



Role of Neutrophil Lymphocyte Ratio, Platelet Lymphocyte Ratio and Lymphocyte Monocyte Ratio in Benign Nodular Goitre and Papillary Thyroid Carcinoma

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KEYWORDS

Neutrophil-Lymphocyte Ratio; Platelet-Lymphocyte Ratio; Papillary Thyroid Carcinoma; Nodular Goitre

ABSTRACT:

Introduction: Inflammation has been widely accepted to play an important role in carcinoma development. There have been conflicting studies regarding systemic inflammatory markers such as neutrophil-lymphocyte ratio(NLR), lymphocyte-monocyte ratio (LMR), and platelet-lymphocyte ratio(PLR)in thyroid lesions.

Aim:The aim was to analyze the association of these inflammatory biomarkers in benign and malignant thyroid lesions, as well as with other clinicopathological variables.

Materials and Methods: This was a retrospective study over a period of 2 years in a tertiary care center, comprising 30 patients diagnosed with benign nodular goiter (NG) and 30 patients diagnosed with papillary thyroid carcinoma (PTC). Neutrophil-lymphocyte ratio(NLR), platelet-lymphocyte ratio (PLR), and lymphocyte-monocyte ratio (LMR) were analysed with the type of lesion and other clinicopathological variables as well.

Results: Both NLR and PLR showed significant associations to tumour size ($p=0.0104$, $p=0.03805$, respectively) and lymph-node metastasis in papillary thyroid carcinoma ($p=0.02019$, $p=0.036$, respectively) LMR did not show statistical significance to tumour size and lympho-nodal metastasis ($p=0.117$, $p=0.346$, respectively).NLR, PLR , and LMR were not significantly increased in cases of papillary thyroid cancer when compared to cases of benign nodular goiter ($p=0.933$, $p=0.108$, $p=0.778$. respectively)

Conclusion: This study indicates that NLR and PLR can be used as readily available alternative markers to help improve the prognostic assessment of patients with papillary thyroid carcinoma.

1. Introduction

Thyroid carcinoma constitutes 3.3% of all neoplasms globally, with an incidence rate of 5.4/100,000 in India. [1] Papillary thyroid carcinoma (PTC) represents 94% of thyroid cancers and, is hence, the most common endocrine malignancy. [2,3]

The incidence of papillary thyroid carcinoma is increasing, which may be associated with the widespread use of ultrasound and fine needle aspiration cytology (FNAC). Papillary thyroid carcinoma has an

excellent survival rate, up to a 10-year survival rate of 93%. [3]

One of the most important targets of the preoperative workup is the prediction or suspicion of malignancy of a nodule. Ultrasound neck and further FNAC are the most adopted methods to stratify the risk of malignancy in thyroid nodules. [2,3]

Recent studies have shown the role of inflammation in cancer pathogenesis.[4] Neutrophil-to-lymphocyte ratio (NLR), Platelet-to- lymphocyte ratio, and Lymphocyte-to- Monocyte ratio are widely recognized systemic



inflammatory biomarkers. [5] The prognostic implication of these markers is seen in various other cancers such as urinary tract, ovarian tumors, and head and neck cancers. [6,7]

The role of systemic inflammatory biomarkers has not been clearly described with regard to thyroid lesions. [7] Due to the low recurrence and excellent survival rate of papillary thyroid carcinoma, it is difficult to clearly understand their prognostic significance. [2,8] Also, there has been lack of research about their relation to adverse clinicopathological features such as lymph node metastasis. [9,10]

2. Objectives

The objective of this study was to analyze the association of inflammatory biomarkers- neutrophil to lymphocyte ratio, platelet to lymphocyte ratio, and lymphocyte to monocyte ratio in benign and malignant thyroid lesions, as well as with other clinicopathological variables.

3. Methods

The study was conducted over 2 years (2018-2020). 60 cases of thyroidectomy specimens were reviewed. Complete clinical, radiological, and laboratory data were analyzed. Patients with histopathologically confirmed diagnoses of multi nodular goiter (NG) and papillary thyroid carcinoma were included in this study. The exclusion criteria were as follows:

1. Hematological disorders
2. Neo-adjuvant chemotherapy or pre-operative radiotherapy
3. Cases of autoimmune/inflammatory thyroid pathologies such as Graves disease; Hashimoto's thyroiditis
4. Cases having pre existing chronic inflammatory conditions

The 60 cases comprised 30 cases of nodular goiter and 30 cases of papillary thyroid carcinoma. Clinicopathological data such as age, sex, tumor size in PTC, and presence/ absence of lymph node metastasis were collected, (Table 1). Blood investigation data performed before surgery were collected.

The NLR, PLR, and LMR were retrieved from the hospital complete cell counts and laboratory data.

Statistical analysis was done using SPSS version 23. Mann-Whitney U tests were performed for numerical data and Chi-square test was performed for categorical data. A p-value of < 0.05 was considered significant.

The relation between tumour size and the ratios of NLR, PLR and LMR were analysed using correlation and linear regression analysis. A receiver operating characteristic curve (ROC) analysis was also performed to ascertain the test strength (NLR, PLR, LMR).

4. Results

The total number of study participants was 60, out of which 49 were female (81.67%) and 11 were male (18.33%). The age of the patients ranged from 30-76 years with a mean age of 45.2 years. The mean white blood cell count was 7.8 ± 1.52 with a range of 4.8-12.5. The mean absolute neutrophil count was 4.56 ± 1.5 , mean absolute lymphocyte count was 2.82 ± 0.66 , and mean absolute platelet count was 265 ± 11.2 . The mean tumour size in cases of PTC was 2.2 cm.

The mean NLR was 1.611, the mean PLR was 93.98 and the mean LMR was 5.025. Patients were divided into two groups using the mean for each ratio as a cut-off. Age, gender, type of lesion, tumor size, and lymph node metastasis variables were analyzed. A cut-off of 2 cm was used for the size of PTC cases.

The NLR and PLR showed statistical significance with respect to tumor size. ($p = 0.0104$, $p = 0.03805$, respectively) (Figure 1, Figure 2).

NLR and PLR showed statistical significance with respect to the lympho-nodal metastasis in PTC ($p = 0.02019$, $p = 0.036$, respectively). LMR did not show statistical significance concerning tumor size and lymph node metastasis ($p = 0.117$, $p = 0.346$, respectively) (Table 2, 3, 4)

The NLR, PLR, and LMR were insignificantly increased in cases of PTC when compared to cases of nodular goiter ($p = 0.933$, $p = 0.108$, $p = 0.778$, respectively). There was no statistical significance of the three ratios across variables of age (NLR: $p =$



0.1165, PLR: $p=0.983$, LMR: $p=0.9$), and gender (NLR: $P=0.562$, PLR: $P=0.973$, LMR: $P=0.511$) (Table 2, 3, 4).

A ROC curve analysis was performed for all three ratios (NLR, PLR and LMR) and results were computed

(Table 5, Figures 3, 4,5). The Spearman's correlation coefficients for NLR, PLR and LMR with regard to tumour size, were 0.526, 0.153 and 0.342, respectively, which was statistically significant in cases of NLR ($p=0.0028$) and PLR ($p=0.041$) but insignificant with regards to LMR ($p=0.064$)

Table 1: Clinical variables of study participants

VARIABLES	N	Percent (%)
AGE		
≤45 Years	28	46.67%
>45 Years	32	53.33%
SEX		
Female	49	81.67%
Male	11	18.33%
LESION		
NG	30	50%
PTC	30	50%
TUMOR SIZE		
≤2cm	12	40%
>2cm	18	60%
LYMPH NODE METASTASIS		
Absent	13	43.33%
Present	17	56.67%

Table 1: Abbreviations:- NG- Nodular Goitre, PTC- Papillary thyroid carcinoma

Table 2: Relationship Between Preoperative Neutrophil –Lymphocyte Ratio and Clinco-Pathological Variables

VARIABLES	NLR≤1.611	NLR > 1.611	P
AGE			
≤45 Years	12	16	0.11655
>45 Years	14	18	
SEX			
Female	21	28	0.562
Male	6	5	



LESION			
NG	16	14	0.09334
PTC	10	20	
TUMOUR SIZE			
≤2cm	7	5	*0.01043
>2CM	3	15	
LYMPHNODE METASTASIS			
Absent	6	7	*0.02019
Present	3	14	

Table 2: Abbreviations:- NLR: Neutrophil-Lymphocyte ratio, NG- Nodular Goitre, PTC- Papillary thyroid carcinoma

*Statistically significant test results (p <0.05)

Table 3: Relationship Between Preoperative Platelet –Lymphocyte Ratio and Clinco-Pathological Variables

VARIABLES	PLR ≤93.98	PLR > 93.98	P
AGE			
≤45 years	10	18	0.983
>45 YEARS	13	19	
SEX			
Female	22	27	0.973
Male	3	8	
LESION			
NG	15	15	0.108
PTC	10	20	
TUMOUR SIZE			
≤2cm	6	6	*0.03805
>2cm	4	14	
LYMPHNODE METASTASIS			



Absent	6	7	*0.0363
Present	4	13	

Table 3: Abbreviations:- PLR: Platelet-Lymphocyte ratio, NG- Nodular Goitre, PTC- Papillary thyroid carcinoma

*Statistically significant test results (p <0.05)

Table 4: Relationship Between Preoperative Lymphocyte-Monocyte Ratio and Clinco-Pathological Variables

VARIABLES	LMR $\leq$ 5.025	LMR > 5.025	P
AGE			
$\leq$ 45 years	12	16	0.933
>45 years	16	16	
SEX			
Female	23	26	0.474
Male	6	5	
LESION			
NG	17	13	0.0789
PTC	11	19	
TUMOUR SIZE			
$\leq$ 2cm	7	5	0.117
>2cm	5	13	
LYMPH NODE METASTASIS			
Absent	7	8	0.346
Present	6	11	

Table 4: Abbreviations:- LMR: Lymphocyte-Monocyte ratio, NG- Nodular Goitre, PTC- Papillary thyroid carcinoma

Table 5: ROC curve characteristics for NLR, PLR and LMR

RATIO	AREA UNDER CURVE (AUC)	CUT OFF POINT	YOUDEN'S INDEX	SENSITIVITY	SPECIFICITY
NLR	0.626	1.436	0.267	86.67%	40%
PLR	0.621	90.62	0.233	80%	43.33%
LMR	0.521	4.65	0.133	63.33%	46.67%

Table 5: Abbreviations:- NLR-Neutrophil-Lymphocyte Ratio, PLR-Platelet-Lymphocyte Ratio, LMR-Lymphocyte-Monocyte Ratio, AUC- Area under curve, ROC-Receiver operator Characteristic Curve

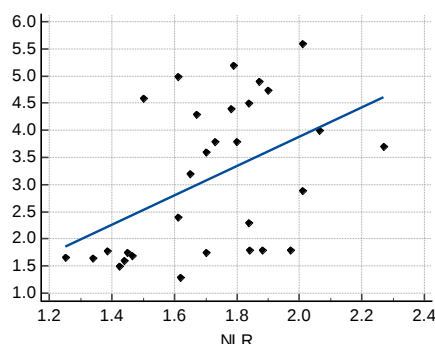


Figure 1: Scattergram of Tumour size and NLR by linear regression analysis

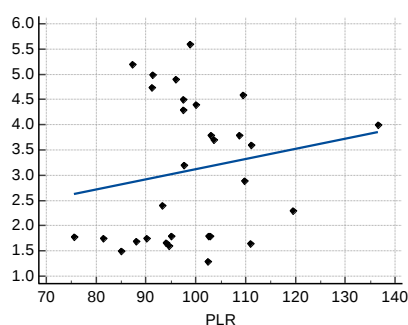


Figure 2: Scattergram of Tumour size and PLR by linear regression analysis

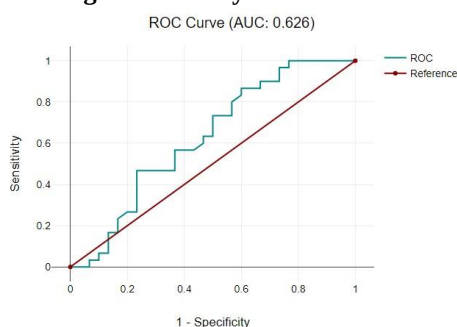


Figure 3: ROC Curve Analysis of NLR

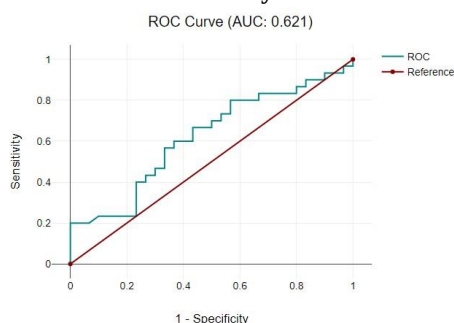


Figure 4: ROC Curve Analysis of PLR

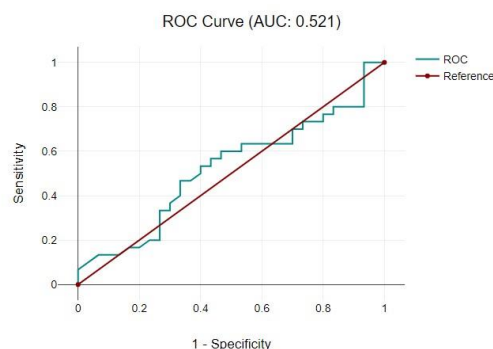


Figure 5: ROC Curve Analysis of LMR

5. Discussion

It is widely accepted that inflammation has cancer modeling as well as cancer-inhibiting properties. It also induces tumor angiogenesis, proliferation, and metastasis through the action of various inflammatory mediators such as cytokines and chemokines; thereby playing an important role in cancer pathogenesis. [11-13] Absolute counts of neutrophils, lymphocytes, and platelets, or expressed as ratios, are surrogate systemic inflammatory markers and have been known to have a prognostic association with various cancers. [7]

There have been several studies aimed at identifying the role of systemic inflammatory markers in thyroid lesions. The role of inflammatory biomarkers in PT has not been fully investigated. [14] Prior studies have found that higher pre operative NLR and PLR levels are associated with higher stage, poorer survival as well as recurrence in patients with PTC. [15]

Ari and Gunver (2019) analysed NLR and PLR in patients with thyroiditis and papillary thyroid carcinoma in comparison to healthy controls. In their study, the NLR was significantly higher in patients with thyroiditis and non-significantly higher in patients with papillary cancer in comparison to healthy controls. The PLR was significantly higher in patients with thyroiditis as well as papillary cancer than in healthy controls. In this study all three ratios (NLR, PLR, LMR) were non significantly higher in cases of papillary thyroid carcinoma in comparison to benign nodular goiter. [4]

A controversy exists as to whether inflammatory biomarkers can be used to differentiate benign thyroid nodules and thyroid carcinoma. Liu et al. (2016) conducted a recent meta-analysis that combined the



outcomes from 6 studies, involving 6283 patients. They reported that the pretreatment NLR values did not significantly differ between patients with benign nodules and differentiated thyroid carcinoma. However, they reported that an overall, high level of NLR significantly correlated with larger tumor size and metastasis. They also found that the association of NLR and metastasis was only significant for the subtype of papillary thyroid carcinoma. [16]

Manatakiset al. (2017) found increased NLR in papillary thyroid carcinomas with a poorer histopathological profile such as multifocality, extrathyroidal invasion, and lymph node metastasis. [10]

Kim et.al concluded that the 5-year disease-free survival rate was significantly worse in papillary thyroid carcinoma patients with $NLR \geq 1.5$ as compared to those with $NLR < 1.5$ ($p = 0.013$). [8]

The findings of the present study were in conjunction with these previous studies, whereas significant increase of NLR in tumors having a size greater than 2cm, as well as those with the presence of lymph node metastasis, was observed.

Riguetto et al.(2021) analyzed the role of preoperative PLR in differentiated thyroid cancers and found a significant association of higher PLR in patients with distant metastasis. [17] In this study as well, there was a significant association of PLR with higher tumor size and the presence of lymph node metastasis.

The limitations of this study include the limited number of patients and its retrospective design. The second limitation is the possibility that the ratios of NLR, PLR, and LMR can be affected by a wide number of factors. Larger, controlled studies with a prospective model are needed to obtain more unambiguous results in the future.

6. CONCLUSION

In our study, we found that both NLR and PLR correlated significantly with higher tumor size and the presence of lymph node metastasis. Routine analyses can provide these parameters easily and hence, can be used to improve the assessment of

prognosis in patients with papillary thyroid carcinoma.

References

1. Panato C., Vaccarella S., Dal Maso L., Basu P., Franceschi S., Serraino D., Wang K., Lei F., Chen Q., Huang B., Mathew A., 2020. Thyroid Cancer Incidence in India Between 2006 and 2014 and Impact of Overdiagnosis. *J Clin Endocrinol Metab.* 105(8),2507–2514
2. Yokota M., Katoh H., Nishimiya H., Kikuchi M., Kosaka Y., Sengoku N., Watanabe M., Yamashita K., 2020. Lymphocyte-Monocyte Ratio Significantly Predicts Recurrence in Papillary Thyroid Cancer. *J Surg Res.* 246,535-543.
3. Gambardella C., Mongardini FM., Paolicelli M., Bentivoglio D., Cozzolino G., Ruggiero R., Pizza A., Tolone S., Del Genio G., Parisi S., Bruscianno L., Cerbara L., Docimo L., Lucido FS., 2023. Role of Inflammatory Biomarkers (NLR, LMR, PLR) in the Prognostication of Malignancy in Indeterminate Thyroid Nodules. *Int J Mol Sci.*24(7),6466
4. Ari A., Gunver F., 2019. Comparison of neutrophil-lymphocyte ratio and platelet-lymphocyte ratio in patients with thyroiditis and papillary tumors. *J Int Med Res.* 47(5),2077-2083
5. Feng J., Wang Y., Shan G., Gao L., 2020. Clinical and prognostic value of neutrophil-lymphocyte ratio for patients with thyroid cancer: A meta-analysis. *Medicine.* 99(20), e19686.
6. Kumar K.TAK., Upadhyaya K., Nair VG., 2018. Pre-Operative Assessment of Lymphocyte Monocyte Ratio in Ovarian Neoplasms. *Annals pathol. lab. med.* 5 (5), 419-423
7. Cheong TY., Hong SD., Jung KW., So YK., 2021. The diagnostic predictive value of neutrophil-to-lymphocyte ratio in thyroid cancer adjusted for tumor size. *PLOS ONE.* 16(5), e0251446
8. Kim JY., Park T., Jeong SH., Jeong CY., Ju YT., Lee YJ., Hong SC., Ha WS., Choi SK., Jung EJ., 2014. Prognostic importance of baseline neutrophil to lymphocyte ratio in



- patients with advanced papillary thyroid carcinomas. *Endocrine*. 46(3), 526-31
9. Kim SM., Kim EH., Kim BH., Kim JH., Park SB., Nam YJ., Ahn KH., Oh MY., Kim WJ., Jeon YK., Kim SS., Kim YK., Kim IJ., 2015. Association of the Preoperative Neutrophil-to-lymphocyte Count Ratio and Platelet-to-Lymphocyte Count Ratio with Clinicopathological Characteristics in Patients with Papillary Thyroid Cancer. *Endocrinol Metab* . 30(4), 494-501.
 10. Manatakis DK., Tseleni-Balafouta S., Balalis D., Soulou VN., Korkolis DP., Sakorafas GH., Plataniotis G., Gontikakis E., 2017. Association of Baseline Neutrophil-to-Lymphocyte Ratio with Clinicopathological Characteristics of Papillary Thyroid Carcinoma. *Int J Endocrinol*. 2017,8471235.
 11. Göksu M., Alakuş H., 2023. Relationship Between Tumor Size and Neutrophil–Lymphocyte Ratio in Patients with Papillary Thyroid Carcinoma. *Cerrahpasa Med J*. 47(1),19-22
 12. Greten FR., Grivennikov SI., 2019. Inflammation and Cancer: Triggers, Mechanisms, and Consequences. *Immunity*. 51(1), 27-41
 13. Hart PC., Rajab IM., Alebraheem M., Potempa LA., 2020. C-Reactive Protein and Cancer-Diagnostic and Therapeutic Insights. *Front Immunol*. 11,595835
 14. Zhang Z., Xia F., Wang W., Huang Y., Li X., 2021. The systemic immune-inflammation index-based model is an effective biomarker on predicting central lymph node metastasis in clinically nodal-negative papillary thyroid carcinoma. *Gland Surg*.10(4),1368-7
 15. Chen W., Wei T., Li Z., Gong R., Lei J., Zhu J., Huang T., 2020. Association of the Preoperative Inflammation-Based Scores with TNM Stage and Recurrence in Patients with Papillary Thyroid Carcinoma: A Retrospective, Multicenter Analysis. *Cancer Manag Res*. 12,1809-1818.
 16. Liu JF., Ba L., Lv H., Lv D., Du JT., Jing XM., Yang NJ., Wang SX., Li C., Li XX., 2016. Association between neutrophil-to-lymphocyte ratio and differentiated thyroid cancer: a meta-analysis. *Sci Rep*.6,38551
 17. Riguetto CM., Barreto IS., Maia FFR., Assumpção LVMD., Zantut-Wittmann DE., 2021. Usefulness of pre-thyroidectomy neutrophil-lymphocyte, platelet-lymphocyte, and monocyte-lymphocyte ratios for discriminating lymph node and distant metastases in differentiated thyroid cancer. *Clinics*.76,e3022