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Correlation of Platelet-Lymphocyte Ratio towards the Incidence of Follicular Thyroid Carcinoma

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ABSTRACT

Background: Recently, there is some consistent evidence that the inflammatory process is related to the development and progression of cancer. Platelet-lymphocyte ratio (PLR) may acts as simple biomarker for predicting the occurrence of cancer. Since fine needle aspiration could not distinguish between follicular thyroid carcinoma and benign lesion, the researchers were interested in conducting research correlation of PLR towards incidence of follicular thyroid carcinoma in Dr Soetomo Hospital Surabaya.
Methods: This study used secondary data from medical record of surgical pathology report diagnosed with follicular thyroid carcinoma who had undergone thyroid surgery at RSUD Dr. Soetomo Surabaya. Preoperative complete blood count was investigated then platelet-lymphocyte ratio was counted.
Results: The total research subjects were 40 people, consisting of 31 women (77.5%), 9 men (22.5%). Among three analyses between gender, age, and PLR towards follicular thyroid carcinoma, there is only one analysis which statistically had significant difference, that is correlation between PLR value towards incidence of follicular thyroid carcinoma (p value = 0.003). Two remaining analyses showed there were no statistically significant difference between gender (p value = 0.451) and age (p value = 0.336) towards follicular thyroid carcinoma. It was also found that patients with the higher PLR value had eight point five times higher suffering follicular thyroid carcinoma than those who had low PLR value.
Conclusion: According to this study, there was a statistically significant difference between PLR towards incidence of follicular thyroid carcinoma. The higher platelet-lymphocyte ratio (PLR) value, it is more likely to develop follicular thyroid carcinoma.

***Keywords*:** Platelet lymphocyte ratio, platelet-lymphocyte ratio, follicular thyroid carcinoma

INTRODUCTION

Thyroid nodules are common clinical problem. These nodules can be benign or malignant. Solitary (single) nodules have a tendency towards malignancy. Epidemiological studies show the prevalence of palpable thyroid nodules of approximately 5% in the female population and 1% in men living in parts of the world where iodine intake is adequate. Ultrasonography (USG) can detect the presence of thyroid nodules in 19%-68% of randomly selected individuals, with a higher frequency in women and the elderly. The clinical significance of thyroid nodules lies in the need to exclude thyroid cancer, which occurs in 7%-15% of cases depending on age, sex, history of radiation exposure, family history and other factors. Well differentiated thyroid cancer, which includes papillary and follicular thyroid cancer, occupies the largest percentage (90%) with a prevalence of 80-84% and 6-10%, respectively, of all types of thyroid cancer. Both types of tumors originate from thyroid follicular epithelial cells. They are histopathologically different from poorly differentiated (medullary carcinoma) arising

from parafollicular cells (C cells) and undifferentiated anaplastic carcinoma which together account for 5-7% of cases. In the United States, approximately 63,000 new cases of thyroid cancer are predicted to be diagnosed in 2014 compared to 37,200 in 2009. The annual incidence has almost tripled from 4.9 cases per 100,000 in 1975 to 14.3 per 100,000 individuals in 1975 in 2009 with papillary thyroid cancer being the most common type.[1,2,3.]

Fine needle aspiration (FNA) is still the most important diagnostic modality and is often used in thyroid nodules. However, the sensitivity of FNA in thyroid cancer is 84%-93% and specificity is 75%-99%. Nearly 20% of FNA results go undiagnosed, due to sampling errors or poor preparation technique. The main problem in the evaluation of thyroid pathology is differentiating between benign and malignant nodules, at least 15% of all thyroid nodules are present clinically detectable was found to be malignant and one third of these FNA cytological evaluations were unable to provide a definite diagnosis. Follicular thyroid cancer histopathologically exhibits transcapsular or vascular invasion and is distinguished from papillary by the absence of the characteristic features of its nucleus. FNA examination is not able to distinguish follicular thyroid cancer and benign lesion (follicular adenoma) because capsular and vascular invasion cannot be observed only by FNA. Therefore, most FNA results in the interpretation of follicular neoplasms that fall into the indeterminate category, this type of lesion requires minimal lobectomy/ ismulobectomy as a follow-up diagnostic procedure to obtain tissue specimens. Vries coupe is not recommended because it is difficult to assess capsular and vascular invasion, especially tumors with irregular capsules and different thicknesses [4,5,6,7,8].

Recently, there is some consistent evidence that the inflammatory process is related to the development and progression of cancer. Platelets are markers of the inflammatory process and are involved in the progression of tumor invasion. Several studies have revealed that the inflammatory process is related to the prognosis of cancer patients, but there is still little research on the prognosis of thyroid cancer. The platelet/lymphocyte ratio (PLR) is a simple biomarker that can act as a marker/ prognostic tool for well-differentiated thyroid cancer. PLR is a hematological parameter that is easy to do and determine and does not require a lot of cost so that it can be used in various populations to determine survival risk and the risk of recurrence of thyroid cancer. The rationale for this PLR measurement is the quantitative expression of the systemic inflammatory response and reflects the relationship between tumorogenesis and chronic inflammation. The study by Ozmen et al. stated that higher PLR and neutrophil-lymphocyte ratio (NLR) were associated with higher thyroglobulin levels indicating lower survival rates, and were superior to CRP in predicting the incidence of well-differentiated thyroid cancer. Another study conducted by Rianto et al. concluded that there was a statistically significant difference in platelet-lymphocyte ratio and mean platelet volume between benign and malignant thyroid nodules where the platelet-lymphocyte ratio and mean platelet volume were higher in thyroid cancer than in the benign thyroid nodule group. [9,10,11]

Based on previous studies, the researcher did not find a study that specifically discussed the correlation between PLR measurements towards the incidence of follicular thyroid cancer, so the researchers were interested in conducting research on the correlation between the value of the platelet/lymphocyte ratio in Dr Soetomo Hospital Surabaya with the incidence of follicular thyroid cancer.

METHODS

This study is an analytic study to obtain correlation between PLR towards incidence of the follicular thyroid carcinoma with a case-control study design. This study used secondary data from medical record of

surgical pathology report diagnosed with follicular thyroid carcinoma who had undergone thyroid surgery at RSUD Dr. Soetomo Surabaya. At the same time, preoperative complete blood count was investigated then platelet-lymphocyte ratio was counted.

The sample in this study was 40 people, from consecutive sampling between 2012 until 2019. The inclusion criteria in this study included patients who had a complete medical record with surgical pathology report diagnosed with follicular thyroid carcinoma. The exclusion criteria included patient who had incomplete medical record, patient who had history of chemotherapy treatment, underwent treatment with antibiotic or immunosuppressant drugs, chronic or acute infection, and patient with liver disease or chronic kidney disease.

RESULTS

The total research subjects were 40 people, consisting of 31 women (77.5%), and 9 men (22.5%). Research subjects have an age range starting from the lowest age of 21 years and the highest age of 80 years with the average age in this study was 47.03 ± 12.82 years. The age of the research subjects were grouped into 4 groups, most of which were low risk women (≤ 50 years) totalling 21 (52.5%) people, followed by high risk women (> 50 years) as many as 10 (25%) people, men -high risk men (> 40 years) as many as 5 (12.5%) people, and low risk men (≤ 40 years) as many as 4 (10%) people. From a sample of 40 people, the platelet count was obtained with the lowest value being 149 x 10^3 cells/µl and the highest being 547 x 10^3/cell/µl with an average platelet count of 292.80±90.13 x 10^3 cells l.

In this study, the platelet count category was grouped into 3 groups, where most of the subjects in this study had a platelet count of 150-450 x 10^3 cells/µl as many as 38 (95%) people, followed by a platelet count <150 x 10^3 cells/l. l as many as 1 (2.5%) people, and platelet count > 450 x 10^3 cells/µl as many as 1 (2.5%) people. Based on the lymphocyte data, the lowest lymphocyte count was 0.10 x 10^3 cells/µl and the highest lymphocyte count was 4.037 x 10^3 cells/µl with an average lymphocyte count of 1.834 ± 0.682 x 10^3 cells/µl. In this study, the category of the number of lymphocytes was grouped into 3 groups, where most of the subjects in this study had a total of 0.8 4 x 10^3 cells/µl totalling 37 (92.5%) people followed by a lymphocyte count < 0.8 x 10^3 cells/µl as many as 2 (5%) people, and the number of lymphocytes > 4 x 10^3 cells/µl in 1 (2.5%) people.

Table 1. Characteristic of Subject Research

Characteristic of Subjeect Research		Total	Total	Min	Max	Mean	Std. Deviation
Sex	Male	9 (22,5%)	40 (100%)	-	-	-	-
	Female	31 (77,5%)					
Age	Female Low Risk (≤ 50 y.o)	21 (52,5%)	40 (100%)	21	80	47,03	12,82
	Female High Risk (> 50 y.o)	10 (25%)					
	Male Low Risk (≤ 40 y.o)	4 (10%)					
	Male High Risk (> 40 y.o)	5 (12,5%)					
Platelet (10^3)	< 150	1 (2,5%)	40 (100%)	149	547	292,80	90,13
	150-450	38 (95%)					
	> 450	1 (2,5%)					
Lymphocyte (10^3)	< 0,8	2 (5%)	40 (100%)	0,10	4,037	1,834	0,682
	0,8– 4	37 (92,5%)					
	> 4	1 (2,5%)					
Platelet Lymphocyte Ratio	High	21 (52,5%)	40 (100%)	91,06	407,62	167,516	65,716
	Low	19 (47,5%)					
Pathological Anatomy	Follicular Carcinoma	20 (50%)	40 (100%)	-	-	-	-
	Follicular Adenoma	20 (50%)					
Platelet Lymphocyte Ratio	Follicular Carcinoma	20 (50%)	40 (100%)	91,06	407,62	200,798	74,472
	Adenoma Follicular	20 (50%)	40 (100%)	97,39	226,89	134,23	31,408

The gender in this study it was found that most of the research subjects were women, as many as 31 people, consisting of 14 (45.2%) people experiencing follicular carcinoma and 17 (54.8%) people having follicular adenoma, while the male as many

as 9 people consisting of 6 (66.7%) people had follicular carcinoma, and 3 (33.3%) people had follicular adenoma.

Table 2 – Correlation Sex and Incidence of Follicular Thyroid Carcinoma

Research Subject Characteristic		PA Post Op		Total	*P value*
		Follicular Carcinoma (%)	Follicular Adenoma (%)		
Sex	Male	6 (66,7%)	3 (33,3%)	9 (100%	0,451
	Female	14 (45,2%)	17 54,8%)	31 (100%)	
Total		20 (50%)	20 (50%)	40 (100%)	

Table 3 – Correlation Age and Incidence of Follicular Thyroid Carcinoma

Karakteristik Subjek Penelitian		PA Post Operasi		Total	*P value*
		Karsinoma Folikuler (%)	Adenoma Folikuler (%)		
Usia	Perempuan resiko rendah (≤ 50 tahun)	11 (52,4%)	10 (47,6%)	21 (100%)	0,336
	Perempuan resiko tinggi (> 50 tahun)	3 (30%)	7 (70%)	10 (100%)	
	Laki-laki resiko rendah (≤ 40 tahun)	2 (50%)	2 (50%)	4 (100%)	
	Laki-laki resiko tinggi (> 40 tahun)	4 (80%)	1 (20%)	5 (100%)	
Total		20 (50%)	20 (50%)	40 (100%)	

The low-risk group of women (≤ 50 years) as many as 21 people consisting of 11 (52.4%) people with follicular carcinoma and 10 (47.6%) people experiencing follicular adenoma. The group of high-risk women (> 50 years) consisted of 10 people consisting of 3 (30%) people with follicular carcinoma and 7 (70%) people with follicular adenoma. The group of low-risk men (≤ 40 years) consisted of 4 people consisting of 2 (50%) people with follicular carcinoma and 2 (50%) people with follicular adenoma. The group of men at high risk (> 40 years) consisted of 5 people consisting of 4 (10%) people with follicular carcinoma and 1 (2.5%) people with follicular adenoma**.**

Table 4 – Correlation Between PLR and Surgical Pathology Report

Research Subject Characteristic		PA Post Operative		Total	*P value*	OR (CI : 95%)
		Carcinoma (%)	Adenoma (%)			
Ratio Trombosit/ Limfosit	High	17 (68%)	8 (32%)	25 (100%)	0,003	8,5 (1,861-38,817)
	Low	3 (20%)	12 (80%)	15 (100%)		
Total		20 (50%)	20 (50%)	40 (100%)		

In this study, the value of the platelet/lymphocyte ratio was mostly high, as many as 25 people consisting of 17 (68%) people had follicular carcinoma and 8 (32%) had follicular adenoma, while the platelet/lymphocyte ratio was low (<129, 56) as many as 15 people consisting of 3 (20%) people had follicular carcinoma and 12 (80%) people had follicular adenoma.

DISCUSSION

In this study, the proportion of follicular thyroid cancer and follicular adenoma was balanced (50%: 50%). It was found that most of the patients had high PLR (52.5%). This data is further detailed regarding the PLR value of the carcinoma group in the range of 91.06 to 407.61 with a mean of 200.79 while the adenoma group is 97.39 to 226.89 with a mean of 134.23. These results are consistent with the researcher's hypothesis that high PLR is in line with the degree of thyroid follicular malignancy. In this study, 25 people had high PLR values consisting of 17 (68%) people with follicular carcinoma and 8 (32%) people with follicular adenoma. while the PLR value was low (<129.56) as many as 15 people consisting of 3 (20%) people had follicular carcinoma and 12 (80%) people had follicular adenoma.

Furthermore, an analysis of the correlation between PLR values towards the incidence of follicular thyroid carcinoma was carried out. The PLR value is the platelet count divided by the lymphocyte

count. The PLR value of 129.56 has been agreed to be the cut-off point based on previous research which is divided into two categories: high PLR (>129.56) and low (<129.56) (Rianto et al., 2019). Analysis of the correlation between PLR values towards the incidence of follicular thyroid carcinoma was performed using the Chi-Square statistical test with p value = 0.003 ($p < 0.05$). This means that there is a statistically significant difference between the value of the platelet-lymphocyte ratio (PLR) to the incidence of follicular thyroid carcinoma.

Furthermore, the researchers got an Odds Ratio (OR) of 8.5 (95% CI: 1.861-38.817) which means that someone who has a high platelet/lymphocyte ratio (PLR) (> 129.56) has an 8.5 times chance of developing carcinoma. follicular thyroid versus platelet/lymphocyte ratio (PLR) was low (<129.56). However, the researchers found interesting data, namely from 20 patients with follicular thyroid carcinoma, 3 of them had low PLR. So it is necessary to look for other underlying risk factors such as genetic factors, a history of iodine consumption or other factors that can trigger the development of follicular thyroid carcinoma.

The role of simple hematological parameters such as PLR is being developed. The underlying rationale is that PLR is a quantitative expression of the systemic inflammatory response and reflects the relationship between tumorogenesis and chronic inflammation. A high PLR may result from thrombocytosis or lymphopenia. Increased proinflammatory cytokines induce proliferation and megakaryocytes are converted to platelets. The role of platelets here is to support tumor growth and metastasis, due to the ability of platelets to produce and release growth factors such as vascular endothelial growth factor (VEGF) which together with other growth factors trigger angiogenesis and vascularization resulting in an increase in tumor growth rate. Platelets also stabilize the attachment of tumor cells to the endothelium and assist the migration of tumor cells out of the vasculature. Several proinflammatory cytokines such as IL-1 and IL-6 also trigger the proliferation of megakaryocytes resulting in thrombocytosis. Thrombocytosis is associated with a poorer prognosis in many cancers and a larger platelet size is metabolically and enzymatically active as illustrated in the MPV. In this case, platelets act as pro-tumor. Systemic inflammation causes an immunosuppressive effect which then leads to lymphopenia and lymphocyte dysfunction. Especially for thyroid tumors, recent research has revealed an imbalance of activity between immune suppressive and anti-tumor cells during the process of thyroid carcinogenesis. The importance of lymphocytes is emphasized as tumors with a high density of lymphocytic infiltration tend to have a better prognosis. Cytotoxic CD8+ T cells (CTL), natural killer (NK), and T NK cells (NKT cells) have important roles in the prevention of tumor growth due to their cytotoxic function and ability to induce apoptosis and destroy cancer cells. In this case, lymphocytes act as anti-tumor[12,13,14,15]

The focus of this study is to analyze the correlation between PLR towards the incidence of follicular thyroid carcinoma, which is calculated by dividing the platelet value by the preoperative lymphocyte value, then the result appears as the platelet/lymphocyte ratio. Apart from the function of platelets that support tumor growth and metastasis as well as the function of lymphocytes that are able to destroy cancer cells, researchers do not view the components of platelets and lymphocytes as separate variables for the incidence of follicular thyroid carcinoma. High PLR can arise as a result of thrombocytosis or lymphopenia which according to the analysis of this study can be a parameter for the incidence of follicular thyroid carcinoma. With this understanding, it can be concluded that low PLR is caused by low platelet values or high lymphocyte values. Platelet/lymphocyte ratio (PLR) has recently been accepted as a novel inflammatory marker that has been reported

to be biochemically involved in the development of invasive thyroid tumors. Complete blood count which includes the number of platelets and lymphocytes is one of the simple and commonly performed tests, especially in the pre-therapy of thyroid tumor patients. The results of this study also indicate that the platelet/lymphocyte ratio (PLR) is a strong potential parameter in a diagnostic approach for follicular thyroid cancer because it is a simple, inexpensive, and reproducible examination at almost no additional cost.[16,17,18]

CONCLUSION

The average PLR value in follicular thyroid carcinoma and follicular thyroid adenoma patient were 200.79 and 134.23 respectively. There was a statistically significant difference between the higher PLR towards the incidence of follicular thyroid carcinoma. The higher platelet-lymphocyte ratio (PLR) value, it is more likely to develop follicular thyroid carcinoma. Patients with the higher PLR value had eight point five times higher suffering follicular thyroid carcinoma than those who had low PLR value.

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