DOAJ DIRECTORY OF OPEN ACCESS JOURNALS
P-ISSN: 2548-5962
E-ISSN: 2548-981X
https://ojs.unud.ac.id/index.php/jbn
ORIGINAL ARTICLE
JBN Jurnal Bedah Nasional

The Association Between Preoperative Serum Thyroid-Stimulating Hormone and Neutrophil-Lymphocyte Ratio as Predictors of Papillary Thyroid Cancer

William Stevenson[1], Nico Lumintang[2], Sherly Tandililing[2], Windy Mariane Wariki[3]

[1] Department of General Surgery, Faculty of Medicine, Sam Ratulangi University, Manado Indonesia.
[2] Head and Neck Division, Department of Surgery, RSUP Prof Dr. R.D. Kandou, Manado, Indonesia.
[3] Department of Community Medicine, Faculty of Medicine, Sam Ratulangi University, Manado, Indonesia.

*Corresponding author: doc.stevensons@gmail.com.

ABSTRACT

Aim: This study aims to evaluate the correlation between blood thyroid stimulating hormone levels and neutrophil lymphocyte ratio prior to thyroidectomy in patients with papillary thyroid cancer, as well as the potentiality of those as predictors of papillary thyroid cancer. **Methods:** Thyroid nodule patients over the age of 18 who received treatment at Prof. Dr. R.D. Kandou General Hospital between 2020 and 2024 and who fulfilled the requirements for research inclusion underwent thyroidectomy surgery. The study used a retrospective, descriptive-analytical strategy. **Results:** The association between TSHs and papillary thyroid cancer was significant with a p-value of 0.025, sensitivity of 51.1%, and specificity of 73.9%; the ROC analysis was performed for TSHs with the results of the AUC value analysis = 0.634 (95% CI: 0.518 – 0.749) with p value = 0.028; NLR and papillary thyroid cancer was significant with a p-value <0.001, sensitivity of 68.9%, and specificity of 100%; the ROC analysis was performed for NLR values with the results of the AUC analysis value = 0.852 (95% CI: 0.766-0.938) with p value = <0.001. **Conclusion:** NLR is advised as a better predictor of papillary thyroid cancer than TSHs.

Keywords: NLR, TSHs, predictors of papillary thyroid cancer.

DOI: https://doi.org/10.24843/JBN.2025.v09.i01.p03

INTRODUCTION

Thyroid cancer is the most common endocrine malignancy. Over the past three decades, the incidence of thyroid cancer has tripled in the United States and developing countries worldwide. Early diagnosis and management are crucial for thyroid cancer.[1]

Inflammation has been linked with the development of many cancers and is involved almost all of the pathogenic steps of malignancy initiation and propagation including its dissemination. An elevated ratio of Neutrophils-to-Lymphocytes (NLR) is the simplest marker of systemic inflammatory response.[2]

We decided to investigate relationship between neutrophil-lymphocyte ratio and preoperative serum thyroid-stimulating hormone as predictors of papillary thyroid cancer because no prior research between these two variables and easily applicable test in clinical practice. Therefore, this study aims to evaluate the correlation between blood thyroid stimulating hormone levels and neutrophil lymphocyte ratio prior to thyroidectomy in patients with papillary thyroid cancer, as well as the potentiality of those as predictors of papillary thyroid cancer

METHODS

This study is a descriptive-analytic study with a retrospective approach. The target population for this study consists of Thyroid nodule patients over the age of 18 who received treatment at Prof. Dr. R.D. Kandou General Hospital between 2020 and 2024. The

age criterion of >18 years is selected due to the high incidence of thyroid nodules in this age group.

The inclusion criteria in this study: 1) Patients over 18 years of age with thyroid nodules who sought treatment at the surgery clinic of Prof. Dr. R.D. Kandou General Hospital, 2) Patients who underwent preoperative TSH and NLR examinations prior to thyroidectomy, 3) Patients who underwent thyroidectomy surgery, and 4) Patients who underwent histopathological examination of thyroid tissue post-thyroidectomy

Meanwhile, the exclusion criteria in this study are: Patients with clinical hypothyroidism, clinical hyperthyroidism, acute infectious diseases, Hashimoto's Thyroiditis, levothyroxine, antithyroid drugs, corticosteroids, or other immunosuppressive medications.

The sample size calculation was based on this equation:

$$n = \left[\frac{Z\alpha + Z\beta}{0.5 \ln \frac{1+r}{1-r}}\right]^2 + 3$$

Explanation:

- n: sample size
- α: Type I error set at 5%, giving Zα=1.96
- β: Type II error set at 20%, giving Zβ=0.84
- r: correlation coefficient between the two variables in the study, set at 0.19
- The value of r = 0.19, r is based on a study by Huang et al., with p<0.0001
- ln: natural logarithm

Based on the sample size formula, the minimum sample size required for this study is 90 participants. The sampling technique used in this study is purposive sampling. Subjects who meet exclusion criteria will not be included as samples.

The independent variables in this study are Preoperative thyroid stimulating hormone (TSH) Levels and Preoperative Neutrophil-to-Lymphocyte Ratio (NLR). Meanwhile, the dependent variable in this study is Papillary Thyroid Cancer.

Preoperative Neutrophil-Lymphocyte Ratio (NLR) is the ratio number between absolute neutrophil count and absolute lymphocyte count measured preoperative thyroidectomy. Preoperative TSH test is TSH hormone levels using a blood sample taken from a vein in the patient's arm preoperative thyroidectomy. Papillary Thyroid Cancer (PTC) is malignant neoplasm of thyroid follicular cells with papillary growth pattern on histopathology examination

The data collection process in this study is as follows: 1) Obtain permission and inform relevant parties, such as Prof. Dr. R.D. Kandou Hospital and the Hospital Ethics Committee, about the purpose and benefits of the research, 2) Select patients with thyroid nodules who are receiving treatment at the Surgery Clinic of Prof. Dr. R.D. Kandou Hospital. Data will be collected from patients who undergo thyroidectomy surgery and have histopathological examination of thyroid tissue, 3) Patients who meet the inclusion criteria will be included in the research sample, 4) Data on preoperative NLR and serum TSH levels will be taken from laboratory examination results, 5) Patients who do not meet the inclusion criteria or who meet exclusion criteria will be excluded from the study, 6) Data recording and analysis will be conducted, 7) Data will be reported.

The data processing will mostly be done using the SPSS statistical software (version 27.1). As an initial step, raw data will be entered into a Microsoft Excel file, which provides a comprehensive and user-friendly

platform for data entry. The subsequent data processing and all statistical analysis will be performed using this statistical software. The data is presented in tabular form and graphic accompanied by a descriptive explanation.

Data collection will take place at Prof. Dr. R.D. Kandou General Hospital in Manado. Information will be obtained from medical records after the researcher has received approval from the Ethics Committee of Prof. Dr. R.D. Kandou Hospital.

RESULTS

Characteristics of research subjects

Based on age distribution (**Table 1**), the average age of the research subjects was 54.58 years with a standard deviation of 12.555. According to gender distribution, the majority of the samples were female, with 58 individuals (63.7%), while 33 individuals (36.3%) were male.

Table 1. Characteristics of Age and Gender of Research Subjects

Characteristics	Minimum	Maximum	Mean	SD
Age	26	80	54.58	12.55
Gender	**Sum**	**Percentage (%)**		
Male	33	36.3		
Female	58	63.7		
Total (n)	91	100		

Based on the results of the histopathological examination (**Table 2**), among the 91 research samples, 45 subjects (49.5%) were confirmed to have papillary thyroid cancer, and 46 subjects (50.5%) had benign thyroid nodules.

Table 2. Neoplasm Type Based on Histopathological Results

Neoplasm type	Frequency (n)	Percentage (%)
Papillary thyroid cancer	45	49.5
Benign thyroid nodule	46	50.5
Total (n)	91	100

Table 3 shows the laboratory results for NLR and TSH levels in the study. The lowest NLR value was 1.11, the highest was 5.07, with an average of 2.4846 and a standard deviation of 1.08190. For the TSH levels, the lowest value was 0.74 mIU/L, the highest was 2.63 mIU/L, with an average of 1.5601 mIU/L and a standard deviation of 0.48493.

Neutrophil/Lymphocyte Ratio and TSH of Research Subjects

Table 3 shows the laboratory results for NLR and TSH levels in the study. The lowest NLR value was 1.11, the highest was 5.07, with an average of 2.4846 and a standard deviation of 1.08190. For the TSH levels, the lowest value was 0.74 mIU/L, the highest was 2.63 mIU/L, with an average of 1.5601 mIU/L and a standard deviation of 0.48493.

The Association Between TSH and Papillary Thyroid Cancer

A chi-square analysis of the association between TSHs and papillary thyroid cancer revealed a significant p-value of 0.025, sensitivity of 51.1%, and specificity of 73.9%.

Table 3. Preoperative NLR and TSHs Examination Results

Examination type	Minimum	Maximum	Mean	SD
Pre-operative NLR	1.11	5.07	2.4846	1.08
Pre-operative TSHs	0.74	2.63	1.5601	0.48

The Association Between Papillary Thyroid Cancer And NLR

NLR and papillary thyroid carcinoma were significantly correlated, according to chi-square analysis, with a p-value <0.001, a sensitivity of 68.9%, and a specificity of 100% (**Figure 1**).

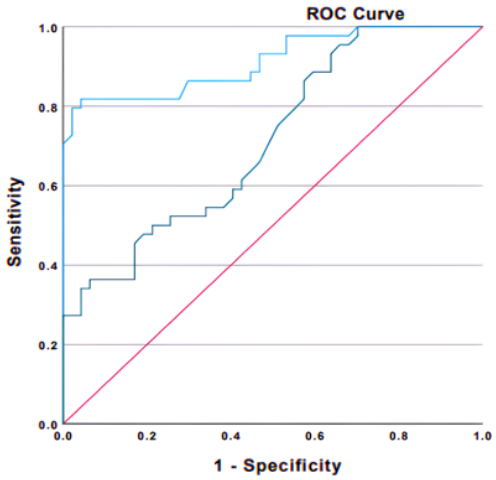

Figure 1. Sensitivity and Specificity for NLR (light blue) and TSH (dark blue).

DISCUSSION

Regarding the distribution of gender, the majority of the respondents were female, with 58 individuals (63.7%), and male respondents numbered 33 (36.3%). This finding is consistent with the literature, which states that malignant thyroid nodules occur three times more often in women than in men. In our study, the average age of the subjects was 54.58 years, with the youngest being 26 years old and the oldest 80 years old. These findings consistent with the study by Maulana et al., where thyroid nodules were found to be more common in women than men, with an average age of 50.54 ± 13.8 years.[3]

Kim studied 1,759 patients with differentiated thyroid carcinoma who underwent thyroid surgery at Chonnam National University Hwasun Hospital. Serum TSH levels were significantly higher in patients with thyroid carcinoma compared to the control group, with average TSH levels of 1.95 ± 0.9 mIU/L and 1.62 ± 0.8 mIU/L, respectively ($p < 0.001$).[4]

Both benign and malignant thyroid tumours express functional TSH receptors on the plasma membrane, and in vitro studies have shown that TSH increases adenylate cyclase activity, leading to cAMP production and cell growth through receptor stimulation. Thyroid stimulating hormone levels were higher in patients with thyroid cancer compared to those with benign nodules. The risk of malignancy in patients with thyroid nodules increased with serum TSH concentrations, even within the normal range. Papillary thyroid carcinoma expresses TSH receptors. TSH, through interaction with TSH

receptors, is a major growth factor for the thyroid.[5–8]

In our study, the serum TSH values ranged from 0.74 to 2.63, with a mean of 1.5601 and a standard deviation of 0.48493. Based on the ROC analysis, the AUC for TSH was 0.634 (95% CI: 0.518–0.749) with a p-value of 0.028. This indicates a significant relationship between serum TSH levels and the risk of papillary thyroid cancer. Our findings are consistent with the studies conducted by Golbert et al., and Hannah Nieto.[5,9]

A study by Golbert et al. examined 615 thyroid nodule patients. Thyroid cancer was found in 47 patients (29.4%) out of 160 who had thyroidectomies. Regardless of the testing method, cancer patients had higher average blood TSH levels than patients with benign nodules: 2.25 vs. 1.50 (CLIA; $p = 0.04$) and 2.33 vs. 1.27 (ECLIA; $p = 0.03$).[5]

Hannah Nieto et al. found that the risk of malignancy increased with elevated serum TSH levels. Nieto found that preoperative serum TSH concentration could independently predict the presence of malignancy in patients with thyroid nodules. TSH measurement to identify high-risk thyroid nodules in routine clinical practice is an interesting, cost-effective, and non-invasive approach to optimize thyroid cancer diagnosis.[9]

Inflammation is a protective process that occurs in organisms as a response to tissue damage. Various types of leukocytes migrate to the site of tissue injury. This migration is mediated by chemotactic and adhesion proteins, including integrins. The first migrating cells are neutrophils, macrophages, and mast cells, all of which secrete Reactive Oxygen Species (ROS), vasoactive molecules such as histamine and leukotrienes, as well as cytokines, chemokines, and proteases that remodel the extracellular matrix. Inflammation is typically an auto-limited process. However, persistent or abnormal inflammation, or failure of anti-inflammatory mechanisms, can result in chronic inflammation.[10]

Leukocytes physiologically secrete ROS and reactive nitrogen species to eliminate pathogens. However, these highly reactive metabolites induce the production of peroxynitrite and other mutagenic agents that can cause DNA damage. Cancer cells release cytokines and chemokines, which support cancer cell growth and recruit leukocytes to the cancer site. Pro-inflammatory cytokines produced by cancer cells play a crucial role in cancer progression.[10]

Systemic inflammation plays an important role in the pathophysiology of cancer. The pathophysiology of the inflammatory response to cancer is marked by increased angiogenesis and DNA damage. Monocytes and lymphocytes work as anti-tumour agents. Low lymphocyte and monocyte counts have been seen in advanced-stage malignancies and are linked to a poor prognosis. Monocytes cause cancer cells to undergo apoptosis in order to decrease angiogenesis, which in turn reduces invasion and the advancement of cancer. Specifically, low lymphocyte levels are associated with immune suppression in cancer patients. Neutrophilia is believed to occur due to paraneoplastic activity from the primary tumour or production of Granulocyte Colony-Stimulating Factor (G-CSF).[11]

In our study, we found a high Neutrophil-Lymphocyte Ratio (NLR $\geq$ 2.4846) in 31 individuals (68.89%), all of whom were diagnosed with papillary thyroid cancer. The lowest NLR was 1.11, the highest was 5.07, with a mean of 2.4846 and a standard deviation of 1.08190. Based on ROC analysis, the AUC for NLR was 0.852 (95% CI: 0.766–0.938) with a p-value < 0.001. This indicates a

significant relationship between NLR levels and the risk of papillary thyroid cancer. Our findings are consistent with the studies conducted by Seretis, Manatakis, Xue Zhang, and Scognamillo.[12–14]

In addition, cancer cells generate inflammatory signals and promote inflammation. Cytokines released by inflammatory cells interact with the bone marrow, which produces neutrophils and lymphocytes. NLR may be an indicator of inflammation because there is compelling evidence linking systemic inflammation to neutrophilia and lymphocytopenia.[15]

Monocytes and lymphocytes act as anti-tumor. Low levels of lymphocytes and monocytes are associated with poor prognosis and have been observed in advanced cancer. Low lymphocytes are associated with suppression of the immune system in patients with cancer. Neutrophilia is thought to occur due to paraneoplastic activity of the primary tumor or production of Granulocyte Colony Stimulating Factor.[12,16]

Seretis et al. found high NLR values (>2.5) in patients with papillary thyroid microcarcinoma (PTMC). The NLR values in benign thyroid nodules and PTMC showed a significant statistical difference (p=0.001).[12] Manatakis studied the diagnostic accuracy of the Neutrophil-Lymphocyte Ratio (NLR) and Platelet-Lymphocyte Ratio (PLR) in detecting occult papillary thyroid microcarcinoma (PTMC) in 397 patients who underwent thyroidectomy between 2007 and 2016. NLR was significantly higher in the papillary thyroid carcinoma and microcarcinoma groups compared to benign lesions (p = 0.026).[13]

Xue Zhang et al. studied 487 thyroid tumour patients, measuring neutrophils (NE), leukocytes, monocytes, lymphocytes, platelets, monocyte/lymphocyte ratio (MLR), NLR, and platelet/lymphocyte ratio (PLR). They found that the serum levels of PLR, NLR, CRP, and IL-27 in thyroid adenoma (TA) and differentiated thyroid carcinoma (DTC) were higher than in the control group.[17]

Scognamillo et al. conducted a retrospective study of 112 patients over five years at the University of Sassari Surgery Department, divided into two groups: 50 patients with papillary thyroid cancer (Group A) and 62 patients with benign thyroid nodules (Group B). They found that the average NLR was significantly higher in the papillary thyroid cancer group compared to the benign thyroid nodule group.[3]

Although promising in terms of sensitivity, the NLR value can be influenced by medical conditions that affect the type count value of leukocytes such as acute infection, viral or bacterial infection, allergic reaction, cardiovascular disease, connective tissue disease, administration of certain medications). Lymphocytopenia can occur due to infections, malnutrition, connective tissue disorders, severe stress, and strenuous physical exercise.[3]

However, when it comes to predicting papillary thyroid cancer, the combination of NLR and TSHs does not work well. Numerous unstudied variables, including NK cells, ROS, NO, IL-6, and IL-37, may have contributed to the pathophysiology of thyroid cancer. This study's weaknesses were a result of its retrospective cross-sectional design.

CONCLUSION

NLR are more potential than TSHs as predictors of papillary thyroid cancer. Therefore, it is recommended to use NLR as a predictor for papillary thyroid cancer.

ACKNOWLEDGEMENT

With utmost respect and sincere gratitude, my thanks to my supervisors, Dr. Nico

Lumintang SpB(K)KL, Dr. Sherly Tandililing SpB(K)KL, and Dr. Windy Mariane Virenia Wariki, M.Sc, Ph.D, who have provided invaluable guidance, suggestions, and encouragement throughout the research process until the completion of this final project.

DISCLOSURE

No conflict of interest

REFERENCES

1. Monson JR, Weiser MR. Sabiston Textbook of Surgery, 18th ed. The Biological Basis of Modern Surgical Practice. *Dis Colon Rectum*. 2008 Jul;51(7):1154.
2. Tiwari PK, Varghese B, KK Arunjeet, et al. Feasibility of The Use of Neutrophil To Lymphocyte Ratio (NLR) As An Adjunct To Cytology To Suggest Thyroid Malignancy: A Prospective Study [Internet]. 2021. Available from: https://www.researchsquare.com/article/rs-539030/v1
3. Maulana A, Dwi Wibowo M. Description of Neutrophil-Lymphocyte Ratio in Patients with Thyroid Nodules Description Study at Dr Soetomo Hospital Period January 2018 – December 2020. *International Journal of Research Publications*. 2022;100(1):142-167.
4. Kim HK, Yoon JH, Kim SJ, et al. Higher TSH level is a risk factor for differentiated thyroid cancer. *Clin Endocrinol (Oxf)*. 2013;78(3):472–7.
5. Golbert L, de Cristo AP, Faccin CS, et al. Serum TSH levels as a predictor of malignancy in thyroid nodules: A prospective study. *PLoS One*. 2017;12(11):e0188123–e0188123.
6. Fiore E, Rago T, Provenzale MA, et al. Lower levels of TSH are associated with a lower risk of papillary thyroid cancer in patients with thyroid nodular disease: thyroid autonomy may play a protective role. *Endocr Relat Cancer*. 2009;16(4):1251–60.
7. Demircioglu ZG, Demircioglu MK, Aygun N, et al. Relationship Between Thyroid-Stimulating Hormone Level and Aggressive Pathological Features of Papillary Thyroid Cancer. *Sisli Etfal Hastan Tıp Bul*. 2022;56(1):126–31.
8. Petranović Ovčariček P, Verburg FA, Hoffmann M, et al. Higher thyroid hormone levels and cancer. *Eur J Nucl Med Mol Imaging*. 2020;48(3):808–21.
9. Nieto H, Boelaert K. Women In Cancer Thematic Review: Thyroid-stimulating hormone in thyroid cancer: does it matter? *Endocr Relat Cancer*. 2016;23(11):T109–21.
10. Guarino V, Castellone MD, Avilla E, et al. Thyroid cancer and inflammation. *Mol Cell Endocrinol*. 2010;321(1):94–102.
11. Liu J, Du J, Fan J, et al. The Neutrophil-to-Lymphocyte Ratio Correlates with Age in Patients with Papillary Thyroid Carcinoma. *ORL*. 2015;77(2):109–16.
12. Seretis C, Gourgiotis S, Gemenetzis G, et al. The significance of neutrophil/lymphocyte ratio as a possible marker of underlying papillary microcarcinomas in thyroidal goiters: a pilot study. *The American Journal of Surgery*. 2013;205(6):691–6.
13. Manatakis DK, Tseleni-Balafouta S, Tzelves L, et al. Diagnostic Accuracy of Preoperative Neutrophil-to-Lymphocyte and Platelet-to-Lymphocyte Ratios in Detecting Occult Papillary Thyroid Microcarcinomas in Benign Multinodular Goitres. *J Thyroid Res*. 2018;2018:3470429.
14. Mulita F, Verras GI, Dafnomili VD, et al. Thyroidectomy for the Management of

Differentiated Thyroid Carcinoma and their Outcome on Early Postoperative Complications: A 6-year Single-Centre Retrospective Study. *Chirurgia (Bucur)*. 2022;117(5):556.

15. Haider N, Mahmood Z, Khalid F, et al. Neutrophils to lymphocytes ratio between benign and malignant thyroid nodule. *Pak J Med Sci*. 2021;37(7):1908–11.
16. Offi C, Romano RM, Cangiano A, et al. Evaluation of LMR, NLR and PLR as predictors of malignancy in indeterminate thyroid nodules. *Acta Otorhinolaryngol Ital*. 2021;41(6):530–6.
17. Zhang X, Li S, Wang J, et al. Relationship Between Serum Inflammatory Factor Levels and Differentiated Thyroid Carcinoma. *Technol Cancer Res Treat*. 2021;20:1533033821990055–1533033821990055.