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The performance of various laboratory parameters to differentiate follicular thyroid carcinoma and follicular thyroid adenoma

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ABSTRACT

Background: Thyroid cancer continues to be a problem all over the world, with the number of cases increasing year after year. We aimed to examine the association between various laboratory parameters and follicular-type thyroid nodules. We also examined the performance of several parameters to differentiate malignant and benign follicular thyroid lesions.
Methods: This is a retrospective cohort study to determine the association between various laboratory parameters and follicular-type thyroid nodules in Dr. Soetomo General Hospital, Surabaya.
Results: A total of 62 patients were examined. The NLR in the follicular carcinoma group was 2.26 ± 1.35, whereas the NLR in the adenoma group was 2.72 ± 0.74. The average lymphocyte in the follicular carcinoma group was significantly higher than the adenoma group, 2.20 ± 0.78 vs. 1.76 ± 0.82. With a cut-off value of 2.405, NLR had a 69.40% accuracy rate for diagnosing a follicular adenoma (sensitivity: 70%; specificity: 69.2%, PPV: 30.4%, NPV: 92.3%). Lymphocyte had an accuracy of 80.6% in detecting follicular carcinoma (cut-off: 1.625; sensitivity: 80.8%; specificity: 80.0%, PPV: 95.5%, NPV: 44.4%). With an accuracy of 72.6% (cut-off: 270.500; sensitivity: 71.2%; specificity: 80.0%, PPV: 94.9%, NPV: 34.8%), platelet value is a promising parameter for differentiating follicular cancer and adenoma. There was a significant relationship between NLR, lymphocyte, and platelet with follicular-type thyroid nodules ($P < 0.05$ for all).
Conclusion: NLR, lymphocytes, and platelets are potential biomarkers that can be used to differentiate follicular thyroid carcinoma and follicular thyroid adenoma.

Keywords: *neutrophil-lymphocyte ratio, thyroid nodule follicular type*.
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INTRODUCTION

Thyroid gland malignancy is one of the most frequent types of head and neck cancer. Thyroid cancer is still an issue across the world, with the number of cases rising every year. Between 1975 and 2009, SEER-based research (Surveillance, Epidemiology, and End Results) in the United States found a three-fold rise in incidence, from 4.9 to 14.3 cases per 100,000 population.[1] Thyroid cancer accounted for 3.3 percent of all cancer cases and 1% of all cancer deaths in Indonesia, according to GLOBOCAN 2018 statistics.[2] The pathogenesis of thyroid cancer pathogenesis is still widely investigated, and various mechanisms have been reported, such as *p53* mutation and dysregulation of the mitogen-activated protein kinase (MAPK) and phosphatidylinositol-3 kinase (PI3K)/AKT pathways.[3,4]

Ultrasound examination and cytological examination with a fine needle biopsy (fine needle aspiration biopsy/ FNAB) can be used to diagnose thyroid gland diseases.[5] However, clinical examination, sonography, or cytology alone are insufficient to differentiate between benign follicular adenoma and malignant follicular carcinoma. Extracapsular invasion characteristics are the sole way to identify follicular thyroid carcinoma from tissue pathology results.[6] The delay in determining the diagnosis, of course, makes the treatment plan for the patient less than optimal. Several genetic testing approaches are now being offered to identify thyroid nodules with probable malignancy. The meta-analysis study conducted by Fnais *et al*. reported that the sensitivity value of BRAFV600E was only 52%.[7] With a relatively low sensitivity value, it means that BRAFV600E is not an ideal examination as a screening method for thyroid malignancy. Other widely used genetic tests are Affirma-GEC, TyroSeq v2, ThyGenX/ThyraMIR, and RosettaGX Reveal.[8] A meta-analysis study that validated the genomic examination method against the Bethesda III and Bethesda IV classification systems reported that Affirma-GEC and TyroSeq v2 had fairly good results, and both had fairly comparable results.[8]

The ratio of neutrophils to lymphocytes is one of the indicators that might be employed. Inflammatory indicators in the blood have been linked to an increased risk of cancer. The body's inflammatory response will naturally be activated in cancer, resulting in an increase in inflammatory components such as neutrophils, lymphocytes, platelets, and CRP. The neutrophil-to-lymphocyte

ratio (NLR) has been used to diagnose and predict the prognosis of individuals with various diseases. Another study also reported that NLR is a potential marker to differentiate benign and malignant thyroid disorders, where the NLR value was found to be significantly increased in follicular thyroid malignancies.[9] In this study, we aimed to examine the association between various laboratory parameters and follicular-type thyroid nodules. We also examined the performance of several parameters to differentiate malignant and benign follicular thyroid lesions.

METHODS

Study design and participants

This is a retrospective cohort study conducted at Dr. Soetomo General Hospital (Surabaya, Indonesia). Between January 1st, 2015, and December 31st, 2019, we analyzed 62 medical records of patients with follicular-type thyroid nodules who had surgery at Dr. Soetomo General Hospital. Samples were taken by randomized purposive sampling based on inclusion and exclusion criteria. The inclusion criteria are patients with follicular thyroid cancer or follicular adenoma who have undergone surgery and are supported with the histopathological examination and patients who have not undergone chemotherapy or radiotherapy. The exclusion criteria are incomplete medical record data. The laboratory parameters measurement was performed at the Clinical Pathology Installation of Dr. Soetomo General Hospital (Surabaya, Indonesia) and was carried out within 14 days before surgery. The Dimension Chemistry System (Siemens, USA) was used to measure albumin, SGOT, SGPT, blood urea nitrogen (BUN), serum creatinine, and serum electrolytes. The Sysmex XN-3000 was used to measure the complete blood count, PPT, and APTT parameters.

Data collection

We reviewed medical records of patients with follicular thyroid cancer or follicular adenoma who underwent surgery and histopathological examination of the thyroid gland. We collected the gender, age, complete blood count, liver function test, renal function test, albumin test results and histopathological type data from medical records. All the data were obtained from both paper-based medical records and electronic medical records.

Statistical analysis

The data were analyzed using SPSS 25.0 (IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp). The data are presented in the form of frequency distribution tables and cross-tabulations. The data will be tested using the chi-square test or Mann-Whitney U test. A p-value of less than 0.05 was considered statistically significant. The ROC analysis was used to determine the cut-off value in distinguishing malignant- or benign-thyroid nodules.

RESULTS

Patient characteristics

In this study, we recruited 62 people for further analysis. Of the 62 subjects, female (47/62; 75.8%) was found to be higher than male (15/62; 24.2%). From the aspect of age, most of the subjects were in the 50 – 59 years age group (24/62; 38.7%), followed by the 40 – 49 age group (12/62; 19.4%), the 30 – 49 age group. 39 (11/62; 17.7%), age group more than equal to 60 years (8/62; 12.9%), and age less than 30 years (7/62; 11.3%). With the age of 50 as the cut-off, it was found that the number of patients aged less than 50 was almost the same as that of patients over 50 (30/62; 48.4% vs. 32/62; 51.6%). Patient characteristics are shown in Table 1.

Characteristics of laboratory results on research subjects

In general, it was found that the averages of various laboratory parameters were still within normal limits. The results of the examination showed that the patient's average hemoglobin value was 12.81 ± 1.58; the mean leukocyte was 7,500 ± 1,720; the mean platelet count was 285,990 ± 75,240; mean albumin was 4.02 ± 0.35 g/dL. The results of our analysis also showed that the average kidney and liver function examinations of the research subjects were still within normal limits. Table 2 summarizes the laboratory findings for all research subjects.

Characteristics of laboratory results in adenoma and follicular carcinoma patients

We analyzed the characteristics of laboratory results in patients with follicular adenoma and follicular carcinoma. The laboratory results for the two study groups (follicular carcinoma and adenoma) are shown in Table 3. In the follicular carcinoma group, the mean hemoglobin was 12.71 ± 1.58; the mean leukocyte was 7,610 ± 1,740; the mean platelet count was 294,190 ±73,990; mean albumin was 4.01 ± 0.32 g/dL. In the adenoma group, the mean hemoglobin was 13.30 ± 1.55; the mean leukocyte was 6,960 ± 1580; the mean platelets were 243,320 ±70,250; the mean albumin was 4.07 ± 0.49 g/dL. Other lab results such as liver function, kidney function, electrolytes, and blood clotting also gave results that were still within normal limits in both study groups. The results of the NLR laboratory examination in the follicular carcinoma group had an average of 2.26 ± 1.35, and in the adenoma group, an average of 2.72 ± 0.74. For PLR examination, the follicular carcinoma group gave an average result of 143.85 ± 57.3,7, and the adenoma group gave an average result of 146.22 ± 34.64. We found that the value of lymphocytes was significantly higher in follicular carcinoma patients than in follicular adenoma patients (P = 0.012). A similar tendency was found in the platelet parameter, where we found that platelet value was significantly higher in follicular carcinoma patients than in follicular adenoma patients (P = 0.026). Interestingly, we revealed that the NLR value was significantly higher in follicular adenoma than in follicular carcinoma patients (P = 0.018).

ROC analysis of laboratory results in adenoma and follicular carcinoma

Laboratory results used in the analysis were NLR, PLR, platelets, leukocytes, albumin, hemoglobin, PPT, APTT, and lymphocyte. We utilized ROC analysis to determine the cut-off value of each parameter (Figure 1).

We found that there were several parameters with a tendency to be higher in follicular adenoma. Analysis of the NLR value for adenomas gave an AUC value of 0.726 with a 95% CI range of 0.565-0.887 and P = 0.025. Analysis of PLR values for

Table 1. Demographic data of subjects in this study.

Characteristics	n	Percentage
Sex		
Man	15	24.2
Woman	47	75.8
Age		
<30	7	11.3
30-39	11	17.7
40-49	12	19.4
50-59	24	38.7
≥60	8	12.9
Less than 50	30	48.4
Over 50	32	51.6

Table 2. Laboratory profiling for subjects in this study.

Laboratory Parameters	Min	Max	Mean	Standard Deviation
Complete blood count				
Hb	8.80	16.60	12.81	1.58
Leukocytes	4.86	11.77	7.50	1.72
Platelets	149.00	547.00	285.99	75.24
Lymphocytes	0.01	4.04	2.13	0.80
Neutrophil	2.27	8.94	4.48	1.43
monocytes	0.03	0.91	0.50	0.16
Eosinophils	0.00	1.34	0.30	0.25
Basophils	0.01	0.40	0.06	0.06
Liver function test				
SGOT	9.00	70.10	22.81	11.21
SGPT	11.20	121.00	29.89	19.82
Renal function test				
BUN	6.00	25.10	11.92	3.64
Serum creatinine	0.40	1.60	0.79	0.21
Blood coagulation				
PPT	9.10	19.00	10.77	1.43
APTT	20.80	70.10	28.53	6.17
Albumin	3.10	4.70	4.02	0.35
Serum electrolyte				
Sodium	127.00	149.00	140.45	4.98
Potassium	3.00	4.80	3.85	0.46
Chloride	96.00	112.00	103.41	3.41

adenomas gave an AUC value of 0.585 with a 95% CI range of 0.427-0.742 and P = 0.400. Analysis of albumin values for adenomas gave an AUC value of 0.545 with a 95% CI range of 0.303-0.788 and P = 0.654. Analysis of hemoglobin values for adenomas gave an AUC value of 0.576 with a 95% CI range of 0.391-0.761 and P = 0.450. Analysis of PPT values for adenomas gave an AUC value of 0.624 with a 95% CI range of 0.436-0.813 and P = 0.217. Analysis of APTT values for adenomas gave an AUC value of 0.520 with a 95% CI range of 0.311-0.729 and P = 0.841.

We also noted that there were parameters with a tendency to be higher in follicular carcinoma patients, such as platelet and leucocyte. Analysis of platelet values for follicular carcinoma gave an AUC value of 0.723 with a 95% CI range of 0.541-0.905 and P = 0.026. Analysis of leukocyte values for follicular carcinoma gave an AUC value of 0.738 with a 95% CI range of 0.556-0.919 and P = 0.018. The ROC analysis results are shown in Table 4.

Performance of laboratory results to differentiate benign and malignant follicular lesions

In the previous analysis, we found that NLR, platelets and lymphocytes could differentiate follicular carcinoma and adenoma with the results indicated by a significant P value. Further analysis showed that with a certain cut-off value, we could calculate the performance of diagnostic parameters through the values of sensitivity, specificity, PPV, NPV and accuracy. We found that the NLR had a 69.40% accuracy rate for detecting a follicular adenoma using a cut-off value of 2.405 (sensitivity: 70%; specificity: 69.2%, PPV: 30.4%, and NPV: 92.3%). We also found that the platelet value is a potential parameter to detect a follicular carcinoma, with an accuracy value of 72.6% (cut-off 270.500; sensitivity: 71.2%; specificity: 80.0%, PPV: 94.9%, and NPV: 34.8%). The lymphocyte value was also revealed to be a parameter that can be used to detect a follicular carcinoma with an accuracy of 80.6% (cut-off 7.38; sensitivity: 55.8%; specificity: 90.0%, PPV: 96.7%, and NPV: 28.1%). Table 5 shows the performance of NLR, platelets, and lymphocytes to distinguish between benign and malignant follicular thyroid nodules.

DISCUSSION

In this study, we revealed that the number of females in this study outnumbers the number of male participants. The number of females in sex is more than three times that of men, with 47 females and 15 males. This finding is consistent with earlier research that suggests thyroid cancer is more likely in women. The previous study reported a similar result that women had a higher risk of developing thyroid

Table 3. The laboratory results for the two study groups.

Parameter laboratorium	Karsinoma folikuler (*n* = 52)				Adenoma (*n* = 10)				P value
	Min	Max	Mean	St. Dev	Min	Max	Mean	St. Dev	
CBC									
Hb	8.80	16.60	12.71	1.58	10.70	15.80	13.30	1.55	0.449
Leukocytes	4.86	11.77	7.61	1.74	5.21	11.03	6.96	1.58	0.200
Platelets	149.000	547.000	294.190	73.990	167.000	393.200	243.320	70.250	0.026*
Lymphocytes	0.01	3.57	2.20	0.78	1.19	4.04	1.76	0.82	0.012*
Neutrophil	2.27	8.94	4.50	1.53	3.41	5.47	4.37	0.82	0.969
Monocytes	0.03	0.91	0.49	0.17	0.29	0.84	0.53	0.16	0.394
Eosinophils	0.00	1.34	0.31	0.26	0.08	0.54	0.25	0.17	0.639
Basophils	0.01	0.40	0.06	0.07	0.02	0.13	0.05	0.03	0.359
LFT									
SGOT	9.00	70.10	23.09	11.89	14.00	32.00	21.32	6.87	0.946
SGPT	11.20	121.00	30.85	21.27	12.00	37.00	24.90	8.20	0.893
RFT									
BUN	6.00	25.10	12.16	3.71	6.00	16.00	10.70	3.09	0.307
Serum creatinine	0.49	1.60	0.80	0.21	0.40	1.10	0.75	0.23	0.420
Blood coagulation									
PPT	9.30	19.00	10.75	1.52	9.10	12.10	10.86	0.91	0.216
APTT	20.80	70.10	28.64	6.60	22.50	31.80	27.96	3.30	0.841
Albumin	3.10	4.70	4.01	0.32	3.40	4.70	4.07	0.49	0.651
Serum electrolyte									
Sodium	127.00	149.00	140.63	5.17	132.00	143.00	139.50	3.92	0.570
Potassium	3.10	4.80	3.87	0.44	3.00	4.70	3.74	0.55	0.483
Chloride	96.00	108.00	103.11	3.07	99.00	112.00	105.00	4.71	0.366
Neutrophil/ Lymphocytes ratio	1.06	9.04	2.26	1.35	1.35	3.93	2.72	0.74	0.018*
Platelet/Lymphocytes ratio	84.59	352.47	143.85	57.37	97.40	226.89	146.22	34.64	0.358

**P < 0.05*

tumors than men.[10] According to the age distribution of the study's participants, there were about equal numbers of people under the age of 50 and those beyond the age of 50. The 50-59 years old group had the greatest number of patients, followed by the age group of more than 60 years. These findings are consistent with the findings of Albores-Saavedra *et al.*, who found that the incidence of follicular carcinoma rises with age. However, this study discovered a reduction in the number of people in the 60-year-old age group.[11] This could be due to the fact that the number of research subjects was insufficient, so it could not properly represent the population of patients with follicular carcinoma.

Follicular carcinoma looks like a follicular adenoma under the microscope.

Table 4. The result of ROC analysis in this study.

Parameter	AUC	95% CI		P value
		Lower bound	Upper bound	
Towards adenoma				
NLR	0.737	0.574	0.901	0.018*
PLR	0.592	0.433	0.752	0.358
Albumin	0.545	0.303	0.788	0.654
Hb	0.576	0.391	0.761	0.450
PPT	0.624	0.436	0.813	0.217
APTT	0.520	0.311	0.729	0.841
Towards carcinoma				
Lymphocyte	0.753	0.569	0.936	0.012*
Platelet	0.723	0.541	0.905	0.026*
Leucocyte	0.629	0.456	0.801	0.200

**P < 0.05*

Table 5. **The performance of various laboratory parameters to differentiate follicular adenoma and carcinoma.**

Parameters	Cut-off	Sensitivity	Specificity	PPV	NPV	Accuracy
Towards adenoma						
NLR	2.405	70.0%	69.2%	30.4%	92.3%	69.4%
Towards follicular carcinoma						
Platelets	270.500	71.2%	80.0%	94.9%	34.8%	72.6%
Leukocytes	1.625	80.8%	80.0%	95.5%	44.4%	80.6%

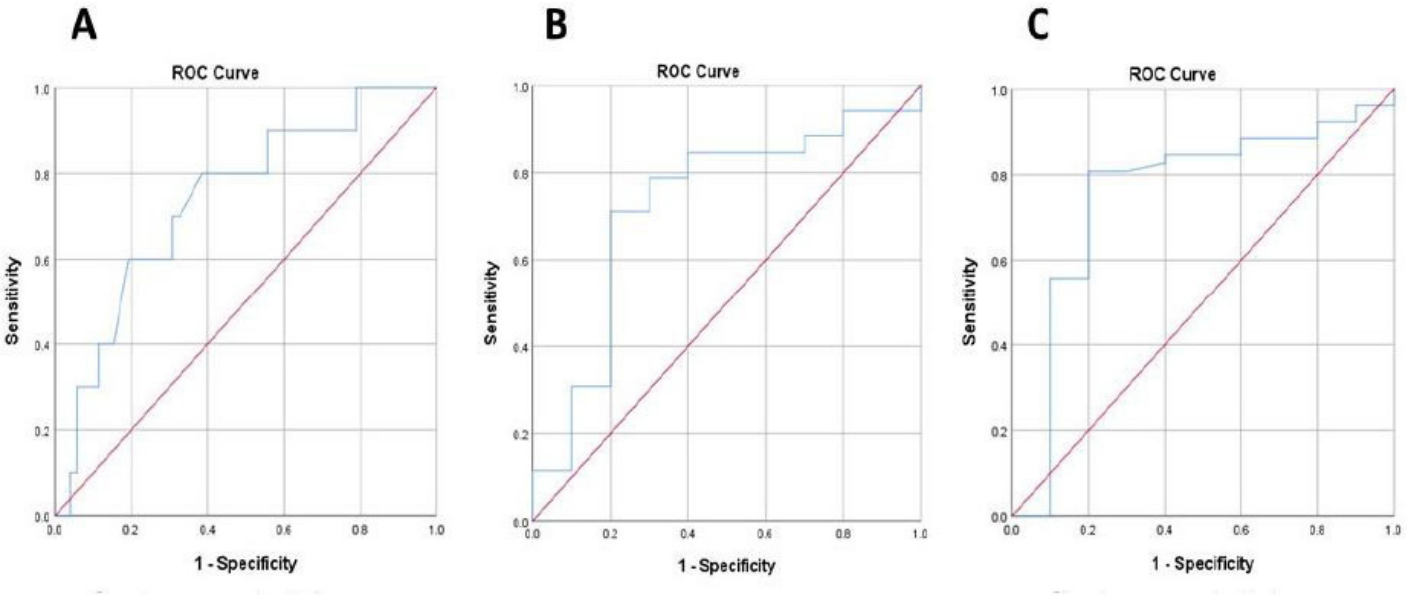

Figure 1. ROC curve analysis to determine the cut-off value (A) NLR (B) Platelet (C) Lymphocyte.

Follicular carcinoma is more cellular, with a thick and irregular capsule with necrosis and mitosis frequently present. On the basis of cytology alone, follicular cancer and follicular adenoma cannot be discriminated against. Capsular invasion, vascular invasion, extra-thyroid tumor expansion, lymph node metastases, and systemic metastases distinguish follicular carcinoma from follicular adenoma.[6] Therefore, the investigation of other biomarkers that can be used to differentiate between these follicular thyroid nodules might be necessary to help clinicians in daily practice.

The underlying mechanisms between chronic inflammation and cancer have been investigated extensively over the last decade.[12] Blood neutrophils have long been recognized as indicators of the systemic inflammatory response because they are essential mediators of the inflammatory response. The adaptive immune system's lymphocytes, on the other hand, have developed to provide a more flexible defensive mechanism as well as greater protection against reinfection with the same virus. Tumor-associated neutrophilia and/or lymphopenia are regarded as a paraneoplastic symptom or a nonspecific response to cancer-associated inflammation owing to local tissue damage and cytokine release, especially in the event of malignancy.[13] The systemic inflammatory response that occurs can be checked simply by looking at the neutrophil/lymphocyte ratio. Previous studies have shown that the neutrophil-lymphocyte ratio has been introduced clinically to evaluate systemic inflammation, and this ratio has been studied for its predictability in various diseases, including breast cancer, cardiovascular disease, testicular germ cell tumor and survival in malignancy.[14-16] In this study, we found that NLR value can be used to differentiate follicular adenoma and follicular carcinoma. These results are in accordance with a previous study that showed that a high NLR could be used as a prognostic indicator for differentiated thyroid carcinoma.[17] Broadly speaking, high NLR is associated with larger tumor size, multifocal tumors, lymph node metastases, and higher TNM staging, all of which may indicate a more aggressive tumor with more advanced stages.[18] Another study also demonstrated an association between high NLR and poor tumor profile in terms of extrathyroidal invasion, multifocal tumors, bilateral side involvement, and the presence of lymph node metastasis.[19] The results of the analysis of the PLR variable showed insignificant results in differentiating between adenoma and carcinoma. The results obtained in this study are not in line with the results of previous studies. Recent studies have shown that NLR and PLR are significantly increased in patients with follicular and papillary thyroid malignancies and also at other studies with different carcinoma, such as cervical cancer.[20] Different results found in this study might be caused by the lack of the

number of research subjects to be able to provide significant results.

In this study, we revealed that lymphocyte was significantly higher in patients with follicular thyroid carcinoma. Thyroid cancer is surrounded by a significant number of reactive immune cells, including lymphocytes. Lymphocytes within and/or surrounding thyroid tumors are associated with more severe disease. A comprehensive examination of the immune cells that respond to thyroid cancer found that lymphocyte subsets predict disease severity differently in patients with thyroid cancer. The majority of tumor-associated T cells were CD4+ T cells, and higher CD4+ T cell frequency corresponded directly with tumor size. Tregs were continuously found within lymphocyte aggregates, and Tregs frequency was found to be strongly correlated with illness severity.[21] Lymphocyte plays an important role in tumor pathogenesis, such as gastric cancer, breast cancer, and thyroid cancer.[21-23] Lymphocyte, as the basic components of the adaptive immune system, is linked to a better tumor profile by suppressing tumor cell proliferation, limiting migration, and preventing metastases.[24] Previous research has also demonstrated that the increasing lymphocyte count improves survival in people with advanced cancer.[25]

Platelets are a type of blood cell that aids in the coagulation of blood. Platelets are a type of biomarker that can help anticipate how a surgical surgery will turn out. Because platelets play such a crucial role in the wound healing process, irregularities in platelets may influence the surgical procedure's outcome. Our study revealed that platelet could be used as potential biomarkers capable of distinguishing follicular adenoma from follicular cancer. Platelets have a good specificity value for predicting follicular cancer. Platelet is known to have key roles in cancer progression and inflammation. Platelets can be activated by cancer cells and used as physical shields against blood shear pressures and natural killer (NK) cells. Platelets that have been triggered may also control hematopoietic and immunological cell migration toward the tumor site.[26]

There are several limitations to this study. This study was conducted in one referral hospital. Therefore, the findings in this study might not be sufficient to describe the condition in Indonesia in general. However, we believe that the findings could still be used as preliminary data in Indonesia. Second, the number of subjects in this study is relatively low. Further study with a higher number of subjects or a nationwide-multicenter study might be important to provide better results.

CONCLUSION

NLR, lymphocytes, and platelets are potential biomarkers that can be used to differentiate follicular thyroid carcinoma and follicular thyroid adenoma.

CONFLICTS OF INTEREST

No competing interests were declared.

ETHICAL CLEARANCE

This study was reviewed and approved by the Medical Ethical Committee of Dr. Soetomo General Hospital, Surabaya, Indonesia (Ref. No.: 0706/LOE/301.4.2/XII/2021) following the guidelines of the Declaration of Helsinki.

AUTHOR CONTRIBUTION

Conceived the study: SK. Designed the study: SK, DHS, and SS. Analyzed the data: SK, DHS, and SS. Wrote the manuscript: SK and DHS. Review the manuscript: DHS and SS.

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