Does the Preoperative Neutrophil-to-lymphocyte Ratio and Platelet-to-lymphocyte Ratio Associate with Clinic-pathological Characteristics in Papillary Carcinoma of Thyroid

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Citation

Shrestha BL, KC AK, Rajbhandari P, Dhakal A, Shrestha KS. Does the Preoperative Neutrophil-to-lymphocyte Ratio and Platelet-to-lymphocyte Ratio Associate with Clinic-pathological Characteristics in Papillary Carcinoma of Thyroid. *Kathmandu Univ Med J.* 2021;74(2):225-9.

ABSTRACT

Background

Thyroid cancer is associated with local and systemic inflammatory activities. Many systemic inflammatory markers including the neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) had shown credible and independent prognostic biomarkers in different malignant conditions. These markers are easy to reproduce, measure and inexpensive also. So, the preoperative evaluation of NLR and PLR is helpful in evaluating tumor growth and prognosis of papillary carcinoma of thyroid.

Objective

To evaluate the association of pre-operative NLR and PLR with clinic-pathological characteristic in papillary carcinoma of thyroid.

Method

This was a retrospective study performed in thirty one patients with the diagnosis of papillary carcinoma of thyroid. Preoperative NLR and PLR values were correlated with the clinical parameters like age, gender, lymph node metastasis, tumor size and pathological features (e.g., multifocality, bilaterality, extrathyroidal spread).

Result

There were thirty one patients, amongst which 13 were male and 18 were female. Similarly, the age distribution ranges from 27-68 years. The value of NLR was 2.37±1.09, and the value of PLR was 96.69±49.53.The increase in NLR was associated with increase in tumor size with statistically significant results. Similarly, increase in PLR was associated with increase in tumor size and multifocality with statistically significant results.

Conclusion

Increase NLR and PLR is associated with lymph node metastasis, extra thyroidal extension, multifocality of tumor and also bilaterality, so the risk can be stratified beforehand with measurement of NLR and PLR.

KEY WORDS

Lymph node metastasis, Neutrophil-to-lymphocyte ratio, Papillary carcinoma of thyroid, Platelet-to-lymphocyte ratio

INTRODUCTION

Thyroid cancer, the most common endocrine tumor, is associated with local and systemic inflammatory activities. Many systemic inflammatory markers including the neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR), had shown credible and independent prognostic biomarkers in lung, ovarian, gastric, hepatocellular, colorectal, esophageal, and pancreatic cancers.[1-6] These markers are easy to reproduce, measure and inexpensive also. So, the preoperative evaluation of NLR and PLR is helpful in evaluating tumor growth and prognosis of papillary carcinoma of thyroid.

Recently different studies have shown that the tumor microenvironment and systemic inflammatory response play important roles in many human cancers, with potential mechanisms involved in promotion of tumor cell growth, angiogenesis, invasion, and metastasis.[7,8]

There are limited studies in literature and in context of Nepal, this kind of study has not been done yet. The aim of our study is to find the association between NLR and PLR with clinic-pathological characteristics in papillary carcinoma of thyroid.

METHODS

This was a retrospective study performed in department of otorhinolaryngology and head and neck surgery, Dhulikhel Hospital, Kathmandu University Hospital. Total of thirty one patients with papillary carcinoma of thyroid diagnosed by histopathology results after thyroid surgery between April 2015 and October 2018 were enrolled in this study. The study was approved by institutional review committee. The clinical parameters of age, gender, blood indices (NLR and PLR), lymph node metastasis, tumor size and pathological features (e.g., multifocality, bilaterality, extrathyroidal spread) were collected. The tumor size was reported as the largest lesion dimension measured during a histopathological examination. The data which were devoid of any above mentioned information were excluded from the study.

The preoperative NLR was calculated by dividing the absolute neutrophil count (ANC) by the absolute lymphocyte count (ALC). Similarly, PLR was calculated by dividing the absolute platelet count (APC) by the ALC during the study. The automatic analyzer of coulter counter D5 supreme machine (Avoltor company, India) was used for blood count analysis in our institution. We divided the cohort into two groups: high NLR and PLR group, and low NLR and PLR group. Since there was not any exact cut off value in literature to mention the high or low NLR and PLR, so we had made the cut off point as 2.37 for NLR and 96.69 for PLR for both gender by analyzing the mean. The clinicopathological variables, which were stratified by the NLR and PLR were analyzed.

For statistical analysis, the cross tabulation with Chi-square and Fisher's exact test (2- tailed) if necessary was used to compare categorical variables and linear by linear association. The p value of < 0.05 was taken as significant.

RESULTS

There were total thirty one patients with male 13 and female 18. Similarly, the age distribution ranged from 27-68 years. The value of NLR was 2.37 ± 1.09, and the value of PLR was 96.69 ± 49.53.

As shown in table 1, increased in NLR is associated with increase in tumor size with statistically significant results. Likewise, lymph node metastasis, multifocality, extra thyroidal extension and bilaterality is more in increased NLR but statistically not significant. Similarly, increased in PLR is associated with increased in tumor size and multifocality mainly with statistically significant results.

Also, lymph node metastasis and extra thyroidal extension is more in increased PLR but statistically not significant.

DISCUSSION

Our study is one of the first to analyze the preoperative NLR and PLR as predictive marker in clinic-pathological characteristic in papillary carcinoma of thyroid in Nepali population.

The exact mechanism of association between high NLR with poor cancer prognosis remains unclear, however, the hypothesis is that NLR mainly reflect the systemic inflammatory process and immunity status of a patient. So, an increase in NLR shows higher anti-inflammatory activity and cause increase circulating cytokines, including interleukin-17 (IL-17), interleukin-1 receptor a (IL-1R a), IL-6, IL-7, IL-8, IL-12 and monocyte chemotactic protein-1.[9,10] Hence, these inflammatory cytokines leads to a tumor microenvironment causing promotion of tumor invasion.[9-11]

Apart from this, neutrophils also cause vascular endothelial growth factor (VEGF) generation and inhibit the secretion of tumor necrosis factor-a (TNF-a) which has been hypothesized to play an important role in tumor proliferation and angiogenesis.[12,13] Thus, an increase in neutrophil level is responsible for advanced tumor stage.

Similarly, lymphocytes causes tumor shrinkage by inducing natural killer lymphocytes and stimulate giant cells in tumors to release cytokines, including interferons and TNF-a. Hence, decrease in lymphocyte number may lead to decrease antitumor activity.[14,15] So, imbalance in NLR leads to rapid and uncontrolled growth, and may lead to metastasis of tumor.[9]

In our study, we found that the preoperative increase in NLR is related with large tumor size which is statistically

Table 1. Showing the patient characteristics according to pre-operative neutrophil to lymphocyte ratio and platelet to lymphocyte ratio.

Variables	Number (n =31)	NLR < 2.37	NLR ≥ 2.37	P Value	PLR < 96.69	PLR ≥ 96.69	P Value
Age							
< 45 years	26	13	13	0.58	14	12	0.570
≥ 45 years	5	0	5		2	3	
Gender							
Male	13	5	8	1.00	4	9	0.048
Female	18	8	10		12	6	
Lymph node metastasis							
Present	19	6	13	0.262	8	11	0.183
Absent	12	7	5		8	4	
Multifocality							
Present	14	4	10	0.275	4	10	0.02
Absent	17	9	8		12	5	
Tumor size (cm)	4.1±1.59	3.68±0.44	4.69±0.34	0.01	3.05±1.01	4.19±0.98	0.009
Extra thyroidal extension							
Present	8	2	6	0.412	2	6	0.08
Absent	23	11	12		14	9	
Bilaterality							
Present	12	5	7	1.00	6	6	0.88
Absent	19	8	11		10	9	

significant. Also, the lymph node metastasis, multifocality, bilaterality and extra thyroidal extension is more in patients with increase NLR but it was statistically not significant. The summary of comparative association among different studies in literature and our study is as shown in table 2.

There is also meta-analysis performed over 40,000 patients with variety of solid tumors which showed that increase NLR was associated with unfavorable outcome.[12]

Table 2. Different studies in the literatures showing association of NLR with clinicopathological characteristics of PTC.

Variables	Association not found with clinicopathological characteristics	Association found with clinicopathological characteristics
Age	Liu et al.[16] Kim et al.[18] Gong et al.[20] Manatakis et al.[22] **Our study**	Liu et al.[17] (lower NLR in patients < 45 years) Lang et al.[19] (lower NLR in patients < 45 years) Kim et al.[21] (lower NLR in patients ≥ 45 years)
Gender	Liu et al.[16], Liu et al.[17], Kim et al.[18], Lang et al.[19], Gong et al.[20], Manatakis et al.[22] **Our study**	-
Lymph node metastasis	Liu et al.[16], Liu et al.[17], Kim et al.[18], Lang et al.[19], Kim et al.[21], **Our study**	Gong et al.[20], Manatakis et al.[22]
Multifocality	Liu et al.[16], Kim et al.[18], Lang et al.[19], Kim et al.[21], **Our study**	Gong et al.[20], Manatakis et al.[22]
Tumor size	Liu et al.[17], Cho et al.[23], Kim et al.[21], Manatakis et al.[22]	Liu et al.[16], Kim et al.[18], Lang et al.[19], Gong et al.[20], **Our study**
Extra thyroidal extension	Liu et al.[16] , Liu et al.[17], Kim et al.[18], Lang et al.[19], Kim et al.[21], **Our study**	Manatakis et al.[22]

The PLR is a novel and important inflammatory index because it has been used as a prognostic marker in different types of cancers eg; gastric, ovarian, colorectal, pancreatic cancer and cholangiocarcinoma.[23,24] It has been reported to be biochemically involved in the progression of tumor invasion.

Recent studies have shown the use of the PLR in a diagnostic approach to malignancy and inflammatory events.[25] The core mechanism about the association between an increase PLR and the biological behavior of cancer cells remain unclear. One hypothesis is that megakaryocyte mediated thrombocytosis may result from the release of proinflammatory mediators like IL-1, IL-2, and IL-6.[26]

Different studies suggest that platelets support the growth via angiogenesis and also have an obvious association with tumor metastasis via invasion of immune system.[27-29] Apart from this, platelet also hamper the lysis of tumor cells by NK cells.[30] Likewise, decrease circulating lymphocytes have been observed as a biomarker for poor survival in various cancer because lymphocytes has important role in cell mediated immunity and T cell demolition.[31,32]

Similarly, preoperative increase PLR in our study is associated with large size of tumor and multifocality which is statistically significant. It is also associated with extrathyroidal extension and lymph node metastasis but statistically not significant.

Study performed by Kim showed that the increase preoperative PLR may be a significant predictor of lateral lymph node involvement in patients with papillary carcinoma of thyroid, which differ from our study though in our study increase PLR was associated with lymph node metastasis and extrathyroidal extension of tumor but it was statistically not significant.[28] Similarly, the study performed by Ari et al. showed that the PLR ratio was significantly high in papillary carcinoma but they had not studied the different prognostic variables like we did.[34]

The main limitations of our study is the selection bias as it is retrospective study. The sample size is also low and we have not evaluated the C-reactive protein level during routine preoperative evaluation as the value of neutrophils and lymphocytes may be affected by inflammation, infections, medications and other non-cancerous causes. So, we recommend that there should be prospective and large sample size study in multi-institutional level for more accurate results.

CONCLUSION

Since increase NLR and PLR is associated with lymph node metastasis, extra thyroidal extension, multifocality of tumor and also bilaterality, so the risk can be stratified beforehand with measurement of NLR and PLR.

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