C-reactive protein to LymphocytE count ratio could be a reliable mArkeR of thyroiditis; the CLEAR-T study

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Abstract
Inflammation of the thyroid gland is referred to as thyroiditis and is associated with inflammation. Recent studies found significant association between thyroiditis and novel inflammatory and metabolic markers, as well as C-reactive protein (CRP). CRP/lymphocyte count ratio (CLR) is a novel inflammatory marker that associated with various conditions and has not been studied in thyroiditis, yet. We aimed to investigate CRP to lymphocyte count ratio in patients with thyroiditis and to compare to those in healthy subjects. Patients with thyroiditis that presented to internal medicine outpatient clinics of our institution between January 2019 and August 2021 were enrolled to the retrospective study. Healthy volunteers were enrolled as control group. CLR of the thyroiditis and control groups were compared. Median CLR of the thyroiditis and control groups were 3.14 (0.14%–38)% and 0.4 (0.03–8.86)%, respectively (p < .001). The sensitivity and specificity of CLR > 0.43% in detecting thyroiditis were 92% and 58%, respectively (AUC: 0.88, p < .001, 95% CI: 0.85–0.92). CLR was significantly and positively correlated with free T4 (FT4) (r = .18, p < .001) and inversely correlated with thyroid stimulating hormone (TSH) (r = -.52, p = .003) levels. In conclusion, we suggest that high CLR levels may yield additional diagnostic value in patients with thyroiditis.

KEYWORDS
C-reactive protein/lymphocyte count ratio, inflammation, thyroiditis

1 | INTRODUCTION

Inflammation of the thyroid gland is referred to as thyroiditis and can be triggered by infection, autoimmune response, and other causes. Hashimoto's thyroiditis, subacute lymphocytic thyroiditis, postpartum thyroiditis, and subacute granulomatous thyroiditis are the most frequent etiologies of thyroiditis. Although it usually present with painless gland, it may also associate with prominent pain when the cause is infection, trauma, or radiation damage.

Diagnosis of the thyroiditis depends on the history and physical examination findings because it can present either with euthyroidism, hypothyroidism, or thyrotoxicosis. Besides, nonspecific increase in inflammatory markers including C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) may accompany to the clinical course with increased autoantibody titers specifically in Hashimoto's thyroiditis. No other specific tests are available for establishing the diagnosis.

Recent studies found significant association between thyroiditis and novel inflammatory and metabolic markers, including red cell distribution width, neutrophil/lymphocyte counts ratio, and uric acid/HDL ratio. Another novel inflammatory marker is CRP/lymphocyte count ratio (CLR) which reported to be related with pancreas malignancy, cancer of the esophagus, appendicitis, and colorectal cancer.
In present study, we aimed to compare CLR levels of the thyroiditis patients to those in healthy subjects.

2 | METHODS

2.1 | Design, setting, and population

Patients with thyroiditis that presented to internal medicine outpatient clinics of our institution between January 2019 and August 2021 were enrolled to the retrospective study after study protocol was approved by institutional ethics committee (approval no: 2021/261). Healthy controls were volunteers whom visited our clinics for a routine check-up.

2.2 | Anthropometric and laboratory analyses

Age, gender, CRP, hemogram indices (white blood cell count [WBC], neutrophil count [neu], lymphocyte count [lym], hemoglobin [Hb], Hematocrit [Hct], erythrocyte distribution width [RDW], platelet count [PLT], mean platelet volume [MPV], platelet distribution width [PDW]), thyroid stimulating hormone (TSH), free T4 (FT4), and free T3 (FT3) levels of the study population were downloaded from institutional database and recorded. A CLR was simply calculated by division of CRP by lym. Data of the thyroiditis and control groups were compared.

2.3 | Statistical analyses

Statistical analyses were conducted with statistics software (SPSS 18.0 for Windows, IBM Co., Armonk, NY, USA). Normality analysis of the variables was performed with Kolmogorov–Smirnov test. Variables with normal distribution were compared with $t$ test and expressed as mean ± SD. On the other hand, Mann–Whitney $U$ test was used in comparison of the variables without normal distribution, which were expressed as median (interquartile range [IQR]). Categorical variables were compared with $\chi^2$ test and expressed as numbers and percentages. Parsons’s correlation analysis test was used in analysis of correlation between study variables. The sensitivity and specificity of CLR and CRP in detecting thyroiditis were conducted by receiver operating characteristics (ROC) test. Statistical significance was considered when the $p$ value was lower than 5%.

3 | RESULTS

Study population was consisted of 470 subjects; 366 in thyroiditis group and 104 in control group. Mean age of the thyroiditis and control groups were $47 \pm 12$ years and $43 \pm 10$ years, respectively ($p = .11$). Thyroiditis group was consisted of 263 (72%) women and 103 (28%) men, while control group was consisted of 82 (79%) women and 22 (21%) men. Gender of the thyroiditis and control groups was not statistically different ($p = .16$).

There were no significant difference between thyroiditis and control subjects according to WBC ($p = .08$), Hb ($p = .07$), Hct ($p = .07$), PLT ($p = .59$), PDW ($p = .19$), TSH ($p = .09$), FT3 ($p = .35$), and FT4 ($p = .14$) levels. Median neu ($p = .002$), lym ($p < .001$), RDW ($p < .001$), MPV ($p < .001$), and CRP ($p < .001$) levels of the thyroiditis and control groups were significantly different. Table 1 shows the characteristics and data of study population.

Median CLR of the thyroiditis and control groups were 3.14 (0.14–38)% and 0.4 (0.03%–8.86)%, respectively ($p < .001$). The correlation between CLR and other study variables were observed. CLR was significantly and positively correlated with FT4 ($r = .18$, $p < .001$) and inversely correlated with TSH ($r = -0.52$, $p = .003$) levels.

In ROC analysis, the sensitivity and specificity of CLR > 0.43% in detecting thyroiditis were 92% and 58%, respectively (AUC: 0.88, $p < .001$, 95% CI: 0.85–0.92). On the other hand, the sensitivity and specificity of CRP > 0.93 mg/dL in detecting thyroiditis were 91% and 51%, respectively (AUC: 0.87, $p < .001$, 95% CI: 0.84–0.90). Figure 1 shows the ROC curves of CRP and CLR in detecting thyroiditis.

| Table 1 | Characteristics of thyroiditis and control groups |
|---------|-----------------------------------------------|
|         | Thyroiditis group | Control group | $p$ |
| Sex     | n (%)            |                |     |
| Men     | 103 (28%)        | 22 (21%)       | .16 |
| Women   | 263 (72%)        | 82 (79%)       |     |
| Age (years) | 47 ± 12     | 43 ± 10        | .11 |
| Hb (g/dL) | 13.3 ± 1.7     | 13.6 ± 1.3     | .07 |
| Hct (%) | 40 ± 5          | 41 ± 4         | .07 |
| PLT (k/mm$^3$) | 261 ± 92   | 267 ± 70       | .59 |
| WBC (k/mm$^3$) | 7.1 (3.1)   | 6.7 (2.3)      | .08 |
| Neu (k/mm$^3$) | 4.3 (2.7)    | 4 (1.6)        | .002|
| Lym (k/mm$^3$) | 1.8 (0.9)     | 2.2 (0.9)      | <.001|
| RDW (%) | 13.8 (2.9)      | 16.1 (0.9)     | <.001|
| PDW (%) | 16.4 (4.5)      | 15.6 (4.6)     | .19 |
| MPV (fL) | 9.3 (2.1)       | 8.4 (2.9)      | <.001|
| TSH (uIU/mL) | 1.2 (2.3)   | 1.4 (1.2)      | .09 |
| FT3 (pg/mL) | 3.4 (0.8)    | 3.2 (0.5)      | .35 |
| FT4 (ng/dL) | 1.1 (0.5)    | 1.2 (0.2)      | .14 |
| CRP (mg/dL) | 5.6 (20.5)   | 0.8 (1.1)      | <.001|
| CLR (%)  | 3.14 (0.14–38) | 0.4 (0.03–8.86)| <.001|

Abbreviations: CLR, CRP/lymphocyte count ratio; CRP, C-reactive protein; FT3, free T3; FT4, free T4; Hb, hemoglobin; Hct, hematocrit; IQR, interquartile range; Lym, lymphocyte count; MPV, mean platelet volume; neu, neutrophil count; PDW, platelet distribution width; PLT, platelet count; RDW, erythrocyte distribution width; TSH, thyroid stimulating hormone; WBC, white blood cell count.
DISCUSSION

The present study claimed that CLR levels of the patients with thyroiditis were significantly higher than the CLR of healthy population. Interestingly, CLR was inversely and positively correlated with TSH and FT4, respectively. Finally, CLR has considerably high sensitivity and moderate specificity, which are higher than those of CRP, in detecting thyroiditis.

Thyroiditis cause significant amount elevation in circulating inflammatory biomarkers. The prototype of these markers is CRP, which is usually increased in thyroiditis, as well as other inflammatory and infectious conditions. Recently, other inflammatory predictors have been suggested to be useful in the diagnosis of thyroiditis. Authors reported that RDW of the subjects with thyroiditis is higher than the RDW of controls. Kurtkulagi et al. showed that uric acid/HDL cholesterol ratio, another novel biomarker of inflammation, was increased in patients with thyroiditis. Neutrophil/lymphocyte count ratio, another well-established hemogram derived inflammatory indices, is elevated in subjects with thyroiditis compared to health population. These data suggest that inflammatory predictors tend to be higher in thyroiditis. Similarly, we found that CLR was elevated in these patients.

The association between inflammation and CLR has been reported in various studies in the literature. Malignant conditions are associated with chronic low grade inflammation and authors reported that CLR was associated with lung carcinomas. It is also related with colorectal carcinoma. Moreover, elevated CLR levels have been shown in subjects with pancreatic cancer. In a recent report, it has been found that CLR was increased in subjects with cholangiocarcinoma. Not only malignant conditions but also other inflammatory diseases are associated with elevated CLR. Patients with intestinal ischemia have increased CLR values compared to controls. Since thyroiditis is also associated with significant inflammatory burden, we reported elevated CLR levels in these subjects compared to the healthy controls in present study.

Why CLR levels increase in thyroiditis? Inflammatory stimuli based from thyroid tissue may cause an elevation in CRP levels. On the other hand, inflammatory conditions may induce lymphopenia, which was well established in Covid-19 infection. Moreover, autoimmunity may also induce lymphopenia, which is prominent in Hashimoto’s thyroiditis. Interestingly, lymphopenia after traumatic injury has been suggested to be associated with increased mortality. Thus, decreased lymphocyte count is considered to be correlated with increased morbidity and poor outcome. It can be concluded that a combination of CRP and lymphocyte would be a better indicator of inflammation in clinical practice. In fact, in the present work, we showed that CLR could predict thyroiditis with a higher sensitivity and specificity than CRP.

The present study has several limitations that may make its results difficult to interpret in clinical practice. Initially, it was designed retrospectively that not allow authors to control all other contributing inflammatory process which may interact with elevated CLR. Second, study population was relatively small. And finally, it was a single center study. However, to the best of our knowledge, this is the first

FIGURE 1 Receiver operative characteristics (ROC) curves of C-reactive protein (CRP) and CRP/lymphocyte count ratio (CLR) in detecting thyroiditis.
study in literature that reported elevated CLR in patients with thyroiditis.

5 | CONCLUSION

We suggest that high CLR levels may yield additional diagnostic value in patients with thyroiditis. Prospective studies with larger cohort are required to confirm the results of the present preliminary work.

AUTHOR CONTRIBUTIONS

Conception, design: Muhammed Emin Demirkol, Gulali Aktas; data collection: Muhammed Emin Demirkol; analysis and interpretation of data: Muhammed Emin Demirkol, Gulali Aktas; statistical analysis: Gulali Aktas; Writing the first draft: Gulali Aktas; approval of the final manuscript version: Muhammed Emin Demirkol, Gulali Aktas.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

ETHICS STATEMENT

The study was reviewed and approved by the Medical Ethics Committee of Abant Izzet Baysal University (approval number: 2021/261).

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