Relationship Between Serum Inflammatory Factor Levels and Differentiated Thyroid Carcinoma

Xue Zhang, MM¹, Su Li, MM², Jinhui Wang, MM³, Fubao Liu, MD, PhD⁴, and Yong Zhao, MM¹

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)-1β, IL-2, IL-27, and tumor necrosis factor-α (TNF-α) 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-1β, interleukin-1β; 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-α, tumor necrosis factor-α; TA, thyroid adenomas; WBC, white blood cell.

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).¹ 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.² 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 thyroid extension, and lymphatic metastasis remain high, making...
it impedimental to further reduce its mortality and improve the survival rate.\(^3\) 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,\(^4\) which may directly affect cancer cells, stimulate epithelial-to-mesenchymal transition (EMT), interact with chemokines, and augment cancer metastasis.\(^5\) 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-\(\beta\)\(^6\)-\(^12\). Growth of related inflammatory markers like LMR and IL-6 is shown to play an important role in PTC,\(^13,14\) 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 xxx hospital. A total of 487 patients, including 104 with FTC, 200 with PTC and 183 with TA who received surgeries and were confirmed at xxx 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 ± 4.57abc |
| Male/Female | 115/102 | 37/146a | 42/158a | 24/80a |
| WBC(10^9/L) | 6.16 ± 1.09 | 6.52 ± 1.40a | 6.74 ± 1.15ab | 7.13 ± 1.23abc |
| NE       | 3.53 ± 0.99 | 3.86 ± 0.93a | 5.65 ± 2.65ab | 5.71 ± 2.63ab |
| PLT(10^9/L) | 224.62 ± 66.14 | 261.34 ± 39.99a | 347.11 ± 156.15ab | 318.80 ± 101.65ab |
| LY       | 1.92 ± 0.53 | 1.96 ± 0.61 | 2.10 ± 0.80 | 2.18 ± 0.71ab |
| MO       | 0.43 ± 0.10 | 0.45 ± 0.12 | 0.49 ± 0.13ab | 0.53 ± 0.18abc |
| NLR      | 2.01 ± 0.83 | 2.17 ± 0.86 | 2.83 ± 1.05ab | 2.88 ± 1.53ab |
| PLR      | 120.57 ± 40.77 | 146.71 ± 50.37a | 174.63 ± 61.28ab | 158.54 ± 61.52ac |
| 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 ± 0.87ab | 1.91 ± 1.52ab | 1.98 ± 1.30ab |
| TNF-α(pg/mL) | 21.45 ± 8.31 | 27.61 ± 13.69a | 39.13 ± 24.08ab | 43.23 ± 28.29ab |
| IL-1β(kg/ml) | 3.26 ± 1.33 | 3.63 ± 1.30a | 6.05 ± 3.52ab | 6.47 ± 3.92ab |
| IL-2(pg/ml) | 23.58 ± 3.79 | 22.50 ± 3.40a | 21.39 ± 3.47ab | 20.49 ± 3.77ab |
| IL-27(pg/ml) | 65.96 ± 45.27 | 80.49 ± 38.62a | 307.93 ± 134.36ab | 169.37 ± 105.73abc |

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. a p < 0.05 compared with healthy control group. b p < 0.05 compared with thyroid adenomas group. c p < 0.05 compared with FTC group.

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

| Variable | <1cm | ≥1cm | P-value | I-II | III-IV | P-value |
|----------|------|------|---------|------|--------|---------|
| WBC(10^9/L) | 6.97 ± 1.18 | 6.98 ± 1.17 | 0.086 | 6.97 ± 1.17 | 6.97 ± 1.22 | 0.092 |
| NE(10^9/L) | 5.67 ± 2.65 | 5.67 ± 2.66 | 0.091 | 5.66 ± 2.65 | 5.67 ± 2.65 | 0.076 |
| PLT(10^9/L) | 336.57 ± 138.49 | 337.16 ± 141.37 | 0.083 | 335.92 ± 138.53 | 336.91 ± 139.16 | 0.095 |
| MO(10^9/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 | 1.97 ± 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(kg/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-
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; \( P < 0.001 \)) and 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; \( P < 0.001 \)) 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.

**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) 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.

**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\( \beta \),
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,\(^{15}\) PLT and leukocyte,\(^{16,17}\) 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,\(^{14}\) IL-17, and IL-35 with thyroid cancer,\(^{18}\) 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\(_b\), 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 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 |
|----------|----------|----------|-----------|----------|-----------|
| WBC      | 0.585    | 0.535    | 6.095     | 0.755    | 0.535    | 6.095     |
| NE       | 0.727    | 0.419    | 3.499     | 0.470    | 0.972    | 4.801     |
| PLT      | 0.514    | 0.737    | 264.510   | 0.430    | 0.931    | 284.500   |
| LY       | 0.120    | 0.931    | 2.650     | 0.730    | 0.608    | 0.455     |
| MO       | 0.246    | 0.829    | 0.525     | 0.740    | 0.627    | 2.205     |
| NLR      | 0.803    | 0.300    | 1.509     | 0.705    | 0.756    | 145.780   |
| PLR      | 0.617    | 0.622    | 130.527   | 0.550    | 0.585    | 0.245     |
| MLR      | 0.672    | 0.442    | 0.210     | 0.785    | 0.760    | 147.985   |
| NLR+PLR  | 0.617    | 0.622    | 132.036   | 0.785    | 0.760    | 147.985   |
| NLR+MLR  | 0.524    | 0.518    | 1.719     | 0.740    | 0.627    | 2.450     |
| PLR+MLR  | 0.557    | 0.673    | 130.737   | 0.705    | 0.756    | 146.025   |
| CRP      | 0.694    | 0.461    | 0.650     | 0.825    | 0.742    | 1.050     |
| IL-1\(b\) | 0.585    | 0.562    | 3.450     | 0.585    | 0.931    | 5.050     |
| IL-2     | 0.060    | 0.783    | 26.750    | 0.435    | 0.318    | 21.850    |
| IL-27    | 0.809    | 0.419    | 49.400    | 0.815    | 0.912    | 118.100   |

|          | HC vs TA |          | HC vs PTC |          | HC vs FTC |
|----------|----------|----------|-----------|----------|-----------|
| WBC      | 0.725    | 0.464    | 6.175     | 0.808    | 0.552    | 6.385     |
| NE       | 0.535    | 0.836    | 4.502     | 0.567    | 0.907    | 4.996     |
| PLT      | 0.335    | 0.978    | 349.000   | 0.567    | 0.787    | 285.500   |
| LY       | 0.470    | 0.623    | 2.050     | 0.433    | 0.749    | 2.250     |
| MO       | 0.730    | 0.601    | 0.455     | 0.644    | 0.694    | 0.485     |
| NLR      | 0.725    | 0.623    | 2.239     | 0.481    | 0.825    | 2.771     |
| PLR      | 0.705    | 0.557    | 145.647   | 0.269    | 0.858    | 193.421   |
| MLR      | 0.550    | 0.563    | 0.249     | 0.760    | 0.301    | 0.198     |
| NLR+PLR  | 0.745    | 0.672    | 147.886   | 0.481    | 0.825    | 196.367   |
| NLR+MLR  | 0.725    | 0.623    | 2.488     | 0.481    | 0.825    | 2.969     |
| PLR+MLR  | 0.705    | 0.557    | 145.896   | 0.531    | 0.518    | 193.619   |
| CRP      | 0.745    | 0.781    | 1.250     | 0.788    | 0.727    | 1.150     |
| TNF-\(\alpha\) | 0.460    | 0.880    | 38.100    | 0.558    | 0.880    | 38.100    |
| IL-1\(\beta\) | 0.665    | 0.787    | 4.450     | 0.692    | 0.787    | 4.450     |
| IL-2     | 0.405    | 0.595    | 22.250    | 0.250    | 0.372    | 21.850    |
| IL-27    | 0.760    | 0.929    | 143.400   | 0.683    | 0.869    | 124.600   |

**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.
results are consistent with our.19 Ari A et al. reported that NLR
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; MRL, 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; DTC, differentiated thyroid carcinoma.

| 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 (1.002-1.012) | 0.184 | 1.010 (1.002-1.013) | 0.221 | 1.137 (0.014-17.422) | 0.628 |
| MRL              | 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-α            | 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-1β            | 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 |

remains unknown at present. The Mendelian31 randomization
design reported that, the CRP genotypes (4 SNPs) are not
related to the risks of colorectal, lung, prostate, breast, or urin-
ary 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 mani-
festations and B-ultrasound, thyroid cancer, such as FTC, PTC
and TA, can hardly be differentially diagnosed before opera-
Our study, preoperative contents of NE, WBC, PLT, MO, LY, MRL, NLR, PLR, CRP, TNF-α, IL-1β, IL-2, IL-27, 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 iden-
tified in prior work to exhibit predicting significance in a var-
ety of cancer types. In thyroid cancer, NLR and PLR have
diagnostic and predictive significance for advanced differenti-
tiated thyroid cancer and ATC, while the diagnostic and pre-
dictive significance of NMPLR is far superior to that of NLR or
PLR.32 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 mean-
meaningful, which achieved far superior diagnostic effect than the
individual one. Moreover, IL-27 rs17855750 and rs153109

However, the IL-27 role in cancer remains contro-
versial. 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.26,27 In addition, the level of
IL-27Rs 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.28 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.29,30 However, the specific mechan-
ism of circulating CRP levels and tumor microenvironment
have been proved to be associated with PTC occurrence, which is partially consistent with our results. 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.

Authors’ Note
Xue Zhang, Department of Surgical Oncology, Lu’an Hospital Affiliated to Anhui Medical University, Lu’an, China, 237000; Su Li, Department of Oncology Radiotherapy, Lu’an Hospital of Traditional Chinese Medicine, Lu’an, China, 237000; Jin-hui Wang, Department of Cardiothoracic Surgery, Lu’an Hospital Affiliated to Anhui Medical University, Lu’an, China; Fu-bao Liu, Department of General Surgery, The First Affiliated Hospital of Anhui Medical University, Hefei, China, 230022; Yong Zhao, Department of Surgical Oncology, Lu’an Hospital Affiliated to Anhui Medical University, Lu’an, China, 237000, e-mail ZYZY8151@sina.com.

Acknowledgments
Our thanks should go to all the staff for their assistance and suggestions on the present work.

Declaration of Conflicting Interests
The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Ethics Statement
The study design was approved by the Medical Ethics Committee of the Lu’an Hospital Affiliated to Anhui Medical University (Approval Number 2018YJ023) and informed consent was obtained from all participants.

Funding
The author(s) received no financial support for the research, authorship, and/or publication of this article.

ORCID iD
Xue Zhang, MM https://orcid.org/0000-0001-8336-5256

Supplemental Material
Supplemental material for this article is available online.

References
1. Shah JP. Thyroid carcinoma: epidemiology, histology, and diagnosis. Clin Adv Hematol Oncol. 2015;13(4 Suppl 4):3-6.
2. American Thyroid Association Guidelines Taskforce on Thyroid N, Differentiated Thyroid C, Cooper DS, et al. Revised American thyroid association management guidelines for patients with thyroid nodules and differentiated thyroid cancer. Thyroid. 2009;19(11):1167-1214.
3. Lundgren CI, Hall P, Ekborn A, Frisell J, Zedenius J, Dickman PW. Incidence and survival of Swedish patients with differentiated thyroid cancer. Int J Cancer. 2003;106(4):569-573.
4. Diakos CI, Charles KA, McMillan DC, Clarke SJ. Cancer-related inflammation and treatment effectiveness. Lancet Oncol. 2014;15(11):e493-503.
5. Germano G, Allavena P, Mantovani A. Cytokines as a key component of cancer-related inflammation. Cytokine. 2008;43(3):374-379.
6. Candido J, Hagemann T. Cancer-related inflammation. J Clin Immunol. 2013;33(Suppl 1):S79-84.
7. Chang PH, Pan YP, Fan CW, et al. Pretreatment serum interleukin-1beta, interleukin-6, and tumor necrosis factor-alpha levels predict the progression of colorectal cancer. Cancer Med. 2016;5(3):426-433.
8. Ohe Y, Fushida S, Yamaguchi T, et al. Peripheral blood platelet-lymphocyte ratio is good predictor of chemosensitivity and prognosis in gastric cancer patients. Cancer Manag Res. 2020;12:1303-1311.
9. Sun Y, Zhang L. The clinical use of pretreatment NLR, PLR, and LMR in patients with esophageal squamous cell carcinoma: evidence from a meta-analysis. Cancer Manag Res. 2018;10:6167-6179.
10. Ma Z, Qi Z, Shan Z, Li J, Yang J, Xu Z. The role of CRP and ATG9B expression in clear cell renal cell carcinoma. Biosci Rep. 2017;37(6):BSR20171082.
11. Wang M, Wu M, Yang T. The synergistic effect of sorafenib and TNF-alpha inhibitor on hepatocellular carcinoma. EBioMedicine. 2019;40:11-12.
12. Shinagawa K, Yamamoto S, Naruse T, et al. Clinical roles of interleukin-6 and stat3 in oral squamous cell carcinoma. Pathol Oncol Res. 2017;23(2):425-431.
13. Yokota M, Katoh H, Nishimiya H, et al. Lymphocyte-monocyte ratio significantly predicts recurrence in papillary thyroid cancer. J Surg Res. 2020;246:535-543.

14. Kobawala TP, Trivedi TI, Gajjar KK, Patel DH, Patel GH, Ghosh NR. Significance of interleukin-6 in papillary thyroid carcinoma. J Thyroid Res. 2016;2016:6178921.

15. Kilincalp S, Coban S, Akinci H, et al. Neutrophil/lymphocyte ratio, platelet/lymphocyte ratio, and mean platelet volume as potential biomarkers for early detection and monitoring of colorectal adenocarcinoma. Eur J Cancer Prev. 2015;24(4):328-333.

16. Best MG, Wesseling P, Wurdinger T. Tumor-educated platelets as a noninvasive biomarker source for cancer detection and progression monitoring. Cancer Res. 2018;78(13):3407-3412.

17. Morrison L, Laukkanen JA, Ronkainen K, Kurl S, Kauhanen J, Toriola AT. Inflammatory biomarker score and cancer: a population-based prospective cohort study. BMC Cancer. 2016;16:80.

18. Lu Y, Yuan Y. Serum level of interleukin-17 and interleukin-35 as a biomarker for diagnosis of thyroid cancer. J Cancer Res Ther. 2015;11(Suppl 2):C209-211.

19. Ceylan Y, Kumanlioglu K, Oral A, Ertan Y, Ozcan Z. The correlation of clinicopathological findings and neutrophil-to-lymphocyte and platelet-to-lymphocyte ratios in papillary thyroid carcinoma. Mol Imaging Radionucl Ther. 2019;28(1):15-20.

20. Ari A, Gunver F. Comparison of neutrophil-lymphocyte ratio and platelet-lymphocyte ratio in patients with thyroiditis and papillary tumors. J Int Med Res. 2019;47(5):2077-2083.

21. Cho JS, Park MH, Ryu YJ, Yoon JH. The neutrophil to lymphocyte ratio can discriminate anaplastic thyroid cancer against poorly or well differentiated cancer. Ann Surg Treat Res. 2015;88(4):187-192.

22. Naumnik W, Naumnik B, Niewiarowska K, Ossolinska M, Chyczewska E. Novel cytokines: IL-27, IL-29, IL-31 and IL-33. Can they be useful in clinical practice at the time diagnosis of lung cancer? Exp Oncol. 2012;34(4):348-353.

23. Tao YP, Wang WL, Li SY, et al. Associations between polymorphisms in IL-12A, IL-12B, IL-12Rbeta1, IL-27 gene and serum levels of IL-12p40, IL-27p28 with esophageal cancer. J Cancer Res Clin Oncol. 2012;138(11):1891-1900.

24. Lu D, Zhou X, Yao L, Liu C, Jin F, Wu Y. Clinical implications of the interleukin 27 serum level in breast cancer. J Investig Med. 2014;62(3):627-631.

25. Diakowska D, Lewandowski A, Markocka-Macza K, Grabowski K. Concentration of serum interleukin-27 increase in patients with lymph node metastatic gastroesophageal cancer. Adv Clin Exp Med. 2013;22(5):683-691.

26. Hunter CA, Kastelein R. Interleukin-27: balancing protective and pathological immunity. Immunity. 2012;37(6):960-969.

27. Pot C, Apetoh L, Awasthi A, Kuchroo VK. Induction of regulatory Tr1 cells and inhibition of T(H)17 cells by IL-27. Semin Immunol. 2011;23(6):438-445.

28. Il'yasova D, Colbert LH, Harris TB, et al. Circulating levels of inflammatory markers and cancer risk in the health aging and body composition cohort. Cancer Epidemiol Biomarkers Prev. 2005;14(10):2413-2418.

29. Shimura T, Shibata M, Gonda K, et al. Prognostic impact of elevated preoperative C-reactive protein on patients with differentiated thyroid carcinoma. J Surg Res. 2018;231:338-345.

30. Wen W, Wu P, Li J, Wang H, Sun J, Chen H. Predictive values of the selected inflammatory index in elderly patients with papillary thyroid cancer. J Transl Med. 2018;16(1):261.

31. Allin KH, Nordestgaard BG, Zacho J, Tybjærg-Hansen A, Bojesen SE. C-reactive protein and the risk of cancer: a Mendelian randomization study. J Natl Cancer Inst. 2010;102(3):202-206.

32. Zhang L, Luo H, Wang L, et al. Diagnostic and prognostic value of the interleukin 27 serum level in anaplastic thyroid cancer. J Surg Oncol. 2020;122(5):897-905.

33. Nie X, Yuan F, Chen P, et al. Association between IL-27 gene polymorphisms and risk of papillary thyroid carcinoma. Biomark Med. 2017;11(2):141-149.