


# Relationship Between Serum Inflammatory Factor Levels and Differentiated Thyroid Carcinoma

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## Abstract

**Background:** Some evidence supports that the significance of inflammation is linked to a variety of tumors, including thyroid carcinoma. This work measured the preoperative serum inflammatory factors in thyroid tumors to explore their diagnostic values. **Material and Methods:** Altogether 487 thyroid tumor patients were recruited, their neutrophil (NE), white blood cell (WBC), monocyte (MO), lymphocyte (LY), platelet (PLT) counts, together with monocyte/lymphocyte ratio (MLR), neutrophil/lymphocyte ratio (NLR), platelet/lymphocyte ratio (PLR), C-reactive protein (CRP), interleukin (IL)-1 $\beta$ , IL-2, IL-27, and tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) levels were compared with controls. Afterward, the receiver operating characteristics (ROC) curve was plotted to further evaluate the values of these inflammatory markers in diagnosis. In addition, multivariable regression analysis was conducted to analyze all these inflammatory factors. **Results:** Serum PLR, NLR, CRP, and IL-27 levels in thyroid adenoma (TA) and differentiated thyroid carcinoma (DTC) patients were higher than those in controls. Only the areas under the curve (AUC) for CRP and IL-27 were significant in the context of DTC. Besides, the AUC for IL-27 was significant between papillary thyroid carcinoma (PTC) and follicular thyroid carcinoma (FTC) groups, while that for NLR+PLR was also significant between PTC and healthy control groups. According to multivariable logistic regression analysis, IL-27 and CRP were associated with DTC. **Conclusions:** Inflammation plays an important role in TA and DTC progression. Preoperative IL-27 and CRP levels help to differentially diagnose DTC. Moreover, IL-27 assists in distinguishing FTC from PTC, and NLR+PLR is important for the differential diagnosis of PTC.

## Keywords

cancer, diagnosis, histopathology, inflammation, thyroid

## Abbreviations

AUC, areas under the curve; CRP, C-reactive protein; DTC, differentiated thyroid carcinoma; FTC, follicular thyroid carcinoma; IL-1 $\beta$ , interleukin-1 $\beta$ ; IL-2, interleukin-2; IL-27, interleukin-27; LY, lymphocyte; MO, monocyte; MLR, monocyte/lymphocyte ratio; NE, neutrophil; NLR, neutrophil/lymphocyte ratio; PLT, platelet; PLR, platelet/lymphocyte ratio; PTC, papillary thyroid carcinoma; ROC, receiver operating characteristics; TNF- $\alpha$ , tumor necrosis factor- $\alpha$ ; TA, thyroid adenomas; WBC, white blood cell.

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## Introduction

Thyroid cancer is mainly derived from thyroid follicular cells, one of the cell types distributed in thyroid parenchyma. These cells include interstitial and follicular cells, and mainly form the differentiated thyroid cancer (DTC).<sup>1</sup> Related clinical studies show that, DTC, which can be classified as follicular and papillary cancers, accounts for 1-2% of all human malignancies and 80% of thyroid malignancies.<sup>2</sup> DTC is an endocrine cancer that progresses slowly, with a 10-year survival rate of greater than 90%, but the incidences of capsule invasion, extra thyroidal extension, and lymphatic metastasis remain high, making

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it impedimental to further reduce its mortality and improve the survival rate.<sup>3</sup> It is well known that, one of the important and efficient ways to reduce the mortality of DTC is to diagnose the cancer at the early stage. An increasing number of thyroid tumors are detected at the early stage thanks to the improvement of diagnostic technology and the gradual popularization of physical examinations. However, it still remains difficult to distinguish from benign thyroid tumors, papillary thyroid carcinoma (PTC) and follicular thyroid carcinoma (FTC).

According to recent studies, inflammation exerts a vital part during cancer genesis and development,<sup>4</sup> which may directly affect cancer cells, stimulate epithelial-to-mesenchymal transition (EMT), interact with chemokines, and augment cancer metastasis.<sup>5</sup> A lot of inflammatory factors have been discovered, including CSCF, VEGF, NLR (neutrophil/lymphocyte ratio), PLR (platelet/lymphocyte ratio), MLR (monocyte/lymphocyte ratio), CRP (C-reactive protein), IL-6, IL-10, IL-12, IL-17, IL-23, TNF- $\alpha$  (tumor necrosis factor- $\alpha$ ) and TGF- $\beta$ .<sup>4,6-12</sup> Growth of related inflammatory markers like LMR and IL-6 is shown to play an important role in PTC,<sup>13,14</sup> but there is still little research on FTC, and some findings are controversial. Therefore, the present work aimed to systematically depict the heterogeneities in preoperative inflammatory factors between healthy control subjects, thyroid adenoma (TA) patients and DTC patients including PTC and FTC.

## Materials and Methods

### Patients and Normal Controls

Our study protocol was approved by the Institutional Ethics Committee of xxxx hospital. A total of 487 patients, including 104 with FTC, 200 with PTC and 183 with TA who received surgeries and were confirmed at xxxx Hospital were enrolled between June 1, 2018, and January 31, 2020 into the present work. Additionally, the medical records of 217 healthy individuals receiving annual healthy checkup at the same hospital were reviewed as healthy controls. The patient exclusion criteria were as follows: 1) those who had Hashimoto's thyroiditis; 2) those who did previously undergo a thyroid operation; 3) those receiving acupuncture before surgery; botulinum toxin; hormone therapy (like glucocorticoids) or radiotherapy; 4) those with underlying hematologic disorders, hyperpyrexia, infectious disease, metabolic syndrome, diabetes mellitus, hypertension, severe liver or kidney dysfunction, severe heart disease, malignancies, inflammatory disorder, autoimmune disorder, or the use of medication associated with inflammation; 5) those with incomplete information related to inflammatory marker tests and routine blood tests before surgery. Each eligible patient provided the informed consent to participate in this study.

### Data Extraction

The patient demographic and clinicopathological data, such as sex, age, and pathological type, were retrieved from medical records. After obtaining the informed consent from each

subject, the peripheral blood samples were extracted within 1 week before surgery for inflammatory markers and routine blood tests, which served as one part of standard preoperative workup. For the normal subjects undergoing annual physical examination at this hospital, their peripheral blood was collected to test the same items. Then, each sample acquired was preserved under at lower than 20°C, and each test was carried out by the staff from the Clinical Laboratory Department in our hospital within 2 h. The white blood cell (WBC), neutrophil (NE), lymphocyte (LY), monocyte (MO), platelet (PLT) counts, and CRP levels were obtained from routine blood tests conducted using the normalized automatic counters. Then, the NLR, MLR, and PLR were calculated. Moreover, the levels of interleukin-2 (IL-2), interleukin-1 $\beta$  (IL-1 $\beta$ ), interleukin-27 (IL-27) and TNF- $\alpha$  were determined using the enzyme-linked immunosorbent assay kits (R & D Systems, Minneapolis, MN, USA) in accordance with manufacturer protocols.

### Statistics Analyses

SPSS 24.0 (SPSS, Inc, Chicago, Illinois) was employed for data analysis. First of all, Kolmogorov-Smirnov test was applied to analyze whether the variables were normally distributed. Then, 1-way analysis of variance (ANOVA) or 2-tailed Student t-test was used to analyze data with normal distribution. Mann-Whitney U test was adopted to compare the nonparametric variables between 2 groups. Later, the receiver operating characteristic (ROC) curves were plotted, and the areas under the curve (AUC) were calculated to assess the accuracy of those inflammatory factors mentioned above in diagnosis. Following post hoc analysis, the threshold of outlier was obtained based on the maximum sum of specificity and sensitivity. Besides, univariate and multivariate logistic regression analyses were conducted to better analyze these inflammatory factors. A difference of  $P < 0.05$  (2-tailed) indicated statistically significant.

## Results

### Characteristics of Study Populations and Preoperative Inflammatory factors Compared Among FTC, PTC, ta Patients and Normal Controls

Table 1 shows the details regarding the demographic information of study populations. According to Table 1, thyroid tumors showed remarkably higher levels of WBC, NE, PLT, PLR, CRP, IL-2, IL-1 $\beta$ , IL-27 and TNF- $\alpha$ , while thyroid carcinoma exhibited higher MO and NLR levels, while FTC showed higher LY level than normal controls. The WBC, NE, PLT, MO, NLR, CRP, IL-2, IL-1 $\beta$ , IL-27 and TNF- $\alpha$  levels in PTC and FTC patients were also higher than those in TA group. Compared with TA group, the PLR value in PTC group and the LY count in FTC group increased. Besides, the WBC and MO counts in FTC group markedly increased relative to those in PTC group. The PLR value and IL-27 level of FTC patients decreased relative to those in FTC group. DTC patients were also divided according to the tumor size and stage. When

**Table 1.** Demographic Details and Levels of Inflammatory Markers in Peripheral Blood of Patients With Follicular Thyroid Carcinoma, Papillary Thyroid Carcinoma, Thyroid Adenomas and Healthy Control.

| Variable                | HC             | TA                          | PTC                           | FTC                            |
|-------------------------|----------------|-----------------------------|-------------------------------|--------------------------------|
| NO.                     | 217            | 183                         | 200                           | 104                            |
| Age(years)              | 45.83 ± 6.24   | 45.51 ± 6.79                | 45.87 ± 6.53                  | 42.48 ± 4.57 <sup>abc</sup>    |
| Male/Female             | 115/102        | 37/146 <sup>a</sup>         | 42/158 <sup>a</sup>           | 24/80 <sup>a</sup>             |
| WBC(10 <sup>9</sup> /L) | 6.16 ± 1.09    | 6.52 ± 1.40 <sup>a</sup>    | 6.74 ± 1.15 <sup>ab</sup>     | 7.13 ± 1.23 <sup>abc</sup>     |
| NE                      | 3.53 ± 0.99    | 3.86 ± 0.93 <sup>a</sup>    | 5.65 ± 2.65 <sup>ab</sup>     | 5.71 ± 2.63 <sup>ab</sup>      |
| PLT(10 <sup>9</sup> /L) | 224.62 ± 66.14 | 261.34 ± 39.99 <sup>a</sup> | 347.11 ± 156.15 <sup>ab</sup> | 318.80 ± 101.65 <sup>abc</sup> |
| LY                      | 1.92 ± 0.53    | 1.96 ± 0.61                 | 2.10 ± 0.80                   | 2.18 ± 0.71 <sup>ab</sup>      |
| MO                      | 0.43 ± 0.10    | 0.45 ± 0.12                 | 0.49 ± 0.13 <sup>ab</sup>     | 0.53 ± 0.18 <sup>abc</sup>     |
| NLR                     | 2.01 ± 0.83    | 2.17 ± 0.86                 | 2.83 ± 1.05 <sup>ab</sup>     | 2.88 ± 1.53 <sup>ab</sup>      |
| PLR                     | 120.57 ± 40.77 | 146.71 ± 50.37 <sup>a</sup> | 174.63 ± 61.28 <sup>ab</sup>  | 158.54 ± 61.52 <sup>ac</sup>   |
| MLR                     | 0.24 ± 0.09    | 0.25 ± 0.10                 | 0.27 ± 0.13                   | 0.26 ± 0.12                    |
| CRP(mg/L)               | 0.86 ± 0.72    | 0.94 ± 0.87 <sup>a</sup>    | 1.91 ± 1.52 <sup>ab</sup>     | 1.98 ± 1.30 <sup>ab</sup>      |
| TNF-α(pg/mL)            | 21.45 ± 8.31   | 27.61 ± 13.69 <sup>a</sup>  | 39.13 ± 24.08 <sup>ab</sup>   | 43.23 ± 28.29 <sup>ab</sup>    |
| IL-1β(pg/mL)            | 3.26 ± 1.33    | 3.63 ± 1.30 <sup>a</sup>    | 6.05 ± 3.52 <sup>ab</sup>     | 6.47 ± 3.92 <sup>ab</sup>      |
| IL-2(pg/mL)             | 23.58 ± 3.79   | 22.50 ± 3.40 <sup>a</sup>   | 21.39 ± 3.47 <sup>ab</sup>    | 20.49 ± 3.77 <sup>ab</sup>     |
| IL-27(pg/mL)            | 65.96 ± 45.27  | 80.49 ± 38.62 <sup>a</sup>  | 307.93 ± 134.36 <sup>ab</sup> | 169.37 ± 105.73 <sup>abc</sup> |

**Abbreviations:** HC, healthy control; TA, thyroid adenomas; PTC, papillary thyroid carcinoma; FTC, follicular thyroid carcinoma; WBC, white blood cell; NE, neutrophil; LY, lymphocyte; MO, monocyte; PLT, platelet; NLR, neutrophil/ lymphocyte ratio; PLR, platelet/ lymphocyte ratio; MLR, monocyte/ lymphocyte ratio; CRP, C-reactive protein; TNF-α, tumor necrosis factor-α; IL-1β, interleukin-1β; IL-2, interleukin-2; IL-27, interleukin-27.

Data were expressed as mean ± standard deviation.

The significance level was set at  $p < 0.05$ . <sup>a</sup>  $p < 0.05$  compared with healthy control group. <sup>b</sup>  $p < 0.05$  compared with thyroid adenomas group. <sup>c</sup>  $p < 0.05$  compared with PTC group.

**Table 2.** Serum Levels of Inflammatory Factors in Relation to Tumor Size and Stage in Patients With DTC.

| Variable                | Size            |                 | P-value | Stage           |                 | P-value |
|-------------------------|-----------------|-----------------|---------|-----------------|-----------------|---------|
|                         | <1cm            | ≥1cm            |         | I-II            | III-IV          |         |
| WBC(10 <sup>9</sup> /L) | 6.97 ± 1.18     | 6.98 ± 1.17     | 0.086   | 6.97 ± 1.17     | 6.97 ± 1.22     | 0.092   |
| NE(10 <sup>9</sup> /L)  | 5.67 ± 2.65     | 5.67 ± 2.66     | 0.091   | 5.66 ± 2.65     | 5.67 ± 2.65     | 0.076   |
| PLT(10 <sup>9</sup> /L) | 336.57 ± 138.49 | 337.16 ± 141.37 | 0.083   | 335.92 ± 138.53 | 336.91 ± 139.16 | 0.095   |
| MO(10 <sup>9</sup> /L)  | 0.50 ± 0.15     | 0.51 ± 0.14     | 0.074   | 0.50 ± 0.15     | 0.50 ± 0.15     | 0.093   |
| NLR                     | 2.85 ± 1.37     | 2.88 ± 1.39     | 0.085   | 2.84 ± 1.37     | 2.88 ± 1.41     | 0.071   |
| CRP(mg/L)               | 1.94 ± 1.43     | 1.97 ± 1.44     | 0.059   | 1.95 ± 1.42     | 1.99 ± 1.47     | 0.054   |
| TNF-α(pg/mL)            | 40.72 ± 25.13   | 40.75 ± 25.12   | 0.088   | 40.68 ± 25.11   | 41.20 ± 26.34   | 0.063   |
| IL-1β(pg/mL)            | 6.36 ± 3.69     | 6.36 ± 3.71     | 0.093   | 6.35 ± 3.53     | 6.37 ± 3.72     | 0.075   |
| IL-2(pg/mL)             | 21.01 ± 3.52    | 21.06 ± 3.55    | 0.069   | 21.03 ± 3.61    | 21.04 ± 3.66    | 0.087   |
| IL-27(pg/mL)            | 256.81 ± 128.27 | 259.35 ± 129.31 | 0.061   | 256.17 ± 126.31 | 260.62 ± 129.42 | 0.053   |

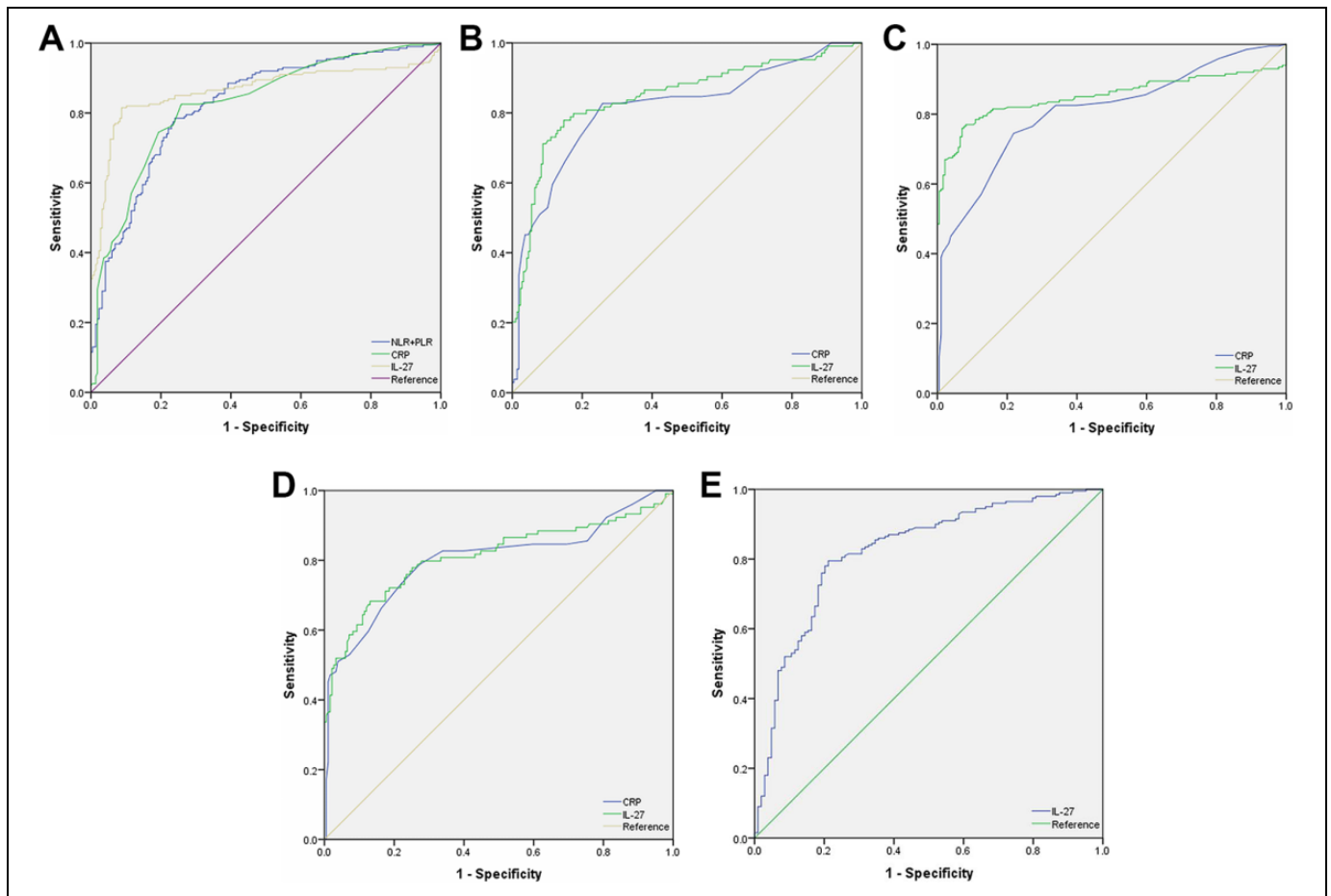
**Abbreviations:** DTC, differentiated thyroid carcinoma; WBC, white blood cell; NE, neutrophil; PLT, platelet; MO, monocyte; NLR, neutrophil/lymphocyte ratio; CRP, C-reactive protein; TNF-α, tumor necrosis factor-α; IL-1β, interleukin-1β; IL-2, interleukin-2; IL-27, interleukin-27.

compared according to tumor size or stage, the WBC, NE, PLT, MO, NLR, CRP, IL-2, IL-1β, IL-27 and TNF-α levels in DTC patients (size ≥1 cm; stage III-IV) were higher than those in DTC patients (size <1 cm; stage I-II), with no significant difference among different groups (Table 2).

### Performances of Inflammatory Factors Together With Corresponding Combinations in the Diagnosis of FTC, PTC and TA Patients

Figure 1 exhibits the performances (ROC curves) of NE, WBC, PLT, MO, LY, MLR, PLR, NLR, CRP, IL-2, IL-1β, IL-27 and TNF-α, as well as their paired combinations like NLR+PLR,

NLR+MLR and PLR+MLR in the diagnosis of thyroid tumor patients. Supplementary Table 1 presents the AUCs and corresponding 95% confidence intervals (CIs). According to the table, compared with normal controls, the AUCs (95% CIs;  $P$ ) for WBC, NE, PLT, LY, MO, NLR, PLR, MLR, NLR+PLR, NLR+MLR, PLR+MLR, CRP, TNF-α, IL-1β, IL-2, IL-27 were 0.565 (0.508-0.622;  $P = 0.025$ ), 0.571(0.515-0.627;  $P = 0.015$ ), 0.666(0.613-0.718;  $P < 0.001$ ), 0.509(0.452-0.566;  $P = 0.753$ ), 0.534(0.477-0.590;  $P = 0.246$ ), 0.541(0.485-0.598;  $P = 0.153$ ), 0.649(0.596-0.703;  $P < 0.001$ ), 0.529(0.472-0.586;  $P = 0.313$ ), 0.649(0.596-0.703;  $P < 0.001$ ), 0.510(0.443-0.557;  $P = 0.943$ ), 0.649(0.595-0.702;  $P < 0.001$ ), 0.570(0.514-0.627;  $P = 0.015$ ), 0.635(0.580-0.691;  $P < 0.001$ ), 0.583(0.527-0.639;  $P = 0.004$ ), 0.429(0.373-0.485;  $P = 0.014$ ) and 0.625(0.571-



**Figure 1.** Diagnostic significance of preoperative WBC (white blood cell), NE (neutrophil), PLT (platelet), LY (lymphocyte), MO (monocyte), NLR (neutrophil/lymphocyte ratio), PLR (platelet/lymphocyte ratio), MLR (monocyte/lymphocyte ratio), CRP (C-reactive protein), TNF- $\alpha$  (tumor necrosis factor- $\alpha$ ), interleukin (IL)-1 $\beta$ , IL-2, IL-27 and their paired combinations like NLR+PLR, NLR+MLR and PLR+MLR for patients with FTC (follicular thyroid carcinoma), PTC (papillary thyroid carcinoma), TA (thyroid adenoma) and healthy controls. **A**, AUC (areas under the curve) 0.824 (95% CI, 0.784-0.864) for NLR+PLR, AUC 0.826 (95% CI, 0.786-0.866) for CRP, and AUC 0.864 (95% CI, 0.824-0.904) for IL-27 between PTC and healthy control group; **B**, AUC 0.815 (95% CI, 0.760-0.869) for CRP and AUC 0.846 (95% CI, 0.795-0.897) for IL-27 between FTC and healthy control group; **C**, AUC 0.852 (95% CI, 0.809-0.895) for IL-27 and AUC 0.807 (95% CI, 0.764-0.851) for CRP between PTC group and TA group; **D**, AUC 0.811 (95% CI, 0.752-0.870) for IL-27 and AUC 0.801 (95% CI, 0.742-0.861) for CRP between FTC group and TA group; **E**, AUC 0.823 (95% CI, 0.773-0.874) for IL-27 between PTC group and FTC group.

0.679;  $P < 0.001$ ) in TA patients, respectively (supplementary Table 1).

Compared with TA or healthy controls, the performances of the above-mentioned inflammatory factors together with related combinations in the diagnosis of PTC or FTC patients were evaluated. It was obtained from ROC analysis in Figure 1A and supplementary Table 1 that, NLR+PLR (AUC, 0.824; 95% CI, 0.784-0.864;  $P < 0.001$ ), CRP (AUC, 0.826; 95% CI, 0.786-0.866;  $P < 0.001$ ), and IL-27 (AUC, 0.864; 95% CI, 0.824-0.904;  $P < 0.001$ ) showed higher potential in predicting PTC patients than in healthy controls. In addition, CRP (AUC, 0.815; 95% CI, 0.760-0.869;  $P < 0.001$ ) and IL-27 (AUC, 0.846; 95% CI, 0.795-0.897;  $P < 0.001$ ) showed higher ability in predicting FTC patients than in healthy controls (Figure 1B, supplementary Table 1). Besides, IL-27 (AUC, 0.852; 95% CI, 0.809-0.895;  $P < 0.001$ ) and CRP (AUC, 0.807; 95% CI, 0.764-0.851;  $P < 0.001$ ) showed higher ability in predicting PTC

patients than in TA patients (Figure 1C, supplementary Table 1). Moreover, IL-27 (AUC, 0.811; 95% CI, 0.752-0.870;  $P < 0.001$ ) and CRP (AUC, 0.801; 95% CI, 0.742-0.861;  $P < 0.001$ ) exhibited greater significance in predicting FTC patients than in TA patients (Figure 1D, supplementary Table 1). Compared with FTC patients, IL-27 (AUC, 0.823; 95% CI, 0.773-0.874;  $P < 0.001$ ) had a higher ability in predicting and differentially diagnosing 2 DTC pathological subtypes (Figure 1E, supplementary Table 1). Table 3 displays the specificity, sensitivity, and threshold for every factor.

### Inflammatory Factors Effects on DTC

The multivariable logistic regression model was constructed for DTC, as presented in Table 4. The results revealed that, WBC, NE, PLT, MO, CRP, IL-2, IL-27 and IL-1 $\beta$  were related to DTC. Meanwhile, the contents of WBC, NE, CRP, IL-1 $\beta$ ,

**Table 3.** Sensitivity, Specificity and Thresholds for the Differential Diagnosis of Inflammatory Markers in Patient With TA, PTC and FTC.

|               | HC vs TA    |             |         | HC vs PTC   |             |         | HC vs FTC   |             |         |
|---------------|-------------|-------------|---------|-------------|-------------|---------|-------------|-------------|---------|
|               | sensitivity | specificity | cutoff  | sensitivity | specificity | cutoff  | sensitivity | specificity | cutoff  |
| WBC           | 0.585       | 0.535       | 6.095   | 0.755       | 0.535       | 6.095   | 0.827       | 0.618       | 6.335   |
| NE            | 0.727       | 0.419       | 3.499   | 0.470       | 0.972       | 4.801   | 0.587       | 0.968       | 4.705   |
| PLT           | 0.514       | 0.737       | 264.510 | 0.430       | 0.931       | 284.500 | 0.567       | 0.931       | 285.000 |
| LY            | 0.120       | 0.931       | 2.650   | 0.470       | 0.65        | 2.050   | 0.558       | 0.650       | 2.050   |
| MO            | 0.246       | 0.829       | 0.525   | 0.730       | 0.608       | 0.455   | 0.577       | 0.793       | 0.515   |
| NLR           | 0.803       | 0.300       | 1.509   | 0.740       | 0.627       | 2.205   | 0.404       | 0.903       | 3.091   |
| PLR           | 0.617       | 0.622       | 130.527 | 0.705       | 0.756       | 145.780 | 0.654       | 0.650       | 134.247 |
| MLR           | 0.672       | 0.442       | 0.210   | 0.550       | 0.585       | 0.245   | 0.779       | 0.355       | 0.191   |
| NLR+PLR       | 0.617       | 0.622       | 132.036 | 0.785       | 0.760       | 147.985 | 0.615       | 0.793       | 137.338 |
| NLR+MLR       | 0.524       | 0.518       | 1.719   | 0.740       | 0.627       | 2.450   | 0.404       | 0.903       | 3.282   |
| PLR+MLR       | 0.557       | 0.673       | 130.737 | 0.705       | 0.756       | 146.025 | 0.654       | 0.650       | 134.438 |
| CRP           | 0.694       | 0.461       | 0.650   | 0.825       | 0.742       | 1.050   | 0.827       | 0.742       | 1.050   |
| TNF- $\alpha$ | 0.585       | 0.677       | 23.750  | 0.610       | 0.834       | 30.550  | 0.567       | 0.945       | 36.950  |
| IL-1 $\beta$  | 0.585       | 0.562       | 3.450   | 0.585       | 0.931       | 5.050   | 0.567       | 0.963       | 5.250   |
| IL-2          | 0.060       | 0.783       | 26.750  | 0.435       | 0.318       | 21.850  | 0.231       | 0.318       | 21.850  |
| IL-27         | 0.809       | 0.419       | 49.400  | 0.815       | 0.912       | 118.100 | 0.779       | 0.853       | 106.000 |

|               | TA vs PTC   |             |         | TA vs FTC   |             |         | PTC vs FTC  |             |         |
|---------------|-------------|-------------|---------|-------------|-------------|---------|-------------|-------------|---------|
|               | sensitivity | specificity | cutoff  | sensitivity | specificity | cutoff  | sensitivity | specificity | cutoff  |
| WBC           | 0.725       | 0.464       | 6.175   | 0.808       | 0.552       | 6.385   | 0.731       | 0.465       | 6.525   |
| NE            | 0.535       | 0.836       | 4.502   | 0.567       | 0.907       | 4.996   | 0.567       | 0.580       | 5.081   |
| PLT           | 0.335       | 0.978       | 349.000 | 0.567       | 0.787       | 285.50  | 0.567       | 0.575       | 285.500 |
| LY            | 0.470       | 0.623       | 2.050   | 0.433       | 0.749       | 2.250   | 0.490       | 0.640       | 2.150   |
| MO            | 0.730       | 0.601       | 0.455   | 0.644       | 0.694       | 0.485   | 0.269       | 0.915       | 0.600   |
| NLR           | 0.725       | 0.623       | 2.239   | 0.481       | 0.825       | 2.771   | 0.192       | 0.910       | 4.071   |
| PLR           | 0.705       | 0.557       | 145.647 | 0.269       | 0.858       | 193.421 | 0.058       | 0.950       | 270.828 |
| MLR           | 0.550       | 0.563       | 0.249   | 0.760       | 0.301       | 0.198   | 0.779       | 0.275       | 0.191   |
| NLR+PLR       | 0.745       | 0.672       | 147.886 | 0.481       | 0.825       | 196.367 | 0.452       | 0.735       | 274.899 |
| NLR+MLR       | 0.725       | 0.623       | 2.488   | 0.481       | 0.825       | 2.969   | 0.544       | 0.539       | 4.262   |
| PLR+MLR       | 0.705       | 0.557       | 145.896 | 0.531       | 0.518       | 193.619 | 0.452       | 0.735       | 271.019 |
| CRP           | 0.745       | 0.781       | 1.250   | 0.788       | 0.727       | 1.150   | 0.144       | 0.930       | 3.000   |
| TNF- $\alpha$ | 0.460       | 0.880       | 38.100  | 0.558       | 0.880       | 38.100  | 0.519       | 0.580       | 39.550  |
| IL-1 $\beta$  | 0.665       | 0.787       | 4.450   | 0.692       | 0.787       | 4.450   | 0.462       | 0.625       | 6.350   |
| IL-2          | 0.405       | 0.595       | 22.250  | 0.250       | 0.372       | 21.750  | 0.356       | 0.410       | 20.750  |
| IL-27         | 0.760       | 0.929       | 143.400 | 0.683       | 0.869       | 124.600 | 0.795       | 0.212       | 209.000 |

**Abbreviations:** HC, healthy control; TA, thyroid adenomas; PTC, papillary thyroid carcinoma; FTC, follicular thyroid carcinoma; WBC, white blood cell; NE, neutrophil; LY, lymphocyte; MO, monocyte; PLT, platelet; NLR, neutrophil/ lymphocyte ratio; PLR, platelet/ lymphocyte ratio; MLR, monocyte/ lymphocyte ratio; CRP, C-reactive protein; TNF- $\alpha$ , tumor necrosis factor- $\alpha$ ; IL-1 $\beta$ , interleukin-1 $\beta$ ; IL-2, interleukin-2; IL-27, interleukin-27.

IL-2 and IL-27 were related to DTC after adjusting for Age. Furthermore, after adjusting for Age and Sex, the levels of CRP, IL-2 and IL-27 also showed significant association with DTC onset.

## Discussion

The present study suggested that, chronic inflammation was significantly associated with carcinoma. As related research goes, factors that can serve as the simple inflammatory system indexes, such as NLR,<sup>15</sup> PLT and leukocyte,<sup>16,17</sup> have been widely used as biomarkers in detecting and monitoring malignancy. Nonetheless, little is known about the relationship of these inflammatory factors, like IL-6,<sup>14</sup> IL-17, and IL-35 with

thyroid cancer,<sup>18</sup> together with their potential as biomarkers for thyroid cancer. Therefore, the present work further assessed the associations of other preoperative blood inflammatory factors with thyroid cancer.

According to our results of tests for peripheral blood inflammatory markers, the WBC, NE, PLT, MO, CRP, IL-1 $\beta$ , IL-27 and TNF- $\alpha$  levels were higher, whereas IL-2 level was lower in TA and DTC groups than those in other groups. This meant that TA and DTC might be associated with inflammation and inflammatory factors. NLR and PLR are valuable inflammatory factors, which reflect the balance between NE or PLT and LY immune response. As suggested in some recent studies, NLR and PLR, which are easily obtained from blood tests, significantly elevate in patients with PTC or FTC, and such

**Table 4.** Impacts of Inflammatory Markers on DTC in Multivariate Model.

|               | Unadjusted          |         | Model I             |         | Model II             |         |
|---------------|---------------------|---------|---------------------|---------|----------------------|---------|
|               | OR (95% CI)         | P-value | OR (95% CI)         | P-value | OR (95% CI)          | P-value |
| WBC           | 1.542 (1.351-1.794) | 0.012   | 1.513 (1.327-1.781) | 0.019   | 2.237 (0.315-10.238) | 0.812   |
| NE            | 2.393 (1.725-3.318) | <0.001  | 2.230 (1.547-3.526) | 0.001   | 2.901 (0.216-21.307) | 0.073   |
| PLT           | 1.070 (1.034-1.108) | <0.001  | 1.013 (1.011-1.264) | 0.141   | 1.006 (0.847-3.571)  | 0.271   |
| LY            | 1.003 (0.994-1.009) | 0.377   | 1.002 (0.992-1.009) | 0.379   | 1.002 (0.491-2.218)  | 0.746   |
| MO            | 1.141 (1.113-1.231) | 0.004   | 1.084 (1.104-1.245) | 0.103   | 1.013 (0.346-1.715)  | 0.417   |
| NLR           | 1.018 (1.005-1.022) | 0.253   | 1.017 (1.004-1.019) | 0.257   | 1.287 (0.612-2.548)  | 0.671   |
| PLR           | 1.011 (1.002-1.017) | 0.184   | 1.010 (1.002-1.013) | 0.221   | 1.137 (0.014-17.422) | 0.628   |
| MLR           | 1.004 (0.995-1.006) | 0.238   | 1.004 (0.998-1.006) | 0.562   | 1.001 (0.913-1.097)  | 0.614   |
| CRP           | 1.401 (1.210-1.721) | <0.001  | 1.392 (1.210-1.718) | <0.001  | 1.384 (1.208-1.715)  | <0.001  |
| TNF- $\alpha$ | 1.136 (1.094-1.177) | 0.118   | 1.132 (1.091-1.172) | 0.124   | 1.088 (0.021-8.159)  | 0.867   |
| IL-1 $\beta$  | 1.987 (1.264-3.124) | 0.003   | 1.875 (1.251-2.815) | 0.011   | 1.507 (0.133-6.143)  | 0.242   |
| IL-2          | 0.588 (0.430-0.802) | 0.001   | 0.760 (0.599-0.973) | 0.014   | 0.829 (0.364-2.176)  | 0.037   |
| IL-27         | 1.161 (1.134-1.189) | <0.001  | 1.158 (1.133-1.187) | <0.001  | 1.146 (1.128-1.185)  | <0.001  |

**Model I** was adjusted for Age; **Model II** was adjusted for Age, Sex.

**Abbreviations:** CI, confidence interval; OR, odds ratio; WBC, white blood cell; NE, neutrophil; LY, lymphocyte; MO, monocyte; PLT, platelet; NLR, neutrophil/ lymphocyte ratio; PLR, platelet/ lymphocyte ratio; MLR, monocyte/ lymphocyte ratio; CRP, C-reactive protein; TNF- $\alpha$ , tumor necrosis factor- $\alpha$ ; IL-1 $\beta$ , interleukin-1 $\beta$ ; IL-2, interleukin-2; IL-27, interleukin-27; DTC, differentiated thyroid carcinoma.

results are consistent with our.<sup>19</sup> Ari A et al. reported that NLR and PLR were higher in patients with papillary thyroid cancer than in healthy individuals, with statistically significant difference in PLR.<sup>20</sup> Similarly, in the current study, PLR was significantly higher in patients with PTC than in healthy individuals, and NLR was also significantly higher. Such inconsistency might be because that, multiple parameters were associated with the study methodology and population. Cho JS et al. also reported that the proportions of PTC and FTC were not significant difference between the high and low NLR groups.<sup>21</sup> The difference in baseline levels among the study populations, such as FTC (104vs34), may be another reason for the difference in research results. In addition, they found that the NLR was significant difference and high in poorly differentiated thyroid cancer (PDTTC) and anaplastic thyroid cancer (ATC) as compared to DTC.

The increased IL-27 contents in serum are detected in lung cancer, esophageal cancer, breast cancer and gastro-esophageal cancer.<sup>22-25</sup> However, the IL-27 role in cancer remains controversial. IL-27 can enhance the antitumor immunity to inhibit regulatory T cell differentiation and angiogenesis. It can also induce IL-10 to resist the proinflammatory immune reactions, thus favoring tumor development.<sup>26,27</sup> In addition, the level of IL-27R $\alpha$  in diverse cancer cell types may be related to effector response suppression and cancer growth promotion. These mechanisms have supported that, inflammation is related to thyroid cancer development and progression.

According to related epidemiological research, the increased CRP (a classical acute phase protein) contents in circulation, may mark the presence of prevalent tumor.<sup>28</sup> It is also reported that, the higher preoperative levels of CRP are associated with DTC, and they may serve as the potential serum biomarker in PTC.<sup>29,30</sup> However, the specific mechanism of circulating CRP levels and tumor microenvironment

remains unknown at present. The Mendelian<sup>31</sup> randomization design reported that, the CRP genotypes (4 SNPs) are not related to the risks of colorectal, lung, prostate, breast, or urinary tract and bladder cancers. The genetic variation outside the CRP locus, such as IL-6 receptor, may partially explain for the relationship between CRP and tumors in the presence of high IL-6 levels in most tumors including thyroid cancer.

Although most patients can be diagnosed by clinical manifestations and B-ultrasound, thyroid cancer, such as FTC, PTC and TA, can hardly be differentially diagnosed before operation. In our study, preoperative contents of NE, WBC, PLT, MO, LY, MLR, NLR, PLR, CRP, TNF- $\alpha$ , IL-1 $\beta$ , IL-2, IL-27 together with corresponding combinations were assessed using the ROC curves, and only CRP and IL-27 had the AUCs of greater than 0.8. In addition, the AUC value of IL-27 was higher than 0.8 between PTC and FTC groups, and that of NLR+PLR was also higher than 0.8 between PTC and healthy control groups. In the present work, the multivariable logistic regression model was also established for thyroid tumor; CRP, IL-2 and IL-27 were relevant to DTC after adjusting for the possible confounding factors. Based on those aforementioned findings, we speculated that CRP and IL-27 were closely related to DTC progression, and that NLR+PLR might also be tightly correlated with PTC progression. NLR+PLR is identified in prior work to exhibit predicting significance in a variety of cancer types. In thyroid cancer, NLR and PLR have diagnostic and predictive significance for advanced differentiated thyroid cancer and ATC, while the diagnostic and predictive significance of NMPLR is far superior to that of NLR or PLR.<sup>32</sup> Similarly, in our study, NLR and PLR were significant for the diagnosis and prediction of PTC cases and healthy individuals, and the combination of NLR+PLR was also meaningful, which achieved far superior diagnostic effect than the individual one. Moreover, IL-27 rs17855750 and rs153109

have been proved to be associated with PTC occurrence, which is partially consistent with our results.<sup>33</sup> The relationship of the FTC incidence with the gene polymorphisms of IL-27 remains unreported, and it may lead to the significantly different levels of IL-27 between PTC and FTC patients. Generally, FTC is identified as a comparatively aggressive subtype, which avoids the unnecessary overhand measures for thyroid tumors. As a result, it is necessary to identify the preoperative peripheral blood inflammatory factors to diagnose DTC. The different expressions of CRP and IL-27 may be potentially used to distinguish PTC and FTC from thyroid tumors. Our preliminary study found that inflammatory factors were not significantly correlated with the progression of thyroid tumors. We will continue to study them further in the later period. The research on the relationships between CRP, IL-27 and pathological tissue and prognosis of DTC is the specific direction of our follow-up further research. Nonetheless, some limitations should be noted in the present work. Firstly, this single-center study had small sizes of TA, PTC and FTC patients. Therefore, the prospective and multicenter studies with larger sample sizes should be performed for confirming these findings. Secondly, false positive results might be obtained when screening the asymptomatic populations due to conditions like systemic inflammation.

## Conclusions

The present work indicates that, inflammation shows a close relationship with thyroid tumor based on our statistical results. The preoperative inflammatory markers, such as CRP and IL-27, may help us differentially diagnose DTC. In addition, IL-27 may partially assist in distinguishing FTC from PTC, and NLR+PLR may play a vital part during the differential diagnosis of PTC.

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## Supplemental Material

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