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

INTRODUCTION
Despite the rarity of thyroid cancer, it remains the most common endocrine neoplasia, and the incidence is increasing ¹. Differentiated thyroid carcinomas
SII in differentiated thyroid cancers

(P/L) ratio (PLR) and the platelet (N)/lymphocyte (L) ratio (NLR) and the platelet
progression and inflammatory parameters such as the neu-
Various studies have shown a relationship between tumour
with the inflammatory response 7,9. 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 cel-
lar 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 investi-
gated the powerful association between cancer and inflam-
mation, and inflammatory cells have been reported to af-
fect 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 Helicobac-
ter 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 car-
cinoma, 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 de-
scribed in thyroid cancers 1. Cells associated with inflam-
mation (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 inexpen-
sive test involving blood collected from the peripheral ven-
ous 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 supe-
rior 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 be-
tween DTCs and histopathological findings and SII values.

Methods

Ninety-three patients, 19 males and 74 females, undergo-
ting total thyroidectomy after thyroid council evaluation fol-
lowing 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 postopera-
tive 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 sam-
ple 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 preopera-
tive complete blood count results, and the SII was calculat-
ed from these. Parameters such as the tumour histological
type, perineural invasion capsule invasion, lymphovascul-
ar 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 × 10⁹ cells/L, in the patient group than in the control group at 395.7 ± 120.3 × 10⁹ 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 × 10⁹ cells/L in patients with PTC and 671.2 ± 338 × 10⁹ 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 × 10⁹ cells/L in the unifocal patients and 745 ± 372 × 10⁹ 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 × 10⁹ 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-

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

|                       | Patients (n = 93) | Controls (n = 33) | p      |
|-----------------------|------------------|------------------|--------|
| **Age**               |                  |                  | 0.13   |
| Min-Max               | 17-79            | 21-65            |        |
| Mean ± SD             | 47.5 ± 12.3      | 44.1 ± 10.6      |        |
| Gender (M/F)          | 19/74            | 12/21            | 0.06   |
| SII                   | 638.2 ± 255.8    | 395.7 ± 120.3    | 0.000* |

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

|                          | Histopathological diagnosis | Multifocality                  |
|--------------------------|-----------------------------|--------------------------------|
|                          | PTC (n = 84)                | FTC (n = 9)                    |
|                          | 634.3 ± 247.4               | 671.2 ± 338                    |
|                          |                             |                                |
|                          | Unifocal (n = 60)           | Multifocal (n = 33)            |
|                          | 569.1 ± 280.1               | 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 (%) | Specificity (%) |
|-------------|-----------|---------|-----|-----------------|-----------------|
| SII         | 0.804     | 454.5   | 0.000 | 72.7            | 67.9            |

(0.715–0.892)

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.

determined a cut-off value for average SII of 715.739 × 10⁹ 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 × 10⁹ 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.

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Conflict of interest statement
The authors declare no conflict of interest.

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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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