

Relationship Between the Neutrophil to Lymphocyte Ratio and Parathyroid Adenoma Size in Patients With Primary Hyperparathyroidism

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The aim of our study was to evaluate the relationship between neutrophil to lymphocyte ratio (NLR) and adenoma size in parathyroidectomized patients who underwent a parathyroidectomy. The neutrophil to lymphocyte ratio has recently become popular as a biomarker for malignant diseases or for estimating tumor size preoperatively. This study aimed to estimate the relationship between adenoma size and NLR. Furthermore, we assessed whether a higher level of NLR is correlated with the presence of parathyroid carcinoma. A retrospective chart review was performed for patients with parathyroid adenoma who underwent parathyroidectomy between January 2012 and August 2014. Data related to age, sex, NLR, parathyroid hormone level (PTH), preoperative calcium, phosphorus, adenoma size, and pathology reports were collected. The neutrophil to lymphocyte ratio was significantly correlated with calcium levels, PTH levels, parathyroid adenoma size, and the presence of cancer. However, there was no correlation between NLR and age, sex, and phosphorus levels. This study is the first to document a positive correlation between NLR and parathyroid adenoma size, as well as the presence of cancer, in patients who underwent surgery as a result of primary hyperparathyroidism.

Key words: Neutrophil – Lymphocyte – Parathyroid adenoma – Primary hyperparathyroidism

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Primary hyperparathyroidism is known for its clinical consequences and is commonly associated with parathyroid hyperplasia, parathyroid adenoma, and parathyroid carcinoma.¹ A parathyroid carcinoma, which is rare, may be observed in patients with a hyperparathyroidism crisis.² Previously, parathyroid hormone (PTH) has been reported to be related to epithelial-mesenchymal interactions, skeletogenesis, and carcinogenesis.^{3,4} In some cases, the treatment of hyperparathyroidism has been reported to result in the total recovery of the associated hematological or autoimmune conditions.⁵⁻⁷ In addition, primary hyperparathyroidism has been advocated to be a pathogenic factor in various immune conditions that have B lymphocyte hyperactivity.⁸

Various biochemical and hematological markers are available to evaluate or document systemic inflammation. However, some markers are costly to use. It is clear that inexpensive methods are needed as indicators for inflammation. The neutrophil to lymphocyte ratio (NLR) is obtained by dividing the neutrophil count by the lymphocyte count. It is considered an inflammatory marker as a result of being readily available, and has been reported to be a cost-effective diagnostic method.⁹ The neutrophil to lymphocyte ratio has been previously studied in various clinical conditions related to systemic inflammation and cancer.¹⁰⁻¹² However, the relationship between NLR and the size of parathyroid adenomas, or the presence of concurrent parathyroid carcinoma, have not been evaluated previously.

As the size of the parathyroid adenoma increases, the risk of malignancy and lymph node metastases also increase in patients with parathyroid adenoma.^{13,14} Therefore, we decided to evaluate the relationship between NLR, parathyroid adenoma size, and the presence of parathyroid carcinoma in parathyroidectomized patients.

Materials and Methods

We retrospectively reviewed the medical data of patients who had undergone parathyroidectomy at our institution for primary hyperparathyroidism due to parathyroid adenoma between January 2012 and August 2014. All patients had high levels of calcium and PTH. The presence of parathyroid adenomas was assessed by neck ultrasonography and localized using Tc 99-Mib1 scintigraphy. The verification of true parathyroid adenoma excision was performed by perioperative rapid PTH level assessment both before and after the resection of the

adenoma. In total, we included 32 patients who had undergone parathyroidectomy for an initial diagnosis of primary hyperparathyroidism. While exploring the neck for the adenoma, we encountered adenomas that had a much larger diameter and irregular margins in 3 patients. Consequently, we wanted these adenomas to be evaluated as intraoperative frozen sections. All 3 patients were diagnosed with parathyroid carcinoma, and therefore there were 29 patients included in the study with parathyroid adenomas and 3 patients with parathyroid carcinoma.

In all patients, data were collected regarding age, sex, NLR, PTH levels, preoperative calcium and phosphorus levels, and adenoma size. Patient-defining parameters were not included in this retrospective study and were not presented in the article. The inclusion criteria were patients treated with parathyroidectomy for an initial diagnosis of parathyroid adenoma. Exclusion criteria included patients with incomplete data, and those with active infections, other known malignancies, long-term steroid treatment, chronic inflammatory or autoimmune diseases, and hematological disorders. These conditions can alter neutrophil and lymphocyte counts.

After parathyroidectomy, patients were followed-up regularly. They were examined on postoperative day 7 and postoperative months 1, 3, and 6. During this period, PTH, calcium, and phosphorus levels were assessed.

Statistical analysis

All statistical analysis was performed with statistical software (SPSS 13.0 for Windows; SPSS, Inc, Chicago, Illinois). First, frequency and descriptive analyses were performed, followed by age and sex analysis. Fisher's exact test was used to evaluate the presence of differences between the study groups for NLR, PTH levels, and parathyroid adenoma size. Pearson correlation test and linear regression analysis were used to evaluate the correlations and relationship between study parameters. A power analysis was not necessary for this retrospective study. Values of $P < 0.05$ were considered to be significant.

Results

The basic demographic and clinical features of the study cohort in this preliminary study are presented in Table 1. The percentage of the elderly patients

Table 1 Basic demographic and clinical features of the study cohort.

	Patients (n = 32)
Age (y), mean \pm SD	53.2 \pm 12.5
Female/male ratio	8/24
Calcium level, mean \pm SD	11.7 \pm 1.7
PTH level, mean \pm SD	663.2 \pm 663.0
Phosphorus level, mean \pm SD	2.8 \pm 0.7
Adenoma size, mean \pm SD	2.9 \pm 1.8
NLR	2.1 \pm 0.9

(>60 years) was 28.1%. There was no relationship between age and NLR. The percentage of female patients was 75%. Sex was not correlated with neutrophil or lymphocyte counts. Furthermore, age and sex were not correlated with PTH levels, calcium levels, and parathyroid adenoma diameter.

A significant positive correlation between increased NLR and parathyroid adenoma diameter was observed (Fig. 1). There was also a positive correlation between NLR and both calcium and PTH levels. Correlations between age, sex, calcium, PTH levels, parathyroid adenoma size, and the presence of cancer are presented in Table 2. The diameters of the parathyroid tumor in the 3 patients with parathyroid malignancy were 6, 6.7, and 8.4 cm. The neutrophil to lymphocyte ratio in these patients was strongly correlated with tumor diameter.

Discussion

The neutrophil to lymphocyte ratio has been suggested as an excellent biomarker for inflamma-

Table 2 Correlations between age, sex, calcium and PTH levels, parathyroid adenoma size, and the presence of cancer.

	NLR	
	<i>r</i> *	<i>P</i> value*
Age	-0.154	0.401
Sex	-0.043	0.817
Calcium	0.513	0.003
PTH	0.472	0.006
Parathyroid adenoma size	0.675	0.000
Presence of cancer	0.578	0.001

*Pearson correlation test; *r* refers to correlation coefficient and *P* < 0.05 is significant.

tory conditions, including malignant diseases, cardiac disorders, vertigo and systemic diseases such as diabetes mellitus, neurological disorders, rheumatological disorders, hypertension, and renal failure.^{9,15,16} Feng *et al*¹⁷ reported a relationship between NLR and tumor diameter in those patients with squamous cell carcinoma of the esophagus. Liu *et al*¹⁸ demonstrated that there was a direct correlation between elevated NLR values and tumor diameter in cases of differentiated thyroid cancer; in addition, they described a correlation between high NLR values and a higher risk of tumor recurrence, which is included in the American Thyroid Association guideline. In our study, we determined that 3 patients had pathologically confirmed parathyroid cancer after undergoing surgery for parathyroid adenoma. There was a strong correlation between the preoperative tumor diameter in these patients

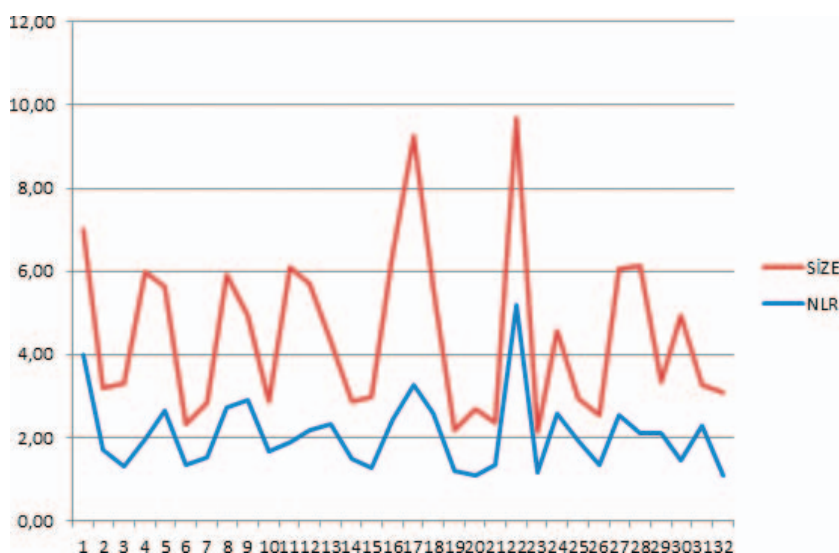


Fig. 1 Linear correlation between parathyroid adenoma size and NLR values.

and their NLR. In the future, preoperative NLR could be used as a biomarker to assess parathyroid cancer risk in patients with parathyroid adenoma, but studies with increased sample sizes will be important to support this hypothesis.

Bae *et al*¹⁹ claimed that larger parathyroid tumor size was a risk factor for malignancy. Quin *et al*¹⁴ also found that patients with parathyroid carcinoma present with significantly increased tumor sizes. In addition, Hsu *et al*¹³ also found that tumor sizes larger than 3 cm have an increased risk of lymph node metastases at presentation. In the present study, we found a positive correlation between NLR and parathyroid adenoma size, which will guide our future investigations regarding the relationship between NLR and the risk of malignancy and lymph node metastases in patients with parathyroid carcinoma.

Lang *et al*²⁰ investigated the clinical significance of NLR in patients with differentiated thyroid cancer in terms of recurrence and occult metastasis. They concluded that NLR was correlated with patient age and tumor diameter. However, in this current study, a correlation between patient age and NLR was not observed.

Multiple studies indicate that carcinogenesis causes chronic inflammation, which results in an increase in the levels of inflammatory markers, such as C-reactive protein and NLR.^{21,22} Moreover, inflammation and carcinogenesis are closely associated with impaired immunity.²³ Thus, the elevated NLR in our patients with malignancy may be related with the inflammatory response to the cancer. Our study investigated the relationship between NLR and parathyroid adenoma size. Our parathyroid disease group included 32 patients with parathyroid tumors. There were 3 patients with parathyroid carcinoma and a significantly higher NLR was found in these patients compared with those without tumors. In patients with cancer, a low lymphocyte count has been associated with the suppression of immunity.²⁴ In addition, a high neutrophil count is thought to result from paraneoplastic activity of the tumor and the production of granulocyte colony-stimulating factor.²⁵ Therefore, elevated NLR levels are associated with low immunity levels in cancer patients. In the patients with parathyroid adenoma in this study, higher neutrophil counts were detected, in contrast to the 3 patients with parathyroid carcinoma who had markedly increased neutrophil levels and reduced lymphocyte levels.

Furthermore, the clinical significance of NLR has been investigated for the discrimination of malignant and benign disorders. Seretis *et al*²⁵ advocated that NLR could be used as a biomarker to discriminate between malignant and benign thyroid disorders. In the present study, although we observed an increased NLR in cases of parathyroid carcinoma, we could not make conclusions about the use of NLR for this purpose as a consequence of the small sample size of parathyroid carcinoma.

The primary limitation of our study arises from its retrospective nature. In addition, the relatively small numbers of patients included illustrate the preliminary nature of this study. Our center is an intermediate volume center for parathyroid surgery and the relatively short study period duration contributed to the small sample size. It is clear that a high volume center or a multicenter prospective study may overcome all of these limitations.

According to our study, elevated NLR levels were directly correlated with parathyroid adenoma sizes. This condition resulted with easily localization of adenomas preoperatively; on the other hand, the increased diameter of adenomas would result with parathyroid carcinoma as in our patients. So that preoperative evaluating of higher NLR levels will serve as a guide for physicians in clinical practice.

Conclusion

This preliminary study is the first to document a positive correlation between NLR and parathyroid adenoma diameter, in addition to PTH and calcium levels in patients treated with surgery for parathyroid adenoma. Moreover, a relationship between parathyroid cancer and higher NLR values compared with parathyroid adenomas was observed. These results will guide our future investigations into the relationship between NLR and the risk of malignancy in this patient population, as well as establishing the presence of lymph node metastases from parathyroid carcinomas according to NLR values. The clinical significance of these findings merits further large-scale prospective investigations.

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