ACTA OTORHINOLARYNGOLOGICA ITALICA 2022;42:150-154; doi: 10.14639/0392-100X-N1665

Thyroid

Systemic immune inflammation index in differentiated thyroid cancers

L'indice infiammatorio immunitario sistemico nei carcinomi differenziati della tiroide

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SUMMARY

Objective. The aim of this study was to investigate the relationship between differentiated thyroid carcinomas (DTCs), histopathological findings and systemic immune-inflammation index (SII) [neutrophil (N) x platelet (P) / lymphocyte (L)] values.

Methods. 93 patients with DTC were included. N, P and L levels were measured, and the relationship between the SII and histopathological findings was determined. The results were compared with the values of 33 healthy controls.

Results. SII values were significantly higher in the patient group than in the control group (p = 0.000). Tumour pathology diagnosis had no significant effect on SII (p = 0.90). Perineural lymphovascular and capsule invasion and extrathyroidal extension also had no significant effect on SII values. SII was significantly higher in patients with more than one tumour focus (p = 0.01). No significant relationship was determined between tumour diameter and SII.

Conclusions. SII is higher in patients with DTC compared to the healthy population. High SII values may be associated with multifocality. According to the results of this study, SII does not affect the histological type, perineural, lymphovascular and capsule invasion, or extrathyroidal extension of DTC.

KEY WORDS: differentiated thyroid cancer, histopathological findings, inflammatory parameters, systemic immune-inflammation index

RIASSUNTO

***Obiettivo**. Lo scopo di questo studio è quello di indagare la relazione tra i carcinomi differenziati della tiroide (DTC), i risultati istopatologici e i valori dell'indice infiammatorio immunitario sistemico (SII) (neutrofili (N) x piastrine (P) / linfociti (L)).*

***Metodi**. In questo studio sono stati inclusi 93 pazienti con DTC. Sono stati misurati i livelli di N, P e L ed è stata determinata la relazione tra il SII e i risultati istopatologici. I risultati sono stati confrontati con i valori di un gruppo di controllo sano di 33 membri.*

***Risultati**. I valori di SII erano significativamente più alti nel gruppo di pazienti rispetto al gruppo di controllo (p = 0.000). La patologia tumorale non ha avuto effetti significativi su SII (p = 0.90). Anche l'invasione linfovascolare perineurale e della capsula e l'estensione extratiroidea non hanno avuto effetti significativi sui valori di SII. Il SII era significativamente più alto nei pazienti con più di un focolaio tumorale (p = 0.01). Nessuna relazione significativa è stata determinata tra diametro del tumore e SII.*

***Conclusioni**. SII è più alto nei pazienti con DTC rispetto alla popolazione sana. Valori elevati di SII possono essere associati alla multifocalità. Secondo i risultati di questo studio, la SII non influenza il tipo istologico, l'invasione perineurale, linfovascolare e capsulare o l'estensione extratiroidea del DTC.*

PAROLE CHIAVE: *carcinoma differenziato della tiroide, reperti istopatologici, parametri infiammatori, dell'indice infiammatorio immunitario sistemico*

Introduction

Despite the rarity of thyroid cancer, it remains the most common endocrine neoplasia, and the incidence is increasing [1]. Differentiated thyroid carcinomas

Received: May 4, 2021
Accepted: January 1, 2022

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How to cite this article: Kars A, Sahin A, Kılıc K, et al. Systemic immune inflammation index in differentiated thyroid cancers. Acta Otorhinolaryngol Ital 2022;42:150-154. https://doi.org/10.14639/0392-100X-N1665

(DTCs), developing from thyroid follicular epithelial cells, constitute approximately 95% of all thyroid cancers [2]. Risk factors for DTCs include a history of radiation to the thyroid gland in childhood, age, female gender and family history. Papillary thyroid carcinoma (PTC) represents approximately 80-85% of malignant epithelial thyroid tumours in developed countries with sufficient dietary iodine intake, while follicular thyroid carcinoma (FTC) is more common in iodine-deficient regions and constitutes approximately 10-15% of all thyroid cancers [3]. Approximately 90% of these cases exhibit good prognosis with a combination of surgical treatment and radioactive iodine therapy. Lobectomy-isthmusectomy or total thyroidectomy, depending on the tumour location, represent the preferred surgical treatment in DTCs due to rates of low recurrence and high survival [4,5].
Inflammation is a physiological and protective mechanism that develops against tissue injury. The process is initiated under the effect of various chemical signals in order to combat pathogens and repair tissue damage. It may also become chronic, depending on the permanent nature of the agents responsible for inflammation and the ineffectiveness of factors responsible for eradicating it [1].
The links between cancer and inflammation and the cellular immune system are known to play a key role in the inflammatory response [6]. Inflammation increases the risk of tumour, plays an important role in cancer progression and affects all tumour stages [7,8]. Previous studies have investigated the powerful association between cancer and inflammation, and inflammatory cells have been reported to affect carcinogenesis [9]. All stages of cancer, including onset, conversion to malignancy, genetic mutation, angiogenesis, tissue infiltration and metastasis, are affected in association with the inflammatory response [7,9].
Relationships have been shown between chronic inflammatory bowel diseases and colon adenocarcinoma, between chronic hepatitis B and C and hepatic carcinoma, between Helicobacter pylori-related gastritis and gastric carcinoma, and between chronic oesophagitis and oesophageal carcinoma [10]. Several studies have reported immune inflammatory cell infiltration in thyroid cancers. Inflammatory factors produced by epithelial cells in thyroid cancers have been shown to prevent cancer cell apoptosis and to increase cancer resistance [1].
Various studies have shown a relationship between tumour progression and inflammatory parameters such as the neutrophil (N)/lymphocyte (L) ratio (NLR) and the platelet (P)/L ratio (PLR) [11-14]. Relationships have also been shown between a high systemic immune-inflammation index (SII) (NxP/L) and prognosis in patients with hepatocellular carcinoma, small cell lung cancer, oesophageal squamous cell cancer (SCC), renal cell carcinoma, colorectal cancer and nasopharyngeal cancer in recent studies [15].
Immune-inflammatory cell infiltration has also been described in thyroid cancers [1]. Cells associated with inflammation (N, P and L) are obtained from peripheral blood and are linked to progression in various tumour types [8]. SII is a parameter calculated using N, P and L values obtained from complete blood count, a routine, simple, and inexpensive test involving blood collected from the peripheral venous system [6]. Studies in recent years have investigated the novel inflammatory parameter SII in various malignancies and have observed correlation with several cancer types [5,7]. Geng et al. [16] described SII as an objective marker superior to indices such as PLR, and NLR. High N and P levels and low L levels produce an increase in SII, resulting in an increased inflammatory response and decreased immune response in cancer patients. High SII levels have an adverse impact on survival in several tumours [8].
The purpose of this study was to examine the relationship between DTCs and histopathological findings and SII values.

Methods

Ninety-three patients, 19 males and 74 females, undergoing total thyroidectomy after thyroid council evaluation following laboratory tests, imaging (thyroid ultrasonography, computed tomography, and scintigraphy) and ultrasound-guided fine-needle aspiration biopsy (FNAB) (performed by a radiologist or endocrinologist, using a 22 gauge needle and a 10-ml injector) and diagnosed with DTC at postoperative histopathological examination, between 2014 and 2019, were included in the study. Twelve men and 21 women, all healthy, presenting to our hospital for routine controls were enrolled as the control group.
The sample size was calculated based on SII levels, since the primary aim of the study was to identify possible change in SII. The estimated difference in SII levels was calculated based on our preliminary study. With 93 patients, the sample size for the control group was calculated as 33, based on a power of 99% and an alpha error of 85%, following the Russ Lenth Piface Java module.
Histopathological findings were examined retrospectively, and demographic characteristics such as age and sex were recorded. N, P and L values were obtained from preoperative complete blood count results, and the SII was calculated from these. Parameters such as the tumour histological type, perineural invasion capsule invasion, lymphovascular invasion, extrathyroidal extension, number of foci and tumour diameter were determined, and their relationships with the SII were investigated. SII values for the age- and sex-matched healthy control group were calculated from complete blood counts, and these were then compared with patient group SII values.

Patients with cardiac diseases such as congestive heart failure, heart valve disease, or myocardial infarction, with autoimmune diseases such as Hashimoto's thyroiditis or Behcet's disease, with white blood cells > 12,000/mL at complete blood count, findings suggestive of infection such as N > 70%, with haematological disease with haemoglobin levels < 12 g/dL or > 18 g/dL, or with sickle cell anaemia, coagulopathy such as Factor 5 Leiden mutation, or distant metastasis were excluded from the study.

Peripheral blood specimens collected from patients in the preoperative period and from the healthy controls were investigated using an automatic haematology analyser (Sysmex XN-1000™, Sysmex Europe GmbH, Japan), and complete blood counts were performed. N, P and L counts were recorded, and SII values were calculated from these values.

Statistical analysis was performed on SPSS 20.0 (IBM Corporation, New York, NY) software. Numerical data were expressed as mean ± standard deviation. Categorical data were analysed using the chi-square test, and numerical data using Student's t or the Mann Whitney U tests, depending on the data distribution characteristics, assessed using the Shapiro-Wilk test. Student's t test was applied in case of normal distribution, and the Mann Whitney U test in case of non-normal distribution. Correlation analysis was performed using the Pearson test. ROC analysis was also performed to estimate a cut-off point for discriminating between healthy individuals and patients with DTC. p values < 0.05 were regarded as statistically significant for all analyses.

Results

93 patients with DTC ranging in age from 17 to 79 years (47.5 ± 12.3) and a 33-member healthy control group ranging in age between 21 and 65 years (mean 44.1 ± 10.6) were included in the study. No significant age difference was determined between groups (p = 0.13). The patient group consisted of 19 men and 74 women, and the control group of 12 men and 21 women. No significant gender difference was seen between groups (p = 0.06). Average SII values were significantly higher, at 638.2 ± 255.8 × 10^9 cells/L, in the patient group than in the control group at 395.7 ± 120.3 × 10^9 cells/L (p = 0.000) (Tab. I).

Examination of the preoperative FNAB results revealed FTC or suspicion of FTC in 56, PTC in 15, benign cytology in 17, and atypical findings of unknown significance in 5. Postoperatively, PTC was detected in 84 patients following histopathological examination, and FTC in 9. Average SII values were 634.3 ± 247.4 × 10^9 cells/L in patients with PTC and 671.2 ± 338 × 10^9 cells/L in those with FTC. Pathological tumour diagnosis had no significant effect on SII (p = 0.70) (Tab. II).

Perineural invasion was positive in 2 patients with PTC, lymphovascular invasion in 5, capsular invasion in 17, and extrathyroidal extension in 5, while capsular invasion was observed in 5 patients with FTC. Due to the insufficient numbers of patients with perineural invasion, lymphovascular invasion and extrathyroidal extension, statistical analysis could not be performed. Capsular invasion was found to have no significant effects on average SII (p = 0.488).

Tumours were unifocal in 60 patients and multifocal in 33. Average SII values were 569.1 ± 280.1 × 10^9 cells/L in the unifocal patients and 745 ± 372 × 10^9 cells/L in the multifocal cases. The difference between these groups was statistically significant (p = 0.01) (Tab. II).

The minimum tumour diameter at histopathological examination was 0.1 cm and the maximum tumour diameter 7 cm. Correlation analysis revealed that tumour diameter had no significant effect on average SII levels (p = 0.563).

ROC analysis revealed a cut-off point for average SII of 454.5 × 10^9 cells/L with 72% sensitivity and 68% specificity in discriminating DTC from healthy individuals (Tab. III, Fig. 1).

Discussion

The present study investigated SII in DTCs, and revealed significantly higher mean SII values in cancer patients than in healthy individuals.

Studies concerning average SII cut-off values have reported differing results. Hu et al. [17] investigated the effect of aver-

Table I. Demographic characteristics of the study and control groups.

	Patients (n = 93)	Controls (n = 33)	p
Age		21-65 44.1 ± 10.6	0.13
Min-Max	17-79		
Mean ± SD	47.5 ± 12.3		
Gender (M/F)	19/74	12/21	0.06
SII	638.2 ± 2 55.8	395.7 ± 120.3	0.000*

** Statistically significant.*

Table II. Effect of histopathological diagnosis and multifocality on SII levels.

		SII	p
Histopathological diagnosis	PTC (n = 84)	634.3 ± 247.4	0.702
	FTC (n = 9)	671.2 ± 338	
Multifocality	Unifocal (n = 60)	569.1 ± 280.1	0.012*
	Multifocal (n = 33)	745 ± 372	

** Statistically significant. PTC: papillary thyroid carcinoma; FTC: follicular thyroid carcinoma; SII: Systemic inflammation index.*

Table III. ROC analysis.

Risk factor	AUC (95%)	Cut-off	p	Sensitivity (%)	Specifity (%)
SII	0.804 (0.715-0.892)	454.5	0.000	72.7	67.9

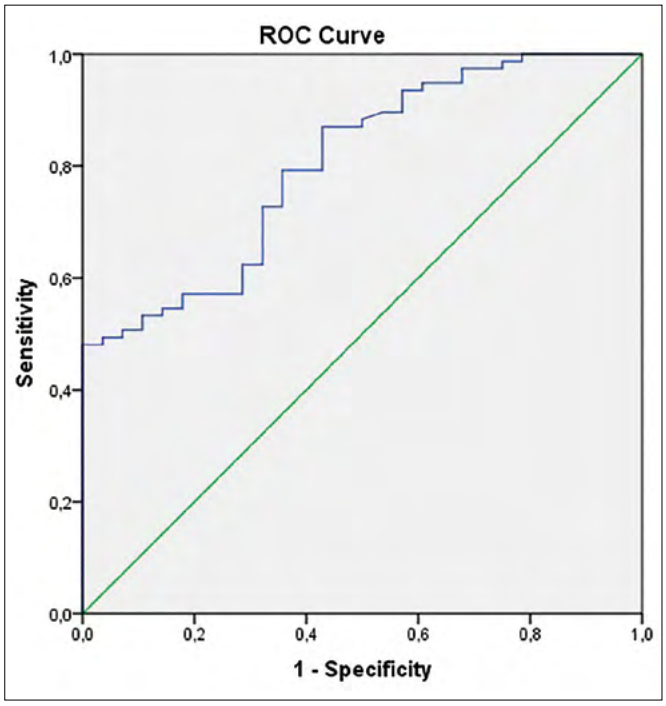

Figure 1. ROC analysis for discrimination between differentiated thyroid carcinomas and healthy individuals. The cut-off value was calculated as 454.5, with 72.7% sensitivity and 67.9% specificity.

age SII on prognosis in HCC and determined a cut-off value of 330 × 10^9 cells/L, reporting that SII ≥ 330 × 10^9 cells/L may be associated with poor prognosis. Chen et al. [18] investigated the usefulness of mean SII in predicting prognosis in patients with colorectal cancer, determined a cut-off value of 340 × 10^9 cells/L (85.7% sensitivity and 52.4% specificity), and described SII as the best predictor of long-term survival and recurrence. In another study, Li et al. [19] identified average SII as an independent prognostic factor in patients with laryngeal SCC. Those authors determined a cut-off value of 517.64 × 10^9 cells/L (66.2% sensitivity and 74.7% specificity). In their study of nasopharyngeal carcinoma, Zeng et al. [20] determined a cut-off value for average SII of 715.739 × 10^9 cells/L, and described SII as a valuable diagnostic and prognostic marker. In the present study, the average SII cut-off value for DTC patients was 454.5 × 10^9 cells/L (72% sensitivity and 68% specificity), and we concluded that values higher than this figure were significant to discriminate between patients with DTC and healthy individuals.

Oztürk et al. [13] investigated early stage SCC of the tongue and showed that high average SII values adversely affected both local recurrence and survival. In their study of SCC of the tongue, Deveci and Sürmeli [15] reported that perineural and lymphovascular invasion, an event of importance in cancer prognosis, was more common in patients with high average SII values, and that average SII was correlated with the extent of poor differentiation in these patients. In contrast, SII values had no effect on perineural, lymphovascular, capsular invasion, or extrathyroidal extension in patients with papillary and follicular thyroid cancer in the present research. Li et al. [6] described average SII as a powerful marker of tumour proliferation and one-year survival in elderly patients with a newly diagnosed with solid tumour. Those authors reported poor tumour differentiation and poor prognosis in patients with high average SII values compared to those with low values. The meta-analysis by Zhong et al. [8] also showed that average SII is a powerful marker of poor prognosis in patients with a solid tumour.

The principal limitation of the present study is the low number of patients exhibiting perineural invasion, capsular invasion, lymphovascular invasion and extrathyroidal extension. This represented a disadvantage in terms of statistical analysis of the relationship between average SII and these histopathological findings, and thus of its effect on prognosis. In addition, since postoperative follow-ups were not recorded, we were unable to draw any conclusions regarding preoperative average SII and disease prognosis. However, the principal aim of this study was to investigate whether average SII is a practicable marker in the diagnosis of DTC.

Further studies are needed to examine the effect of these histopathological findings and prognosis on average SII.

Conclusions

The results of the present study show that SII values are higher in DTC patients than in the healthy population. SII values can be used in differentiating patients with DTC from healthy individuals. However, further studies with larger patient groups are needed to examine the correlation between these values and tumour invasion, and their effect on tumour prognosis.

Acknowledgements

We want to thank to Mr. Carl Austin Nino Rossini for his precious contribution.

Conflict of interest statement

The authors declare no conflict of interest.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Authors' contributions

Conceptualisation: AK and AS. Data curation: AS, MSS, and AB. Formal analysis: AK and KK. Methodology: all authors. Project administration: AK, MSS, and AB. Visualisation: all authors. Writing – original draft: AK, AS, and KK. Writing – review editing: all authors.

Ethical consideration

Approval for this retrospective study was granted by the Ataturk University Medical Faculty Clinical Research Ethical Committee (No. B.30.2.ATA.0.01.00/247).

The research was conducted ethically, with all study procedures being performed in accordance with the requirements of the World Medical Association's Declaration of Helsinki. Written informed consent was obtained from each participant/patient for study participation and data publication.

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