

RESEARCH

Preoperative inflammatory markers for predicting parathyroid carcinoma

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Abstract

Objective: Parathyroid carcinoma is a rare tumor among parathyroid tumors. Aspiration cytology and needle biopsy are generally not recommended for diagnostic purposes because they cause dissemination. Therefore, it is commonly diagnosed by postoperative histopathological examination. In this study, we investigated whether preoperative inflammatory markers can be used as predictors of cancer in patients with primary hyperparathyroidism.

Design: This was a retrospective study.

Methods: Thirty-six cases of parathyroid carcinoma and 50 cases of parathyroid adenoma (PA) operated with the diagnosis of primary hyperparathyroidism and confirmed histopathologically at Ito Hospital were included in this study. Preoperative clinical characteristics and inflammatory markers (neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio, and lymphocyte-to-monocyte ratio (LMR)) were compared and their values in preoperative prediction were evaluated and analyzed.

Results: Preoperative intact-parathyroid hormone ($P = 0.0003$), serum calcium ($P = 0.0048$), and tumor diameter ($P = 0.0002$) were significantly higher in parathyroid carcinoma than in PA. LMR showed a significant decrease in parathyroid carcinoma ($P = 0.0062$). In multivariate analysis, LMR and tumor length diameter were independent predictors. In the receiver operating characteristics analysis, the cut-off values for LMR and tumor length diameter were 4.85 and 28.0 mm, respectively, for parathyroid cancer prediction. When the two extracted factors were stratified by the number of factors held, the predictive ability improved as the number of factors increased.

Conclusion: In the preoperative evaluation, a combination of tumor length diameter of more than 28 mm and LMR of less than 4.85 was considered to have a high probability of cancer.

Key Words

- ▶ lymphocyte-to-monocyte ratio
- ▶ tumor size
- ▶ parathyroid carcinoma
- ▶ preoperative prediction

Endocrine Connections
(2022) 11, e220062

Introduction

Parathyroid carcinoma (PC) is a rare endocrine tumor that accounts for <0.5–5% of patients with primary hyperparathyroidism (1, 2, 3, 4). Complete surgical resection is the only curative treatment for PC. To prevent local recurrence, the lesions should be removed en bloc to a certain extent (2, 5, 6, 7). Patients with PC often have local recurrence or distant metastases, and most die of uncontrolled severe hypercalcemia (2, 6, 7, 8). Accurate

diagnosis before surgery is crucial to reduce the risk of recurrence of PC and allow the required appropriate surgery (9, 10, 11).

Clinical features of PC may include severe hypercalcemia, a palpable neck mass, evidence of local invasion during surgery, or suspicion of distant metastases (2, 10, 12). In contrast, on diagnostic imaging, findings of tumors on cervical ultrasonography (13), diagnoses of PC

using tumor depth–width ratio (14), and expected results of PC using short-to-long axis ratio or tumor shape on CT (15) have been found; however, these tests are not specific to PC unless there are clear findings of invasion or distant metastases. In addition, diagnostic fine-needle aspiration cytology or needle biopsy is generally not recommended for parathyroid glands because of the risk of cell seeding due to damage to the parathyroid capsule. Thus, a differential diagnosis between benign and malignant tumors prior to the treatment of primary hyperparathyroidism is difficult. A problem for clinicians is the lack of specific clinical, biochemical, and imaging features that distinguish PC from parathyroid adenoma (PA). Thus, in clinical practice, PC is often diagnosed through histopathological examinations after surgery and diagnosis after recurrence is also not uncommon (3, 16).

Inflammatory activity has long been implicated as having extensive involvement in the progression of cancer (17), and inflammatory biomarkers reflecting the inflammatory status of patients with cancer have been reported to be prognostic predictive factors in various types of cancer. In particular, among these, the neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and lymphocyte-to-monocyte ratio (LMR) have been reported to be prognostic predictive factors and markers for differentiating benign tumors from malignant tumors in several types of carcinomas (18, 19, 20, 21, 22, 23, 24). Few articles have described the relationship between parathyroid disease and inflammatory markers, and their value as preoperative screening tools remains unknown (25, 26).

Therefore, this study aimed to investigate whether the screening test could help to distinguish between PC and PA in preoperative diagnosis in surgical cases of primary hyperparathyroidism.

Materials and methods

We retrospectively reviewed the medical data of patients who underwent surgery for primary hyperparathyroidism at Ito Hospital from 1979 to 2019. A total of 1415 patients underwent surgery, and data from 36 cases histopathologically confirmed as PC were retrospectively reviewed. In addition, 50 age- and gender-matched patients with histopathologically confirmed PA were included in the study. Postoperative histopathological analysis was conducted by a pathologist using World Health Organization diagnostic criteria (27). PC was defined as a patient with any one of the following microscopic features necessary for

the definitive diagnosis of parathyroid lesion malignancy: (i) vascular invasion, (ii) invasion into adjacent structures or organs, and (iii) metastasis. Patients with secondary or tertiary hyperparathyroidism and those with other causes of vitamin D intoxication, hyperthyroidism, hypercalcemia, and other carcinomas were excluded. In addition, patients with incomplete data and those with active infections, prolonged steroid therapy, chronic inflammatory or autoimmune disease, or hematologic disease were excluded because these may alter neutrophil or lymphocyte counts. For all patients, data on age, sex, blood collection test data (serum calcium, phosphorus, parathyroid hormone (intact PTH), creatinine, alkaline phosphatase (ALP), white blood cell count, and platelet count), and the size of the parathyroid mass were collected from medical charts. The size of the parathyroid mass was determined from the preoperative cervical ultrasonography using the results of the largest diameter of the mass. Inflammation markers were calculated from blood samples taken approximately 2 weeks to the day before the surgery. If multiple measurements were taken, the results from the measurement closer to the date of the surgery were used. LMR was defined as the lymphocyte count divided by the monocyte count, NLR as the neutrophil count divided by the lymphocyte count, and PLR as the platelet count divided by the lymphocyte count.

A receiver operating characteristic (ROC) curve was constructed to estimate the optimal cut-off value for the pre-treatment inflammatory markers. The optimal cut-off value for the ROC curve was determined based on the Youden Index. In addition, analysis of the ability to predict cancer was performed with stratification for the presence or absence of independent predictive factors extracted from the investigation.

Statistical analysis

Continuous variables were expressed as median and interquartile range, and categorical variables were expressed as numbers and percentages. Continuous variables were compared using the Mann–Whitney *U*-test or Kruskal–Wallis test, and categorical variables were compared using Fisher's exact test or chi-squared test. Univariate and multivariate logistic regression analyses were used to compare the two groups, and odds ratios and 95% CIs were calculated. Statistical significance was indicated by a value of $P < 0.05$. Statistical analyses were performed using JMP software (Version 12; SAS Institute Inc., Cary, NC, USA).

This study was approved by the Ethics Committee of Ito Hospital. The study was conducted in accordance with the guidelines described in the Declaration of Helsinki, and

consent was obtained after providing verbal explanation of the study to the patients.

Results

Clinical characteristics of parathyroid carcinoma and parathyroid adenoma

The background characteristics of patients in this study are shown in Table 1. In total, 36 patients with a histopathological diagnosis of PC and 50 patients with a diagnosis of PA were included in the analysis. The median age at surgery for patients with carcinoma and adenoma was 55 years and 59.5 years, respectively. The male-to-female ratio was 1:2.6 for patients with carcinoma and 1:2.3 for patients with adenoma, with no difference in the distribution of sex. The median long diameter of tumors on preoperative cervical ultrasonography was 29 mm for PC and 17 mm for PA, which showed that the tumor diameter was considerably larger in patients with carcinoma. Regarding surgery, all patients with PA underwent parathyroidectomy, 16 patients (44.5%) with PC underwent parathyroidectomy, 13 patients (36.1%) underwent parathyroidectomy and hemithyroidectomy, and 7 patients (19.4%) underwent parathyroidectomy, hemithyroidectomy, and lymph node dissection. In about half of the patients with PC, the surrounding organs (thyroid gland and lymph nodes) other than the parathyroid gland were resected. With regard to lymph node dissection, there was only one case with preoperative imaging findings of suspected metastasis.

Of 36 patients, 13 underwent dissection, and only one patient had histopathological metastasis, whereas the other patients did not have metastasis. Intraoperative findings of suspected infiltration were mainly in the thyroid gland, and only one case of suspected infiltration into the internal jugular vein was treated with a combined resection. The histological characteristics of PC showed the presence of chief cell-based masses in 30 (83.3%) cases and eosinophilic cell-based masses in 6 (16.7%) cases. In PA, chief cell-based masses were found in 28 (56.0%) cases and eosinophilic cell-based masses were found in 13 (26.0%) cases, with a significant difference in the number of chief cell-based masses in PC ($P=0.0081$) (data not shown). Of the patients diagnosed with PC, two (5.6%) underwent external radiation to the neck as an additional postoperative treatment. Postoperative recurrence was observed in four patients (11%). The recurrence site of one patient was local recurrence and distant metastasis, and three patients had distant metastasis. The median follow-up period for PC was 56.7 months.

Analyses of cancer predictive factors

In patients with PC, tumor size, intact PTH, and calcium level were significantly higher than those in patients with PA ($P=0.0002$, $P=0.0003$, $P=0.0048$, respectively). Additionally, LMR was significantly lower in patients with PC than in patients with PA ($P=0.0062$). There were no significant differences in NLR or PLR (Table 1). In multivariate analyses, tumor size and LMR were significant

Table 1 Comparison of patient and tumor characteristics, including preoperative biochemical laboratory values, in patients with parathyroid carcinoma and parathyroid adenoma.

Variables	Carcinoma (n = 36)	Adenoma (n = 50)	P - value
Age (years)	55.0 (46–68.5)	59.5 (46–68)	0.8679
Gender (male/female)	10/26 (27.8/72.2)	15/35 (30.0/70.0)	0.8228
Tumor size (mm)	29 (18–36)	17 (14–24)	0.0002
Intact PTH level (pg/mL)	246.5 (160.0–444.5)	161.0 (118.0–205.5)	0.0003
Calcium level (mg/dL)	11.5 (10.9–12.8)	10.9 (10.6–11.3)	0.0048
Creatinine (mg/dL)	0.74 (0.60–0.90)	0.76 (0.57–0.86)	0.6455
ALP (U/L)	350 (218–512)	294 (234–386)	0.3416
WBC (/μL)	5960 (4880–6900)	5490 (4743–6605)	0.3416
Neutrophils (/μL)	3648 (2936–4384)	3231 (2698–4207)	0.1415
Lymphocytes (/μL)	1784 (1430–2346)	1789 (1475–2076)	0.8233
Monocytes (/μL)	372 (325–479)	292 (259–352)	0.0003
Plt ($\times 10^4/\mu\text{L}$)	23.1 (20.1–28.5)	24.8 (20.6–27.9)	0.7109
NLR	1.90 (1.64–2.46)	1.89 (1.48–2.22)	0.4023
PLR	141.1 (103.6–160.4)	143.4 (110.4–164.8)	0.6418
LMR	4.54 (3.38–6.28)	6.00 (4.40–7.50)	0.0062

Data were expressed as number (%) or median (interquartile range/IQR). Bold indicates statistical significance, $P < 0.05$. Normal range; intact PTH: 15–65 pg/mL, calcium: 8.5–10.0 mg/dL, creatinine: 0.46–1.09 mg/dL, ALP: 38–113 U/L.

ALP, alkaline phosphatase; cLND, central lymph node dissection; hTx, hemithyroidectomy; NLR, neutrophil-to-lymphocyte ratio; PTH, parathyroid hormone; Plt, platelet count; PLR, platelet-to-lymphocyte ratio; PTx, parathyroidectomy; LMR, lymphocyte-to-monocyte ratio; WBC, white blood cell.

independent predictive factors of PC (Table 2). The ROC curve was used to determine the optimal cut-off value for predicting parathyroid cancer in LMR and tumor size (Fig. 1). Results show that the cut-off value for LMR was 4.857, and the area under the curve (AUC) was 0.680 ($P = 0.0048$). The cut-off value for tumor size was 28.0 mm and that for AUC was 0.7351 ($P = 0.0003$). The sensitivity and specificity at the optimal LMR cut-off value of 4.85 for the prediction of PC were 59.9 and 72.0%, respectively. At a cut-off value of 28 mm for tumor size, the sensitivity and specificity for predicting carcinoma were 57.1 and 90.0%, respectively.

In addition, the validity of prediction was assessed using different criteria for LMR values (Table 3). The criteria were the first quartile, the high quartile, the median, the criterion obtained by ROC, the low quartile, and the third quartile, and the sensitivity, specificity, positive predictive value, negative predictive value, and accuracy rate were analyzed. An LMR value of 4.85 or less, which was the criterion obtained by ROC, was noted to be highly predictive of PC.

Stratified analyses of parathyroid carcinoma predictive factors

Two extracted predictive factors (long diameter of the tumor > 28 mm, LMR < 4.85) were stratified by the number of factors. Predictions of cancer were analyzed by stratifying patients into a low-risk group (0 factors), an intermediate-risk group (1 factor), and a high-risk group (2 factors) (Table 4). The combination of long diameter of tumors and LMR showed that the predictive power for cancer was higher in the high-risk group with two factors than in the low-risk group. ($P < 0.001$).

Discussion

Inflammation is strongly associated with cancer, and the levels of inflammatory cells in the peripheral blood,

Table 2 Multivariate analyses of risk factors for parathyroid carcinoma.

Variables	Multivariate analysis	
	OR (95% CI)	P - value
Intact PTH	1.001 (0.998–1.006)	0.2336
Serum calcium	1.239 (0.609–2.562)	0.5512
Tumor size	1.090 (1.026–1.173)	0.0035
LMR	0.763 (0.556–0.994)	0.0445

LMR, lymphocyte/monocyte ratio; OR, odds ratio. Bold indicates statistical significance, $P < 0.05$.

including neutrophils, lymphocytes, and monocytes, have been reported as prognostic factors in various cancers (28, 29). Lymphocytes play an important role in host tumor immunity, for example, by inhibiting cytotoxic cell death and tumor cell proliferation and migration (30, 31, 32). A decline in the level of lymphocytes is believed to undermine the immune response to tumors and promote tumor progression and metastasis (33, 34). Monocytes are known to infiltrate tumors and differentiate into tumor-associated macrophages. Macrophages are involved in tumor growth, invasion, metastasis, neovascularization, and recurrence (35, 36, 37). LMR is an inflammatory marker defined by the ratio of lymphocytes to monocytes; furthermore, low LMR, which reflects the host immune status and tumor progression, may be associated with poor prognosis. In this study, elevated monocyte counts were observed in PC. Higher monocyte counts may indicate more tumor-associated macrophages in the tumor tissue, leading to immunosuppression and tumor growth (38, 39). Many studies till date have suggested that LMR is an independent prognostic factor in other carcinomas (21, 24, 40, 41, 42, 43, 44). LMR has been reported to be useful as a predictive factor for malignancy in other types of carcinomas (45, 46). Till date, however, there have been few reports on parathyroid disease. Lam *et al.* reported that in patients undergoing surgery for primary hyperparathyroidism, the NLR before parathyroidectomy was associated with serum Ca and PTH levels, and that the NLR levels rapidly decrease after parathyroidectomy; however, this was only observed in patients with PA (26). Although Zeren *et al.* reported that preoperative NLR was significantly correlated with Ca level, PTH level, size of adenoma, and presence or absence of cancer, only three patients with cancer were studied (25).

To our knowledge, this is the first study to assess the association with LMR as a predictive factor for malignancy in parathyroid disease. In this study, lower the LMR, higher the probability of PC, which indicates that this factor was a predictive marker for cancer preoperatively. In this study, the optimal cut-off value for LMR was calculated as 4.85 from the ROC curve, which was used as a reference value and evaluated as a predictive factor for cancer. Setting a cut-off value based on the ROC curve can help determine the degree to which sensitivity should be sought, but it depends on the disease and medical condition. In this study, sensitivity and specificity were evaluated using different cut-off values as shown in Table 4, and the cut-off value of 4.85 for LMR was found to be optimal. In utilizing these indices, it is important to reevaluate the interpretation of the values at all times while fully considering the purpose of use, characteristics of the target population, and disease stage.

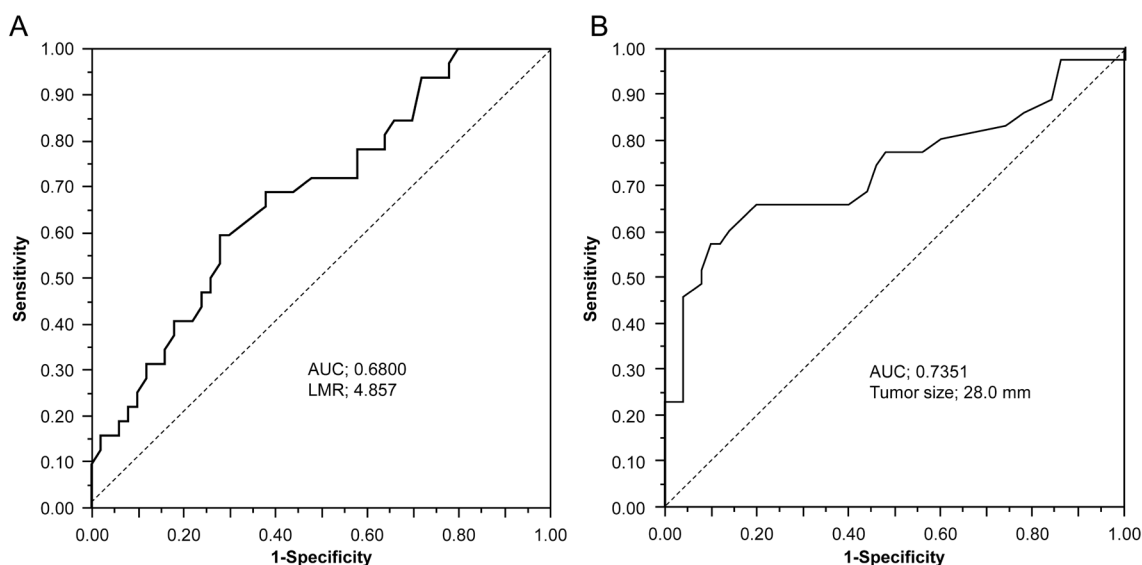


Figure 1

The receiver operating characteristic (ROC) curve to determine cut-off values for lymphocyte/monocyte ratio (LMR) and tumor size. (A) The optimum cut-off point for LMR was 4.857, area under the curve (AUC) was 0.6800, with a sensitivity of 59.4% and a specificity of 72.0%. (B) The optimum cut-off point for tumor size was 28.0 and AUC was 0.7351, with a sensitivity of 57.1% and a specificity of 90.0%.

In this study, parathyroid tumor size was also shown to be an important predictive factor for PC in patients with primary hyperparathyroidism. Bae *et al.* reported that a large parathyroid tumor is a risk factor for malignancy (47). Quin *et al.* also showed that patients with PC had considerably larger tumors (48). In addition, Hsu *et al.* demonstrated that tumors that were at least 3 cm in size were associated with an increased risk of lymph node metastases at disease onset (49). In the present study, 17 (47.2%) of 36 patients with PC had a parathyroid mass that was 30 mm or larger. In the ROC analysis, based on the tumor diameter cut-off value of 28 mm as a predictive factor for PC, the sensitivity and specificity

were noted to be 57.1 and 90.0%, respectively. This study supports the findings of a previous report (50) that states that particular attention should be paid to patients with hyperparathyroidism who have parathyroid masses that are 3.0 cm or larger.

The clinician should be aware of hyperparathyroidism-jaw cancer (HPT-JT) syndrome as an inherited disorder with an increased risk of PC (51). HPT-JT is an autosomal dominant disorder characterized by hyperparathyroidism caused by adenoma or carcinoma and tumors of the jaw and kidney. The causative gene is the HRPT2/CDC73 gene located on chromosome 1q31.2. Approximately 80–90% of patients with HPT-JT develop hyperparathyroidism and approximately 20% develop PC (52, 53). Most of the patients with HPT-JT develop hyperparathyroidism at a young age. In the present study, we did not include the results of genetic testing because of the older age of onset as well as the older age of the patients. When PC is suspected in a young patient, hereditary disease should be considered. We believe that the results of the present study reveal suitable risk factors for relatively elderly patients.

Table 3 Diagnostic validity of LMR at different cut-off values for discrimination of benign and malignant parathyroid glands.

Cut-off values for LMR	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy rate (%)
6.88 ^a	84.4	30	43.5	75	51.2
6.32 ^b	78.1	42	46.3	75	56.1
5.26 ^c	68.8	62	53.7	75.6	64.6
4.85 ^d	59.9	72	57.6	73.5	67.1
4.39 ^e	46.9	76	55.6	69.1	64.6
4.17 ^f	37.5	82	57.1	67.2	64.6

^aThreshold at the point with top 25th percentile (first quartile); ^bThreshold at the point with the top of three-quarter position; ^cThreshold at the point with median; ^dThreshold at a point derived from the receiver operating curve; ^eThreshold at the point with the bottom of three-quarter position (third quartile); ^fThreshold at the point with bottom 25th percentile. LMR, lymphocyte-to-monocyte ratio; NPV, negative predictive value; PPV, positive predictive value.

Table 4 Risk factor stratification in cancer prediction.

	n	OR (95% CI)	P-value
Low risk	41	ref	
Intermediate risk	30	4.09 (1.39–12.92)	0.0101
High risk	15	28.29 (6.10–211.08)	<0.0001

OR, odds ratio.

The purpose of our study was to investigate the possibility of a predictive indicator of cancer diagnosis preoperatively based on preoperative clinical information including inflammatory markers in patients with primary hyperparathyroidism. The LMR can be obtained from peripheral blood and can be easily evaluated. Thus, if cancer can be predicted during the treatment of primary hyperparathyroidism, the LMR can help guide treatment. The addition of tumor size to LMR was shown to increase the ability to predict cancer.

This study has several limitations. First, this is a retrospective single-center study. Secondly, the relatively small sample size inevitably may result in uncontrolled or unrecognized bias. Thirdly, the study was not intended to elucidate the mechanism of decreased LMR in patients with PC. Fourthly, as for the results of hematological parameters, it cannot be denied that there may be some differences in the accuracy of the results due to differences in the equipment used over the years. Thus, a prospective multicenter study with a large sample size is needed to further evaluate the clinical applicability of the present results. However, the inability to prospectively study very rare tumors may also be a limitation of this research.

Conclusion

In patients with primary hyperparathyroidism, a preoperative LMR lower than 4.85 and a tumor larger than 28 mm in diameter may indicate PC. This is the first study to investigate the accuracy of inflammatory markers in the preoperative prediction of PC. It is a simple and optimal combination of markers for predicting the possibility of PC and may help in the selection of appropriate treatment.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

Funding

This work did not receive any specific grant from any funding agency in the public, commercial, or not-for-profit sector.

Acknowledgements

The authors would like to express our gratitude to all the staff members of Ito Hospital who cooperated with this research.

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Received in final form 19 May 2022

Accepted 13 June 2022

Accepted Manuscript published online 14 June 2022