Inflammatory Markers in Thyroid Disease

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***Abstract*- The chronic autoimmune thyroid condition known as Hashimoto's thyroiditis (HT) results in systemic inflammation throughout the body, which enlarges the thyroid gland and produces hypothyroidism. The general features of HT include decreased thyroid follicles, increased titers of thyroid autoantibodies, anti-thyroid peroxidase (Anti-TPO), and anti-thyroglobulin (Anti-TG); thyroid gland hypertrophy; abnormal thyroid functions; morphological changes in thyroid sonography; and Hurthle cells with granular-pink cytoplasm. The neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), monocyte-to-lymphocyte ratio (MLR) , interleukin and systemic immune inflammatory index (SII), system inflammation response index (SIRI), and aggregate index of systemic inflammation (AISI) are examples of new blood inflammatory indices (henceforth BIIXs) that have been tested in nearly every clinical research field and found to be accurate in measuring inflammation, the state of systemic illness, and the prognosis.**

***Index Terms*- Thyroid disease, Epidemiology, Inflammatory marker such as CRP, MLR, NLR, PLR, and Interleukin.**

I. INTRODUCTION

In the general population, thyroid diseases are prevalent. Thyroid nodules with multinodular goiter (MNG), which is an enlargement of the thyroid gland with multiple nodules, and lymphocytic thyroiditis (LT), which is brought on by an autoimmune process, are believed to be benign thyroid disorders with a low risk of cancer (1). The most prevalent endocrinological cancer is thyroid cancer, followed by papillary thyroid carcinoma (PTC) (Research has indicated that PTC is closely associated with inflammation, and PTC is more common in individuals with LT. The literature has frequently shown the co-occurrence of LT and PTC. The gold standard for distinguishing between thyroid problems is histopathology. Numerous serum systemic inflammatory response markers, including the neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio, and lymphocyte-to-monocyte ratio, c- Reactive protein have been shown in recent research to be useful as clinical prognostic indicators for thyroid cancer and other cancer types (2,3,4,5,6). Neutrophils platelets/lymphocytes are the new systemic immune-inflammation index (SII), which can be readily computed from standard blood tests and indicates a patient's inflammatory and immunological condition. Thyroid cancer is the most prevalent endocrine cancer, with the papillary variety being the most prevalent type. Dailey was the first to show the link between PTC and chronic inflammation in thyroid disorders in 1955.Other research has shown a positive correlation between PTC and chronic inflammation, indicating that people with thyroiditis are more likely to develop PTC. However, ironically, thyroiditis has been linked to a better prognosis in cases with papillary thyroid cancer (7,8,9).

II. THYROID DISEASES

Interestingly, the thyroid gland has a high Se concentration when there is a Se insufficiency. The thyroid is one of the organs in the body with the highest Se content (10). This demonstrates the distinctiveness of the human thyroid and the significance of selenium for the thyroid gland. Even yet, there is still more research to be done on the connection between Se and thyroid disorders. Nowadays, low selenium levels are regarded as one of the independent risk factors for thyroid disorders, and treating patients with low selenium levels with

supplements is widely deemed to be helpful for thyroid disorders **(11)**. Since differentiated thyroid cancer (DTC) is on the rise, the incidence of papillary thyroid carcinoma (PTC) is also on the rise globally. This is likely owing to the increased use of fine-needle cytology (FNC) and high-resolution ultrasound (US) **(12,13)**. PTC is currently the most common endocrine cancer, accounting for over 94% of all thyroid cancers and 85% of all follicular-derived well-differentiated thyroid malignancies (**14,15,16**).

In order to better stratify the pre-surgical risk of thyroid cancer, the major Italian societies working in the field developed a new cytological classification in 2014. This classification, known as the SIAPEC-IAP classification, divides thyroid nodules into six groups according to FNA results, offers management advice, and identifies risk factors **(17)**. The ambiguous follicular thyroid lesions (Thyr 3A and Thyr 3B) fall into the third category. They make up 10% to 30% of all cytopathologic diagnoses, and their erratic behavior poses a difficult clinical problem. Suppressing the immune response is necessary to prevent the development of the neoplasm since the host immune system may be closely implicated in tumorigenesis due to factors associated with malignancy. Several systemic inflammatory markers have recently been identified as predictive and prognostic factors for lung, colorectal, pancreatic, breast, and, to a lesser extent, thyroid cancer. These markers include the neutrophil-to-lymphocyte ratio (NLR), the platelet-to-lymphocyte ratio (PLR), and the lymphocyte-to-monocyte ratio (LMR) **(18,19)**.

III. EPIDEMIOLOGY

In the general population, the prevalence rate of primary hypothyroidism ranges from 0% to 3% and 4% to 8% in the United States and from 0% to 3% and 4% to 7% in the European population **(20)**. According to a meta-analytical study conducted in nine European nations, the prevalence of undiagnosed hypothyroidism, encompassing both mild and overt instances, is between 5% and 6% **(21)**. In patients who are iodine adequate, an excess of iodine can suppress the production of thyroid hormones and raise TSH. Thus, it raises the possibility of hypothyroidism. The prevalence of impaired thyroid function is higher in women, older adults over 65, and White persons, however there is little information on ethnic disparities **(22)**. People who have a family history of hypothyroidism are more likely to acquire hypothyroidism due to heredity. TSH transfer from parents to children has a 60% possibility, but free T4 transfer has a 20% to 60% chance **(23)**.

As far as we are aware, this is the first epidemiological study to examine the prevalence of both diagnostic and undiagnosed hypothyroidism, subclinical and clinical hyperthyroidism, and positive thyroid antibodies in the Croatian population that consumes enough iodine. According to our study's findings, the prevalence of clinical and subclinical hypothyroidism was 3% and 7.4%, respectively, whereas the prevalence of clinical and subclinical hyperthyroidism was 0.2% and 1.1%. Furthermore, 17.6% of subjects had positive antibodies and were euthyroid. The majority of these cases had never been diagnosed before. Our cohort had a 6.9% and 2.8% prevalence of undetected subclinical and clinical hypothyroidism, respectively, and a 0.9% and 0.1% prevalence of undiagnosed preclinical and clinical hyperthyroidism. As a result, 93.9% of our population has subclinical hypothyroidism, up from 92.6%.71.4% of those with clinical hyperthyroidism, 83% of those with subclinical hyperthyroidism, and 83% of those with clinical hypothyroidism had no diagnosis. The highest likelihood of diagnosis was among patients with clinical hyperthyroidism (OR = 11.4). Women were more likely to acquire antibody-positive euthyroidism, subclinical hyperthyroidism, clinical hypothyroidism, and subclinical hypothyroidism in addition to having a higher frequency of thyroid diseases. The prevalence of euthyroidism was higher in men. Subclinical hyperthyroidism, clinical hypothyroidism, and subclinical hypothyroidism were more common in participants with positive antibodies. Comparing our findings with those of other research, we found that, although the frequency of hyperthyroidism was fairly similar, the prevalence of hypothyroidism was higher in our nation than in the majority of other nations. In 1953, Croatia enacted its first law requiring salt to be iodinated, requiring 10 milligrams of potassium iodide (KI) per kilogram of salt. Goiter was found to have decreased tenfold in the Croatian population ten years later. Between 1991 and 1993, studies revealed that between 8% and 35% of school-age children had

goiter. As a result, in 1996, 25 mg of KI per kilogram of salt was suggested and established **(24)**.

IV. INFLAMMATORY MARKERS AND THEIR SIGNIFICANCE

- CRP (C-reactive protein)

acute-phase plasma protein C-reactive protein (CRP) was identified by Tillett and Francis (1930) and is made up of five identical polypeptide subunits, each containing 206 amino acids. Plasma cytokines (IL-1β and IL-6) that are primarily generated by macrophages and adipocytes cause an increase in the concentration of CRP (Lau et al. 2005). By binding to phosphocholine on microorganisms, CRP contributes to complement binding and macrophage phagocytosis (opsonin-mediated phagocytosis) of foreign and injured cells. It also plays a significant role in the early immunological defense against infections through innate immunity. Depending on the extent of tissue injury and inflammation, CRP can rise to more than 50,000 times the normal amount, peaking in two days after beginning to rise within six hours. Due to its continuous half-life in plasma, its concentration is dependent on the rate of synthesis (Pepys 1981; Pepys and Hirschfield 2003. Among these acute phase reactants, serum C reactive protein (CRP) has been shown to be notably higher in inflammatory thyroid conditions (25). Therefore, among all thyroid illnesses, it has been noted that the most noticeable increase in CRP in blood or bodily secretions occurs in SAT. Serum CRP has developed into a sensitive indicator of underlying inflammatory pathology, response to treatment, and disease process prognosis in a number of other medical specialities (26). Additionally, C-reactive protein (CRP), as measured by a high sensitivity immunoassay, has been proposed as a powerful predictor of cardiovascular risk because atherosclerosis is thought to be an inflammatory disease. There is no information on CRP in hypothyroid people. Cardiovascular illness, particularly coronary heart disease, has been linked to both SCH and OH (27). Even though it should be given careful consideration when thyroiditis is present, whether it be in the course of Hashimoto's disease, hyperthyroidism, or hypothyroidism brought on by interferon (IFN)-α or amiodarone (AM), CRP is not a commonly measured parameter in the diagnosis of thyroid disorders. The objective of this research was to assess the level of serum high-sensitive CRP (Hs-CRP) as a gauge of inflammation in a variety of thyroid conditions and how it varies according to the disease's stage and duration (28). Hence, among all thyroid conditions, it has been noted that the increase in CRP in blood or bodily secretions is more noticeable in SAT. In numerous different medical specialities, serum CRP has developed into a sensitive indicator of underlying inflammatory pathology, treatment response, and disease process prognosis. It has not yet been widely applied, nevertheless, in the assessment of inflammatory thyroid disorders and in distinguishing them from other illnesses that present with comparable clinical symptoms. This study sought to determine whether serum CRP levels could be used to differentiate between two frequent causes of thyrotoxicosis (29).

- NLR (Neutrophil to lymphocyte ratio)

Numerous serum systemic inflammatory response markers, including the neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio, and lymphocyte-to-monocyte ratio, have been shown in recent research to be useful as clinical prognostic indicators for thyroid cancer and other cancer types. Neutrophils × platelets/lymphocytes are the new systemic immune-inflammation index (SII), which can be readily computed from standard blood tests and indicates a patient's inflammatory and immunological condition **(30)**. Hematological markers have also been examined in thyroid disease in recent research and have been linked to cancer. The ideal NLR level was 1.91 with 89.0% sensitivity and 54.5% specificity, according to Kocer et al. who also noted that it may be employed as a possible marker for differentiating between benign and malignant thyroid diseases. Additionally, NLR was linked to a greater stage of PTC, multifocality, and larger tumor size **(31)**. Increased NLR was linked to greater tumor size, positive lymph nodes, and distant metastases, according to Feng et al.'s evaluation of the relationship between pretreatment NLR and prognosis and clinicopathological characteristics in patients with thyroid cancer. SII and its relationship to thyroid diseases are poorly understood, despite research on NL and thyroid disorders. Our investigation revealed that patients with PTC had considerably higher SII levels, and that benign and malignant illnesses could

be distinguished with 73.8% sensitivity and 72.3% specificity at a level of 654.13 **(32)**. The most extensively studied inflammatory marker in thyroid cancer patients is NLR, and numerous authors have shown a strong correlation between a high NLR and aggressive tumors, lymph node metastases, and a poor prognosis **(33)**.

- MLR (Monocyte to lymphocyte ratio)

The monocyte-to-lymphocyte ratio (MLR) is a recently identified inflammatory measure that is comparable to NLR. A Korean study on endometrial cancer showed that elevated MLR is significantly linked to both cancer-related mortality and cancer recurrence (34). Whether MLR is linked to the severity and prognosis of AE is unknown, though. In order to determine if NLR and MLR are related to the severity and prognosis of AE, this study will examine the clinical features of AE (35).

- PLR (Platelet to lymphocyte ratio)

Poor prognosis is also associated with high PLR, particularly in patients with medullary and papillary thyroid carcinoma. We demonstrated a lower PLR in patients categorized as disease-free and a higher. PLR in individuals with distant metastases. Aside from that, PLR>124 assisted in accurately (78.7%) and sensitively (86.7%) distinguishing distant metastasis from lymph node metastasis. Most of the research has focused on DTC patients, although two Chinese studies indicated that NLR did not show a correlation with a bad prognosis in medullary thyroid carcinoma, whereas a high PLR did **(36)**.

Table 1 -Comparison of NLR, PLR, MLR and blood count of patient with THYR3A with benign and malignant pathology (37).

	Benign 124pts	Malignant 14pts	P
NLR	2.19 ± 0.49	2.21 ± 0.43	0.862
MLR	5.71 ± 1.62	5.53 ± 2.03	0.765
PLR	143.07 ± 44.28	124.2 ± 33.91	0.072
Monocyte(U/μL)	323.03 ± 63.32	342.28 ± 64.07	0.302
Neutrophils(U/μL)	3735.05 ± 413.29	3850.57 ± 370.67	0.290
Platelets(U/μL)	242,787.6 ± 53,465.55	214,412.86 ± 36,322.87	0.016
Lymphocyte(U/μL)	1770.25 ± 334.74	1795.07 ± 335.04	0.796

Table 2- Comparison of NLR, PLR, MLR and blood count of patient with THYR3B with benign and malignant pathology (37).

	Benign 124pts	Malignant 14pts	P
NLR	2.09 ± 0.46	2.39 ± 0.49	<0.0001
MLR	6.33 ± 1.89	5.56 ± 1.58	0.003
PLR	134.9 ± 41.91	143.28 ± 46.54	0.227
Monocyte(U/μL)	306.56 ± 66.10	314.64 ± 63.97	0.419
Neutrophils(U/μL)	3751.19 ± 429.26	3884.3 ± 416.38	0.047
platelets(U/μL)	239,400.35 ± 52,263.05	230,379.69 ± 51,889.76	0.249
Lymphocyte(U/μL)	1848.04 ± 340.47	1678.64 ± 318.78	0.001

- Interleukin

Mostly produced by T lymphocytes, monocytes, macrophages, and endothelial cells, interleukins are tiny protein signalling molecules that are part of the cytokine superfamily. Facilitating communication between immune system cells, controlling inflammation, and regulating transcription factors are among interleukins' primary roles. Vose was the first to describe how interleukins contribute to cancer **(38)** and several investigations conducted in the ensuing decades have verified that interleukins, ranging from il-1 to il-38, are important in a variety of malignancies, including thyroid breast and hepatoma **(39)**.

Interleukins have been linked to the risk of thyroid cancer in a number of genetic investigations. Consequently, interleukin gene testing of high-risk groups, such as those with radiation exposure or a family history of thyroid cancer, may aid in more precise thyroid cancer risk assessment. Genetic investigations in various populations are required to ascertain the clinical significance of interleukins in the risk of thyroid cancer because different populations have distinct heritable variables. The human body's interleukins are also impacted by a wide range of other illnesses, including thyroiditis, immunological disorders, and cancer. Reports on the tumor risk assessment of people with thyroid cancer who also have other illnesses are lacking, nonetheless **(40)**.

V. THE EFFECTS OF INTERLEUKINS IN THYROID CANCER

The proliferation of tumor cells is a crucial stage in the formation of tumors. Interleukins may control thyroid cancer cell proliferation, according to a number of studies. Two activator cytokines, IL-1α and IL-1β, and an inhibitory cytokine, IL-1 receptor antagonist (IL-1ra), are components of IL-1. By binding to the same receptor, the type 1 IL-1 receptor (IL-1R), IL-1α and IL-1β trigger downstream signalling cascades that eventually support the inflammatory and immunological responses (41). IL-1's involvement in cancer has been clearly established (42). Furthermore, it has been established that IL-1 may control thyroid cancer growth via a variety of methods. The results are conflicting because various thyroid cancer cell lines were employed in separate investigations. IL-1α may stimulate Ca2+ channels to increase the growth of PTC cell line NIM1 (43). Thyroid cancer cell growth may also be inhibited by IL-1. IL-1 suppresses the proliferation of the thyroid cancer cell line NPA, which was partly linked to c-myc inhibition (44). On PTC, IL-1β has potent anticancer effects, as well as FTC cell lines (45), via inhibiting invasiveness and proliferation. Additionally, IL-1β had no anti-proliferative effect on ATC cell lines, suggesting that PTC cancer cells running away from IL-1β's antitumor effect could be a sign of anaplasia shift and lead to more aggressive thyroid cancer (46). However, more research is required because the processes behind this process are unclear. Th17 and Th22 cells release IL-22, which binds to the IL-22 and IL-10 receptors to produce its biological effects. Cancer progresses as a result of IL-22's activation of several downstream signalling pathways, such as JAK/STAT3 and MAPK (47). Thyroid cancer migrates and invades more readily when IL-22 stimulates the expression of miR-595, which suppresses the expression of Sox17 (48).

ABBREVIATION

PTC: Papillary Thyroid Carcinoma

DTC: Differentiated Thyroiod Carcinoma

SAT: Subacute Thyroiditis

MAPK: Mitogen Activated Protein Kinase

HS: Hashimoto's Thyroiditis

Anti-TPO: Anti-Thyroid Peroxidase

Anti-TG: Anti-Thyroglobulin

NLR: Neutrophil-To-Lymphocyte Ratio

PLR: Platelet-To-Lymphocyte Ratio

MLR: Monocyte-To-Lymphocyte Ratio

SII: Systemic Immune Inflammatory Index

AISI: Aggregate Index Of Systemic Inflammation

SIRI: System Inflammation Response Index

MNG: Multinodular Goiter

LT: Lymphocytic Thyroiditis

PTC: Papillary Thyroid Carcinoma

CRP: C- Reactive Protein

TSH: Thyroid Stimulating Hormone

KI: Potassium Iodide

VI.CONCLUSIONS

In conclusion, the significance of inflammatory markers in thyroid inflammation lies in the fact that they offer valuable insights on the existence of inflammation in thyroid disorders, particularly autoimmune thyroid disorders such as Hashimoto's

thyroiditis (HT). When compared to healthy controls, patients with thyroid inflammation typically have higher levels of inflammatory markers such as the neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), C R- reactive protein systemic inflammatory index (SII). because they are derived from a wider variety of hematologic parameters, biomarkers of systemic inflammation in patients with thyroidism, provide more accurate information. Systemic inflammation markers did not significantly differ in the current investigation, even among HT patients with hypothyroidism due to chronic inflammation. The link between thyroid disease and underlying inflammatory processes is supported by the fact that both benign and malignant thyroid disorders are linked to changed interleukin expression levels. For these indicators to gain a predictive significance, further prospective research with bigger study populations is needed.

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CONFLICT OF INTERESTS

The authors declare no competing interests.

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