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Differences Neutrophil-Lymphocyte Ratio on Benign and Malignant Thyroid Nodule

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Abstract

Background: Class III and IV of Bethesda classification is less conclusive in the diagnosis of thyroid cancer. Molecular testing as an additional examination is not always available. Inflammation has been implicated in initiation and progression of thyroid cancer. The neutrophil/lymphocyte ratio (NLR) is a simple index of systemic inflammatory response. The aim of this study is to examine the differences of neutrophil-lymphocyte ratio between benign thyroid nodule and malignant thyroid nodule.

Methods: Eighty seven patients with benign and malignant thyroid nodule were analyzed retrospectively. We evaluated neutrophil lymphocyte ratio with result post-operative patological anatomy. Complete blood counts with differential counts were taken before operation. NLR was calculated by dividing preoperative neutrophil count with lymphocyte count. Patients were categorized into low grade (NLR ≤ 1.91) and high grade (NLR = 1.92).

Results: Thyroid nodule were dominant in 78 women patients (89.7%) and 46 patients (58.9%) were malignant. In malignancies, 31 patients (59.6%) were more than 45 year old. Papillary thyroid carcinoma was the most cases with 47 patients (90.39%). The neutrophil lymphocyte ratio was significantly higher in malignant thyroid nodules than benign thyroid nodules.

Conclusion: There was statistically significant difference of neutrophil-lymphocyte ratio between benign thyroid nodule and malignant thyroid nodule.

Keywords:

Neutrophil; Lymphocyte; Thyroid nodule; Inflammation

Abbreviations:

NLR: Neutrophil/Lymphocyte Ratio; FNA: Fine Needle Aspiration; ROS: Reactive Oxygen Species; DNA: Deoxyribo Nucleic Acid; VEGF: Vascular Endothelial Growth Factor; PTC: Papillary Thyroid Carcinoma; FTC: Follicular Thyroid Carcinoma; ATC: Anaplastic Thyroid Carcinoma; MAP: Mitogen Activated Protein; ATA: American Thyroid Association; CRP: C - Reactive Protein

Background

Thyroid nodule is a discrete lesion in the thyroid gland that is radiologically distinct from the surrounding thyroid parenchyma. Thyroid nodules can be caused by many disorders: Benign (colloid nodule, Hashimoto's thyroiditis, simple or hemorrhagic cyst, follicular adenoma and subacute thyroiditis) and malignant (papillary cancer,

follicular cancer, hurthle cell (oncocytic) cancer, anaplastic cancer, mmedullary cancer, thyroid lymphoma and metastases) [1].

About 230,000 new cases of thyroid cancer were estimated in 2012 among w omen and 70,000 among men, with an age-standardized (world population) rate of 6.1/100,000 women and 1.9/100,000 men [2]. Fine needle aspiration (FNA) cytology is generally considered the first line diagnostic test to screen for thyroid cancer. The reported sensitivity of FNA for thyroid cancer is between 84% and 93% and specificity between 75% and 99% [3].

The mediators and cellular effectors of inflammation are important constituents of the local environment of tumours [4]. Tumours have several chemotaxis mechanisms in regulating neutrophil recruitment through chemokines. Once neutrophils arrive at tumour sites, they can be instructed by tumour-derived factors to “tune up” their supporting function.

The role of protomours neutrophils is by secreting Reactive Oxygen Species (ROS) which is known to cause DeoxyriboNucleic Acid (DNA) damage in premalignant cell and drives oncogenic transformation, secreting proangiogenic factor Vascular Endothelial Growth Factor (VEGF) and Bv8. Neutrophils also secrete the matrix metalloproteinase and serine protease that can damage the extracellular matrix and release bioactive growth factors and proangiogenic molecules and may stimulate local immunosuppression by disrupting T cell responses including cell death and T cell recruitment, alllowing growth, development and progression tumours [5].

Neutrophil-lymphocyte ratio (NLR) of thyroid nodules is expected to assist in predicting the risk of malignancy in thyroid nodules, particularly in the results of FNA Bethesda systems class III and IV, which may help the selection of ases for surgery or conservative. In addition, NLR may also confirm benign FNA results in the thyroid, considering there are false negative values of 2% to 10%. This study aims to examine the differences of neutrophil-lymphocyte ratio between benign thyroid nodule and malignant thyroid nodule.

Methods

This study was an observational analytic cross sectional study to examine the differences of neutrophil-lymphocyte ratio in thyroid nodules conducted at Dr. Sardjito Hospital Yogyakarta from January, 2016 to April, 2017.

Sample in this research is patient with thyroid nodule who comes to Dr. Sardjito hospital from January, 2016 to April, 2017 that meets the inclusion and exclusion criteria. Inclusion criteria in this research are: (1) All cases of thyroid nodules performed laboratory tests at Dr. Sardjito hospital; (2) All cases of thyroid nodules undergoing surgery at Dr. Sardjito hospital; (3) FNA results are not metastases. Exclusion criteria in this research are: (1) Thyroid nodules with infectious diseases; (2) Core biopsy without anatomical pathology results.

Independent variable in this study is anatomic pathology on thyroid nodules based on anatomical pathology results after surgery and dependent variable is ratio neutrophil-lymphocyte from laboratory examination which could be on examination of peripheral blood of patients undergoing surgery. The laboratory values are values with a maximum time limit of 1 week before operation, presented in categorical data with a cut of point value off 1.91. RNL ≤ 1.91 is considered low and RNL ≥ 1.91 is considered high [6].

The study sample was chosen consecutively (consecutive sampling) i.e. all subjects meeting the inclusion criteria and willing to participate in the study will be included without randomization. Univariate analysis is used to describe each variable with frequency distribution table and to know the difference between variable by using chi square and t-test.

Table 1: Variable analysis.

Variable		Benign	Malignant	p Value
Sex	Men	3	6	0,735[a]
	Women	32	46	
Age	Minimal	16	16	
	Maximal	84	73	
	Mean	43,51 ± 5,773	45 ± 14,213	0,539[b]

	<45	22	21	0,04[a]
	≥ 45	13	31	
Bethesda				
- Not check	50			
- Check	37			
Bethesda	I	1	0	
	II	3	4	
	III	0	0	
	IV	4	7	
	V	3	11	
	VI	0	4	
Neutrophil-lymphocyte Ratio	≤ 1,91	20	12	0,001[a]
	≥ 1,92	15	40	
	Mean	1,85	2,56	0,0001[b]
a= x2; b= t-test				

Results

In this study, there were 87 patients who met the inclusion and exclusion criteria, according to the calculation of the sample size, the characteristic data of the research subjects can be seen in Table 1.

This study were found 78 thyroid nodules in women (89.7%), with 46 subjects (58.9%) of them are malignant, and only 9 thyroid nodules in men (10.3%). In these study, benign thyroid tumor were found in 16 years old subject as the youngest while 84 years old as the oldest, and for malignant thyroid nodule, the youngest subject is 16 years old and the oldest is 73 years old. Malignancy was found in 31 subjects (59.6%) ≥ 45 years old compared to benign nodule as much as 13 subjects (37.1%).

In this study obtained from 87 subjects, only 37 subjects conducted by FNA while 50 subjects were not done FNA. Thirty seven subjects conducted by FNA, Bethesda class V is the most common results with 14 subjects. In this study found 11 of 14 cases (78.6%) with FNA class V is a carcinoma. This is not much different from the existing literature. Similarly, in Bethesda class VI found 4 out of 4 cases (100%) was a carcinoma in which a positive predictive value of malignant FNA interpretation was between 97%-99% [7].

Most primary thyroid cancers are epithelial tumors that originate from thyroid follicular cells. These cancers develop three main pathological types of carcinomas: papillary thyroid carcinoma (PTC), follicular thyroid carcinoma (FTC) and anaplastic thyroid carcinoma (ATC). Papillary thyroid carcinoma consists of 85-90% of all thyroid cancer cases growth, followed by FTC (5-10%) [8]. This is consistent with the results of this study which found 35 subjects (40.2%) with benign anatomic pathology and 52 subjects (59.8%) malignant, where the most malignancies were found in papillary carcinoma with 47 subjects (90.39%) and 15 of them are follicular variant.

In this study, patients with NLR ≥ 1.92 and malignant nodules were 40 patients from 55 patients and NLR ≤ 1.91 and benign nodules were 20 patients from 32 patients, which was statistically significant difference (p=0,001) [9].

Discussion

Thyroid nodules and malignant thyroid nodules are more common in women. Estrogens is thought to be associated with increased incidence of thyroid nodules and thyroid cancer. The thyroid tissue express estrogen receptor, estrogen receptor α and β, where there is a significant increase of expression level in response to 17β-estradiol. Estrogen receptors are intracellular receptors that serve as transcription factors. Estrogens proote the growth of benign and malignant thyroid nodules by binding to these estrogen receptor nuclei and by activating the mitogen activated protein (MAP) kinase pathway thus mediating the occurrence of mitogenesis [10].

Malignancy increasing with age, most of the tumours occurs in third to sixth decade of life [8]. This may be due to changes in normal thyroid tissue and decreased immune systems occur in line with age [11]. Fine needle aspiration is the preferred method with good sensitivity and cost effectiveness in evaluating thyroid nodules [12]. Only 37 subjects conducted while 50 subjects were not done FNA, this is not in accordance with American Thyroid Association (ATA) guidance recommendations in terms of early diagnosis in screening of thyroid nodules.

The 2 most frequently used markers of active inflammatory status in patients with cancer are C-

reactive protein (CRP) and NLR, because they are reliable and widely available in daily clinical practice and their sensitivity in predicting survival rates has been supported by a large number of studies in various types of cancer [13].

Neutrophil to lymphocyte ratio has emerged as a simple and valid composite marker of systemic inflammatory response. Compared with serum CRP, which is not routinely measured as part of the cancer work up, NLR is inexpensive, easily calculated and universally available [14].

Many cancer survival studies have suggested that NLR is a significant predictor of overall. Patients with elevated NLR have a relative lymphocytopenia and neutrophil leukocytosis in favor of protumour inflammatory response, in different types of cancer. Seretis et al. compared the NLR between those with an incidental papillary microcarcinoma and those with a benign goiter only and found that the former group had a significantly higher mean NLR than the latter group (3.0 *vs.* 1.9, $p<0.001$). The authors concluded that NLR could potentially be used as a biomarker for detecting incidental small PTC in an apparently benign goiter [15].

Kocer et al. demonstrate that NLR is higher in group lymphocytic thyroiditis with papillary thyroid carcinoma and group papillary thyroid carcinoma than multinodular goiter and lymphocytic thyroiditis ($p<0.05$), it may be used for be aware of presence of malignity. This study suggested that use of cut-off value of 1.91 for NLR would be optimum for clinical use to identify patients with PTC as sensitivity of 89% and specificity of 54.5% can be achieved. At this cut-off point negative predictive value was 92%. In this study, mean NLR was found in benign thyroid tumours 1.85 and 2.56 in malignant thyroid tumours, which statistically significant difference ($p=0,0001$). This value is different from the value constraint proposed by Kocer et al. further research is required in determining the sensitivity and specificity values. Nevertheless the use of NLR should not be considered a decisive factor but it only provides an option in strengthening the diagnosis, since histopathology is a gold standard in diagnosis.

Conclusion

There was statistically significant difference of neutrophil-lymphocyte ratio between benign thyroid nodule and malignant thyroid nodule.

Declaration

Ethics approval and consent to participate

Ethics Committee Approval

Medical and Health Research Ethics Committee (MHREC) Faculty of Medicine Gadjah Mada University-Dr. Sardjito Hospital

Ref: KE/FK/0927/EC/2017

The Medical and Health Research Ethics Committe (MHREC) states that the protocol meets the ethical principle outlined in the Declaration of Helsinki 2008 and therefore can be carried out

Consent for Publication

All participants give their consent to participate in this study and that the information will be published in this journal.

Availability of Data and Material

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing Interest

The authors declare that they have no competing interests.

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Author's Contributions

RPN designed, analyzed and interpreted the patient data. DAE performed drafting the manuscript and give final approval of the version to be published. SRI performed revising it critically for important intellectual content. The authors are agree and responsible for the content and writing of the paper. All authors have contributed significantly, read and approved the final manuscript. The authors are

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