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ORIGINAL PAPER

The relationship between urinary iodine levels and the systemic inflammatory index in patients with papillary thyroid carcinoma*

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Abstract

Iodine is a critical component of thyroid hormones, and its deficiency or excess can lead to various thyroid dysfunctions, including thyroid cancer. Papillary thyroid carcinoma (PTC) is the most common type of thyroid cancer. Despite this, the role of iodine, an essential micronutrient for thyroid function, in the pathophysiology and progression of PTC remains an area of active research. The systemic inflammatory index (SII), which includes parameters such as neutrophil, lymphocyte, and platelet counts, serves as a marker of systemic inflammation and has been associated with prognosis in several cancers. This article examines the relationship between urinary iodine levels (UIL) and the systemic inflammatory index in patients diagnosed with PTC, exploring potential implications for the disease. In this study, 121 patients with variously scheduled thyroidectomies were included. Before the procedure, the iodine content of each patient's urine was measured. Based on the findings of the post-operative pathology, the patients were divided into two groups. Thyroid histopathology resulted in the inclusion of benign (n=40) and PTC (n=81) cases in the study. In the post-operative period, the median urinary iodine excretion average was statistically higher in the group with malignant thyroid pathology compared to the benign pathology group. However, no statistical difference was found between the groups when classified according to iodine excretion. The performance of the Systemic Immune-Inflammation Index in predicting malignant pathology results was evaluated using a ROC curve analysis. The ROC curve demonstrated 58% sensitivity and 72.5% specificity at a cutoff point of >485. In conclusion, the findings suggest that the SII is an effective biomarker for assessing histopathology in thyroid surgeries. However, further studies are needed to validate these findings and explore the potential of SII in clinical settings.

Keywords: papillary thyroid carcinoma, median urinary iodine, systemic inflammatory index

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INTRODUCTION

Papillary thyroid carcinoma (PTC) is the most prevalent form of thyroid malignancy, comprising about 80% of all thyroid cancer cases. It is generally associated with a favorable prognosis due to its indolent nature and high survival rates (Nikiforov, Nikiforova 2011). However, the pathophysiological mechanisms underlying PTC development and progression are multifactorial, involving genetic, environmental, and dietary factors. Iodine, an essential micronutrient crucial for thyroid hormone synthesis, plays a significant role in thyroid health. Both iodine deficiency and excess have been implicated in thyroid dysfunctions and malignancies (Feldt-Rasmussen 2001, Liu et al. 2009, Kim et al. 2016, Sakafu et al. 2018). Recent research has highlighted the potential role of inflammation in cancer pathogenesis. Chronic inflammation can create a microenvironment conducive to tumor initiation, progression, and metastasis. The systemic inflammatory index (SII), which combines neutrophil, lymphocyte, and platelet counts, is an emerging biomarker for systemic inflammation and has been associated with prognosis in various cancers (Yang et al. 2018). This article aims to explore the relationship between urinary iodine levels (UIL) and SII in patients with PTC, providing a comprehensive analysis of their potential interplay and implications for disease management.

MATERIALS AND METHODS

This retrospective cohort study included 121 patients diagnosed with thyroid nodules who were admitted to the outpatient clinic for endocrinology and metabolic diseases at a tertiary care center between 2014 and 2024 and required surgery. Inclusion criteria were histologically confirmed PTC, availability of complete clinical and laboratory data, and no prior history of other malignancies or chronic inflammatory diseases. Exclusion criteria included recent thyroid surgery, radiation therapy, or use of medications affecting iodine metabolism or inflammatory markers. This study was submitted to the Ethics Committee of Trakya University Faculty of Medicine and received ethics committee approval in 2024 with the decision TUTF-GOBAEK 2024/316.

Measurement of urinary iodine levels

Urinary iodine concentration (UIC) was measured using a standardized spectrophotometric method. Spot urine samples were collected from each patient and analyzed for iodine content. To account for variations in urinary output, UIC was normalized to urinary creatinine concentration, expressed as μg iodine g^{-1} creatinine. Patients were categorized into three groups based on UIL: iodine deficiency (<100 μg g^{-1} creatinine), iodine sufficiency

(100-199 μg g^{-1} creatinine), and iodine excess (≥200 μg g^{-1} creatinine). The patients' drug use, iodized salt intake, and sociodemographic traits were noted for each patient who was referred for surgery. Excluded from the study were patients with kidney failure, pregnancy, usage of medications that interfere with thyroid hormone metabolism, and pharmaceuticals and substances similar to iodine-containing prenatal vitamins. They were also patients who had undergone iodine-containing contrast material examination during the previous six months. Spot urine samples were collected in the morning, and thyroid function tests were assessed in every case. Urine was transferred into test tubes that had been deiodinated, sealed with paraffin, and kept at +4 C in a box that was protected from light until it was time for the iodine analysis. The International Council for Control of Iodine Deficiency Disorders (ICCIDD) approved a calorimetric seric arsenic acid solution for the manual Sandell-Kolthoff reaction measurement of urine iodine levels (Li, Eastman 2012).

Calculation of systemic inflammatory index

The systemic inflammatory index was calculated using the formula: SII = (neutrophil count × platelet count) / lymphocyte count. Complete blood counts were obtained from routine preoperative blood tests. The SII was analyzed as a continuous variable and categorized into quartiles for subgroup analyses.

Statistical analysis

Descriptive statistics were used to summarize patient demographics, clinical characteristics, UIL, and SII. Various demographic and clinical characteristics were compared between the groups with thyroid benign and malignant pathology results for continuously distributed variables that showed normal distribution. The conformity of quantitative data to normal distribution was examined using the Shapiro-Wilk test. Student's *t*-test was used for continuously distributed variables with normal distribution, the Mann-Whitney *U* test for non-normally distributed variables, and the Chi-Square test for categorical variables. Spearman correlation analysis was used to examine the relationships between variables. ROC analysis was performed to examine the ability of SII values to distinguish patients with malignant pathology results. A p-value of <0.05 was considered the threshold for statistical significance.

RESULTS AND DISCUSSION

In this study, various demographic and clinical characteristics were compared between the groups with benign (n=40) and malignant (n=81) pathology results, and the results are presented in Table 1. The mean age of patients

Table 1

The demographic and clinical characteristics of patients

Variables		Pathology results: benign (n=40)	Pathology results: malign (n=81)	p
Age (years)		49.08 ± 10.42	47.88 ± 11.73	0.585 *
BMI (kg cm^{-2})		28.86 ± 5.46	26.62 ± 3.93	0.281 *
Gender (female)		37 (92.5)	66 (81.48)	0.109 **
Median urinary iodine (μg g^{-1} creatinine)		153.70 ± 105.43	183.19 ± 97.15	**0.043** ***
Fasting blood glucose (mg dl^{-1})		99.97 ± 16.79	103.96 ± 20.62	0.138 ***
SII		439.21 ± 166.57	563.73 ± 278.64	**0.010** ***
MUI (μg g^{-1} creatinine)	<100	13 (32.50)	18 (22.22)	0,094 **
	100-199	19 (47.50)	31 (38.27)	
	≥200	8 (20)	32 (39.50)	
BMI (kg cm^{-2})	normal	12 (30)	14 (17.28)	0,272 **
	overweight	14 (35)	32 (39.50)	
	obesity	14 (35)	35 (43.22)	
Diabetes mellitus (+)		5 (12.5)	13 (16.05)	0.606 **
Pathological lymphocytic thyroiditis (+)		15 (37.50)	47 (58.02)	**0.034** **
Anti-TG (+)		11 (27.50)	33 (40.74)	0.154 **
Anti-TPO (+)		11 (27.50)	37 (45.68)	0.054 **

* Student's t test, ** Chi-Square Test, *** Mann-Whitney U Test, BMI – body mass index, MUI – median urinary iodine, SII – systemic inflammatory index, Anti- TG – Anti thyroglobulin, Anti- TPO – anti thyroid peroxidase

in the benign group was 49.08 ± 10.42 years, while in the malignant group, it was 47.88 ± 11.73 years (p=0.585). The BMI was 28.86 ± 5.46 kg m^{-2} in the benign group and 26.62 ± 3.93 kg m^{-2} in the malignant group (p=0.281). In the benign group, 92.5% were female, compared to 81.48% in the malignant group (p=0.109). The median urinary iodine level was significantly higher in the malignant group (183.19 ± 97.15 μg L^{-1}) compared to the benign group (153.70 ± 105.43 μg L^{-1}, p=0.043). The SII was significantly higher in the malignant group (563.73 ± 278.64) compared to the benign group (439.21 ± 166.57, p=0.010). The presence of pathological lymphocytic thyroiditis was significantly higher in the malignant group (58.02%) compared to the benign group (37.50%, p=0.034). These results highlight significant differences in urinary iodine levels, SII, and the presence of pathological lymphocytic thyroiditis between patients with benign and malignant thyroid pathology, suggesting potential diagnostic markers for distinguishing between these conditions.

Table 2 displays the Spearman correlation coefficients (r) and the corre-

Table 2

Spearman correlation analysis results between variables

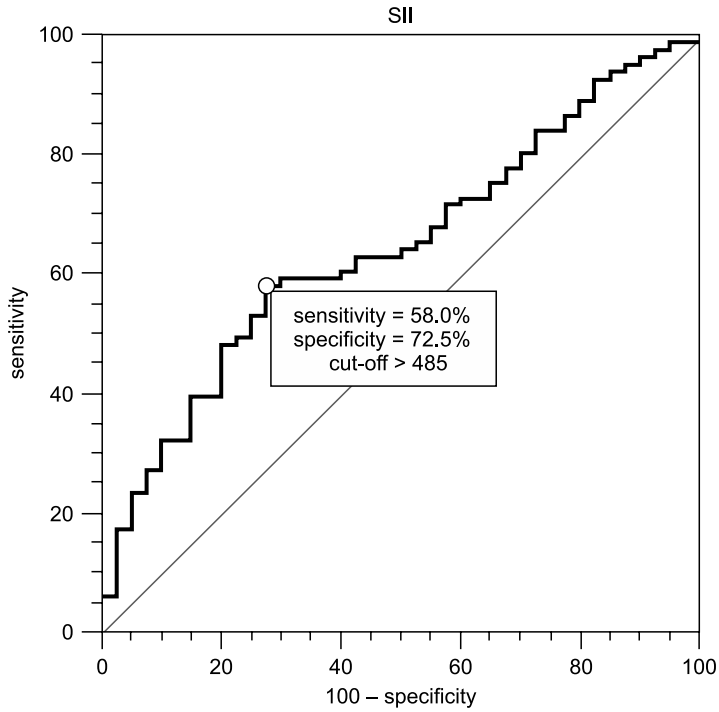
Specification		Pathology results	Age	BMI	Gender	MUI	FBG	SII	DM	PLT	Anti-TG	Anti-TPO
Pathology results	*r*	1.000	-.064	.118	.146	.184	.135	.235	.047	.193	.129	.175
	p	.	.486	.199	.111	**.043**	.139	**.010**	.609	**.034**	.157	.055
Age	*r*	-.064	1.000	.286	.187	.082	.384	-.119	.152	.012	-.033	.073
	p	.486	.	**.001**	**.040**	.371	**.000**	.194	.096	.899	.718	.426
BMI	*r*	.118	.286	1.000	.009	.004	.247	.066	.112	.061	-.014	.082
	p	.199	**.001**	.	.922	.969	**.006**	.474	.220	.507	.881	.371
Gender	*r*	.146	.187	.009	1.000	.217	.151	.027	.086	-.103	-.171	-.007
	p	.111	**.040**	.922	.	**.017**	.099	.767	.347	.260	.060	.942
MUI	*r*	.184	.082	.004	.217	1.000	-.148	.025	-.090	.016	-.025	-.012
	p	**.043**	.371	.969	**.017**	.	.106	.788	.324	.863	.787	.893
Fasting blood glucose	*r*	.135	.384	.247	.151	-.148	1.000	.084	.579	.062	.071	.131
	p	.139	**.000**	**.006**	.099	.106	.	.360	**.000**	.501	.440	.152
SII	*r*	.235	-.119	.066	.027	.025	.084	1.000	.114	.029	.000	-.053
	p	**.010**	.194	.474	.767	.788	.360	.	.212	.749	.996	.566
DM	*r*	.047	.152	.112	.086	-.090	.579	.114	1.000	-.010	-.026	.041
	p	.609	.096	.220	.347	.324	**.000**	.212	.	.910	.774	.657
PLT	*r*	.193	.012	.061	-.103	.016	.062	.029	-.010	1.000	.737	.791
	p	**.034**	.899	.507	.260	.863	.501	.749	.910	.	**.000**	**.000**
Anti-TG	*r*	.129	-.033	-.014	-.171	-.025	.071	.000	-.026	.737	1.000	.581
	p	.157	.718	.881	.060	.787	.440	.996	.774	**.000**	.	**.000**
Anti-TPO	*r*	.175	.073	.082	-.007	-.012	.131	-.053	.041	.791	.581	1.000
	p	.055	.426	.371	.942	.893	.152	.566	.657	**.000**	**.000**	.

PLT – pathological lymphocytic thyroiditis, FBG - fasting blood glucose, DM – diabetes mellitus, BMI – body mass index, MUI – median urinary iodine, SII – systemic inflammatory index, Anti- TG – Anti thyroglobulin, Anti- TPO – anti thyroid peroxidase, *r* – Spearman's correlation coefficient, values range between +1 and -1; +1 indicates a perfect positive correlation, -1 indicates a perfect negative correlation, and 0 indicates no correlation; *p* – statistical significance value, $p<0.05$ indicates that the correlation is significant at the 95% confidence level, $p<0.01$ indicates significance at the 99% confidence level, *N* – sample size, which is 121 in this study

sponding p-values for the relationships between various clinical and demographic variables in patients with different thyroid pathology results. There was a significant positive correlation between the pathology results and Median Urinary Iodine – MUI (r=0.184, p=0.043). The Systemic Immune--Inflammation Index (SII) showed a significant positive correlation with pathology results (r=0.235, p=0.010). Pathological lymphocytic thyroiditis had a significant positive correlation with pathology results (r=0.193, p=0.034). Age was significantly positively correlated with BMI (r=0.286, p=0.001). There was a significant positive correlation between age and fasting blood glucose (r=0.384, p=0.000). Age also showed a significant positive correlation with gender (r=0.187, p=0.040). BMI had a significant positive correlation with fasting blood glucose (r=0.247, p=0.006). Gender was significantly positively correlated with MUI (r=0.217, p=0.017).

The performance of the SII in predicting malignant pathology results was evaluated using the ROC curve analysis. The ROC curve demonstrated 58% sensitivity and 72.5% specificity at a cutoff point of >485. The area under the curve (AUC) was 0.644, with a standard error of 0.051. This result indicates that the AUC is statistically significant (p=0.010) and that the SII has moderate diagnostic accuracy in distinguishing patients with malignant pathology results. The 95% confidence interval for the AUC ranged from 0.544 to 0.744, suggesting that the SII is a moderately effective biomarker for this purpose (Figure 1). Further studies are needed to validate these findings and to explore the potential of SII in clinical settings.

The findings of this study underscore a significant inverse relationship between urinary iodine levels and systemic inflammatory index in patients with papillary thyroid carcinoma. Iodine is a critical component of thyroid hormones, thyroxine (T4) and triiodothyronine (T3), which regulate numerous physiological processes, including metabolism, growth, and development. Adequate iodine intake is essential for normal thyroid function, while both deficiency and excess can lead to thyroid abnormalities. Iodine deficiency is a well-established risk factor for goiter and hypothyroidism, conditions that can predispose to thyroid nodules and malignancies (Feldt-Rasmussen 2001, Zimmermann, Boelaert 2015, Köhrle 2023). Conversely, excessive iodine intake can induce thyroid dysfunctions, including hyperthyroidism and thyroiditis, potentially contributing to thyroid cancer risk (Zhang et al. 2022). In our study, median urinary iodine excretion was found to be statistically higher in cases with papillary thyroid cancer after thyroid surgery than those with benign pathology. However, although the frequency of subgroup analysis was classified according to statistical iodine excretion and the number of patients with malignant grouping range and iodine excretion was high, no statistical significance was found. However, there was a significant positive correlation in Spearman correlation between pathology results and MUI (r=0.184, p=0.043). A comprehensive review and meta-analysis evaluated case-control studies on UIC and PTC. The findings indicated that excessive iodine intake (UIC≥300 μg L^{-1}) is significantly associated with an increased



Area under the curve

test result variable(s): SII

area	standard error	*P*	asymptotic 95% confidence interval: lower bound	asymptotic 95% confidence interval: upper bound
0.644	0.051	0.010	0.544	0.744

Fig. 1. ROC curve analysis of the Systemic Immune-Inflammation Index (SII) in predicting malignant pathology

risk of PTC. Conversely, adequate iodine intake (100≤UIC<200 μg L^{-1}) may provide a protective effect against PTC. However, no significant relationship was found between insufficient iodine intake (UIC<100 μg L^{-1}) or iodine levels above requirements (200≤UIC<300 μg L^{-1}) and PTC incidence. This suggests that while very high iodine levels may increase PTC risk, moderate levels may be beneficial (Zhang et al. 2022). A study conducted in South Korea explored the dietary and urinary iodine status of PTC patients compared to healthy controls. This research found that higher urinary iodine levels were significantly associated with the presence of central lymph node metastasis (CLNM) in PTC patients. This indicates that high iodine intake is not only a risk factor for developing PTC, but it may also influence the severity and metastatic potential of the cancer (Lee et al. 2018). Chronic inflammation is a recognized hallmark of cancer, playing a crucial role in tumorigenesis,

progression, and metastasis. Inflammatory cells and cytokines in the tumor microenvironment can promote genetic instability, angiogenesis, and tumor growth. The systemic inflammatory index, incorporating neutrophil, lymphocyte, and platelet counts, reflects the balance between pro-inflammatory and anti-inflammatory factors in the body (Tian et al. 2022, Zenget al. 2022, Meng et al. 2023, Tabakoglu, Celik 2024). The Systemic Immune-Inflammation Index (SII) has been explored in numerous studies as a prognostic marker for various types of cancer. A meta-analysis encompassing a broad range of cancer types demonstrated that a high SII is significantly associated with poor overall survival (OS). Specifically, high SII levels were correlated with a hazard ratio (HR) of 1.69 for OS, indicating a markedly higher mortality risk than those with lower SII levels. The analysis showed significant predictive power for cancers such as hepatocellular carcinoma, gastric cancer, esophageal squamous cell carcinoma, urinary tract cancer, and non-small cell lung cancer (Yang et al. 2018). While there are many studies evaluating the SII's role in various cancers, specific research on its relationship with papillary thyroid cancer (PTC) is less common. However, the general findings regarding SII's prognostic value can be extrapolated to suggest its potential relevance in PTC. High SII has been associated with worse outcomes in cancers characterized by inflammatory and immune responses, which may include PTC given its pathophysiological mechanisms (Zhanget al. 2021, Vural et al. 2023). In our study, although the relationship between urinary iodine excretion and SII was not statistically significant, it was found that both cases had a positive correlation with thyroid pathology. In particular, SII was found to be statistically higher in cases with malignant thyroid pathology than in benign cases. By calculating the sensitivity and specificity, which is meaningful in the current situation, the cut-off value was found to be >485 for SII.

CONCLUSIONS

This study demonstrates a significant relationship between papillary thyroid carcinoma (PTC), urinary iodine levels, and the systemic inflammatory index (SII). Median urinary iodine (MUI) levels are not associated with higher systemic inflammation. These findings underscore the importance of maintaining adequate iodine nutrition in PTC patients while avoiding excessive iodine supplementation. Additionally, the results highlight the potential therapeutic implications of targeting systemic inflammation in PTC management. Further research is required to validate these findings and to investigate the underlying mechanisms and clinical benefits of iodine supplementation and anti-inflammatory interventions in the management of PTC.

Author contributions

Conceptualization – MC, NTT, EC, BYB, BA, MO, SYC, BE, sample collection – MC, NTT, EC, BYB, BA, MO, SYC, BE, data analyses – MC, NTT, EC, BYB, BA, MO, SYC, BE, data interpretation – MC, NTT, EC, BYB, BA, MO, SYC, BE, writing – original draft – MC, NTT, EC, BYB, BA, MO, SYC, BE, critical review of the manuscript – all the authors, validation – all the authors. All the authors have read and agreed to the published version of the manuscript.

Conflicts of interest

No conflict of interest exists. The authors have no relevant financial or nonfinancial interests to disclose, and agreed to the published version of the manuscript.

Ethics declarations

The Ethics Committee of Trakya University Faculty of Medicine granted approval for the collection of the samples (No: TUTF-GOBAEK 2024/316).

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