their survival times and rates were listed in Table 6 and Figure 3, The PLR was ≥254, the 5-year survival rates were poor in prognosis than that of other two groups (p = 0.001) (Figure 2). There were 34 (7.7%), 2 (12.5%), and 10 (35.7%) were death within 5 years after operation in the patients with PLR ≤ 224, 225 - 253, and ≥254 respectively (p < 0.001). Their mean survival times were shorter in the patients of high score of NLR ≥ 2.58. The 1-, 3-, and 5-yr survival curves demonstrated poor prognosis with higher NLR in Table 5 and Figure 2. Multivariate Cox regression model for predictor of prognosis were found poor in the TMN stage IV having 22.1 times risk than other grades (p = 0.001), and PLR > 254 to having 3.39 times poor prognosis respectively than other groups (p = 0.002) as shown in Table 7.

Table 6. Analysis of five-year survival rate of Kaplan-Meier method in breast cancer patients divided into three groups according P/L ratio.

P/L	N	Death	Survival months		Survival rate (%)		
			Mean	SE	1 yr	3 yr	5 yr
≤224	440	34	123.9	1.3	99	95	92
225 to 253	16	2	70.5	3.3	100	94	87
≥254	28	10	54.7	5.0	89	64	64

Table 7. Multivariate Cox regression model for predictor of breast cancer.

Variables	β	Hazard ratio	95% CI of HR		P value
			Lower	Upper	
Age	0.045	1.046	1.019	1.075	<0.001*
Stage					
I (ref.)		1			
II	1.137	3.118	1.029	9.443	0.044*
III	1.793	6.006	1.915	18.832	0.002*
IV	3.096	22.107	6.897	70.864	0.001*
P/L ratio					
≤224 (ref.)		1			
225 to 253	0.784	2.19	0.516	9.303	0.288
≥254	1.222	3.394	1.585	7.269	0.002*
OP					
BCS (ref.)		1			
MRM	0.524	1.689	0.501	5.686	0.398

*P < 0.05.

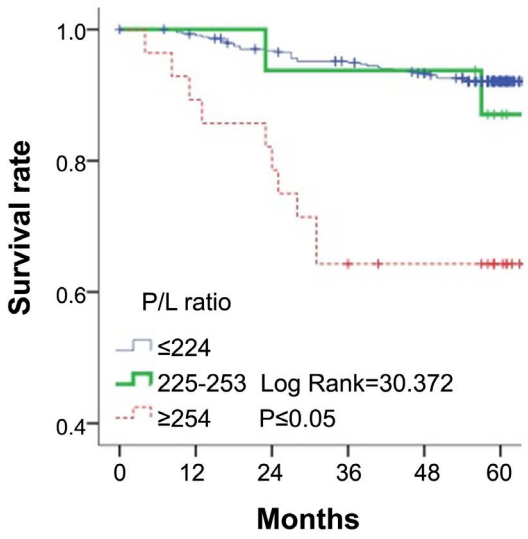


Figure 3. Analysis of five-year survival rate of Kaplan-Meier method in breast cancer patients divided into three groups according P/L ratio (P ≤ 0.05) with Log-rant test.

4. Discussion

The relationship between the inflammatory cells and cancer has been demonstrated by accumulating studies [5] [20]. The pretreatment counts of peripheral inflammatory cells, including neutrophil, lymphocyte and platelet, have demonstrated the strong link between the inflammatory system and prognosis in cancer patients [21]. In particular, NLR and PLR have recently been reported to be significant prognostic factors even in other types of solid cancer [11] [12] [13] [14] [15].

In the neoplastic process, these inflammatory cells are powerful tumor promoters, tumor growth, facilitating genomic instability and promoting angiogenesis. The inflammatory cells will produce chemokines and cytokines that influence the whole tumor bio-enviroment, regulating the growth, migration and differentiation of all cell types in the tumor micro-environment [5] [7] [22] [23]. In addition, these inflammatory cells will release growth factors, promoting angiogenesis and lymphangiogenesis, remodelling the extra-cellular metaprotease to facilitate invasion, and disseminating cells via lymphatics or capillaries, and evading host defense mechanisms in breast cancer. Actually, in a fully developed malignancy, there are excess inflammatory cells in the tumor microenvironment and harbor altered risk for developing cancer or an indicators of prognosis [5] [24] [25]. In our series, the presences of positive breast cancer cells in the lympho-vessel, or lymph-node had a result of poor prognosis.

The role of neutrophils in cancer is multifactorial and reflect a state of host inflammation and they can participate in different stages of the oncogenic process including tumor initiation, growth, proliferation or metastasis [24] [26] [27]. In patients with solid cancers, neutrophils expand both in the tumor microenvironment and systemically, and are generally associated with poor prognosis due to neutrophils as key regulators of cross-talk with host cells and disseminating cancer cells [28]. Lymphocytes are a non-specific commonly used as a marker of host immunity [29] [30]. In recent years, many evidences have demonstrated that the lymphocyte count is an independent prognostic marker in various cancers, such as liver, colorectal, lung cancers in addition to breast cancer [30] [31] [32] [33] [34]. Besides, lymphocyte count and neutrophil-lymphocyte cell ratio were also evaluated with overall survival in advanced cancer patients [19] [29]. Taken together, these results suggested that a low level of lymphocytes may reflect a poor health status and poor prognosis in cancer patients. In our study, lymphocyte less than 16.6%, the 1-yr, 3-yr, and 5-yr survival rate was poor than that of higher percentage of lymphocyte.

NLR is calculated from routine labs for patients and readily available allows it to be conveniently monitored. These clinical findings make NLR a biomarker easy to evaluate, and have potential for the identification of early responders and prognostic relevance associated with clinical outcome [35]. We should note that impact the worse outcome is the presence of inflammation and the neutrophils is an indirect risk and can vary among cancer cell types. However, the normal

NLR values in an adult, non-geriatric, population in good health are between 0.78 and 3.53 [36]. The cutoff level of NLR ranged from 1.93 to 4.8, which effected tendency on the prognosis of breast cancer patients, was reported from the literatures [21] [37] [38] [39]. In our series, the 5-year survival was 84% if NLR ≥ 2.58 and had a same trends of higher NLR having a poor prognosis like other literatures [12] [13]. In a report regarding role of NLR in overall survival, there was no significant difference between patients with high and low NLR with 5-year overall survival of 90.8% and 91.7% ($p = 0.707$). But in triple-negative breast cancer, patients with high NLR was associated with worse 5-year disease free survival rate compared with patients with low NLR (63.4% vs 84.9%, $p = 0.040$) [37]. On the contrary, patients with low NLR had a poorer 3-year disease free survival than patients with high NLR (89.7% vs 94.0%, $p = 0.047$). Neither lymphocyte count nor NLR could predict overall survival independently. Particularly in HER-2-positive breast cancer patients who were treated with adjuvant Trastuzumab, a high lymphocyte count is significantly associated with a poor disease free survival [40].

Platelet granules contain abundance of cancer related factors including adhesion molecules, growth factors, and immunologic molecules [41]. Circulating cancer cells may encounter platelet-derived particles which may serve to activate the platelets and leads to metastasis [10] [42]. Therefore, platelets are well suited to serve as facilitated cancer progression and metastasis which will clearly affect the prognosis [42] [43] [44]. Elevated PLR was associated with reduced overall survival in patients with advanced cancer [17] [45] [46]. The cutoff level of PLR ranged from 104.4 to 250 which effected the prognosis of breast cancer patients, was reported from the literatures [13] [17] [46]. Our results had the same trend and mean survival was shorter if PLR elevated ≥254 in our series. In another study suggested that breast cancer patients with low PLR < 150, treated with neo-adjuvant chemotherapy achieve higher complete pathological response, independently of primary breast cancer molecular subtype [47]. Similarly, a PLR ≥ 250 was associated with worse overall survival rate ($p < 0.001$) and only the PLR was more independently associated with worse outcomes in patients with breast cancer [17]. The combination of NLR and PLR may reflect patients' immunogenic phenotype. Low levels of both NLR and PLR may thus indicate a status of immune system activation that may predict pathological complete response in breast cancer patients treated with neoadjuvant chemotherapy [13]. Taken together, both increased neutrophil and platelet, and decreased lymphocyte that will drive the elevation either NLR or PLR, and will be a predictor for the poor prognosis of breast cancer patients by the routine clinical tests.

In a special subtype of triple negative breast cancer (TNBC) is a more aggressive subtype of breast cancer and this subtype has the poorest prognosis, compared to other subtypes of breast cancer. TNBC is found to have a higher NLR or PLR with a shorter survival rate and an increased tumor recurrence [48] [49]. Among 57 patients of TNBC patients findings suggest that NLR ≥ 2.5 and PLR ≥ 200 are predictive of benefit from platinum-containing chemotherapy [50].

There were 72 patient of TNBC and NLR was ≥2.58 in 21 (29.2%) and PLR ≥ 254 in 4 (5.6%) with poor survival rate in our series. There was still some limitations existed including the applying treatment methods in our patients who follow the treatment guideline under hospital cancer registry center. Therefore, there is still much work to be done before they might be used as validated prognostic markers to reach the clinical setting.

5. Conclusion

The peripheral inflammatory cell counts are players in cancer growth and have a potential role as predictors of survival curves of breast cancer after surgery. Neutrophil, lymphocyte, platelet counts, NLR or PLR are easily to take in our clinical practice and highly associated with an adverse survival rate in our patients. Therefore, we have to pay attention to the trends of peripheral inflammatory cell count and ratio in our practice in order to get a better survival rate by using the treatment modalities where possible.

Contribution of Authors

Study design: C.-G. Ker,
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Conflicts of Interest

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

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