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Original Article

Are systemic inflammatory markers linked to euthyroid nodular goiter?

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Abstract

The role of systemic inflammatory markers (SIMs) in euthyroid nodular goiter (ENG) is unclear. This study evaluated their associations and predictive value for ENG in iodine-sufficient adults. Material and methods: In this prospective, case-control study, 212 euthyroid participants (20–60 years) underwent thyroid ultrasound. Laboratory evaluations included thyroid-stimulating hormone, free thyroxine, anti-thyroid peroxidase antibodies, C-reactive protein, and blood cell counts. Neutrophil-to-lymphocyte ratio (NLR), lymphocyte-to-monocyte ratio (LMR), platelet-to-lymphocyte ratio (PLR), systemic inflammation response index (SIRI), and the systemic immune-inflammation index (SII) were calculated, with logarithmic SIRI [log (SIRI)] and square root SII [sqrt (SII)] transformations. Logistic regression and receiver operating characteristic (ROC) curve analysis were applied. Results: Mean age was 43±9 years (83% female). ENG (n=103) and controls (n=100) did not differ in age, thyroid function, autoimmunity, or SIMs. Age correlated with ENG (ρ=0.148, P=0.032). Log (SIRI) (positive) and sqrt (SII) (inverse) were independent ENG predictors. ROC analysis confirmed log (SIRI) as the strongest, gender-independent predictor of ENG (an area under the curve=0.675, P<0.001; cut-off >0.760). SIRI was the strongest, gender-independent predictor of ENG, while SII was inversely associated.

Keywords: goiter, nodular, inflammation, markers, C-reactive protein

Introduction

Euthyroid nodular goiter (ENG) is defined by single or multiple structural abnormalities in a normally functioning thyroid gland [1, 2]. Ultrasound detection rates range from 19% to 68% [3]. Its prevalence increases with age and is higher in females [1, 4]. Besides causing compressive symptoms, ENG carries a 7–15% malignancy risk [1]. Etiology is multifactorial, involving genetic, environmental, autoimmune, and nutritional factors. Prevalence depends on iodine status, exceeding 30% in severely deficient areas [4]. Its incidence is

increasing even in iodine-sufficient regions, likely due to improved imaging and metabolic or environmental changes [5].

The immune system affects the pathogenesis and progression of thyroid diseases. Systemic inflammatory markers (SIM) including neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and systemic immune-inflammation index (SII), have shown potential in differentiating benign from malignant thyroid disorders, particularly papillary thyroid carcinoma (PTC) [6, 7]. NLR, PLR, SII, and the lymphocyte-to-monocyte ratio (LMR) are associated with the risk and severity of various benign disorders [8]. Higher NLR and PLR indicate immune dysregulation in euthyroid Hashimoto patients [9]. Elevated PLR, NLR, C-reactive protein (CRP), and interleukin-27 (IL-27) have been reported in thyroid adenomas and differentiated thyroid carcinoma (DTC) [10]. Recently, the systemic inflammation response index (SIRI) has emerged as a potential prognostic biomarker in thyroid carcinoma (TC) and other malignancies [11].

The role of SIMs in TC is well established, but their association with ENG remains insufficiently explored. This prospective study aims to: 1) compare demographics, thyroid function, blood cell counts, and SIMs between the ENG and control groups; 2) examine SIM associations with thyroid nodules in euthyroid, age-matched, iodine-sufficient individuals; 3) identify potential inflammatory predictors of ENG; and 4) determine the most accurate predictors based on optimal cut-off values by receiver operating characteristic (ROC) curve analysis.

Material and methods

This prospective, cross-sectional, case-control study was conducted at a secondary center in Bitola, North Macedonia, from October 2023 to March 2025. A total of 212 euthyroid adults (20–60 years) from an iodine-sufficient region were randomly selected and provided written informed consent [12]. Ethics approval was obtained from the Ethics Committee for Human Research at the Faculty of Medicine, University St. Cyril and Methodius in Skopje, North Macedonia (permission number 03-3951/3, 27th September 2022), and the study adhered to the Declaration of Helsinki. Exclusion criteria were: a history of thyroid surgery, hypo- or hyperthyroidism, TC, or pregnancy. Medication use was recorded via a questionnaire. Thyroid ultrasonography was performed by a trained examiner using a 10 MHz linear transducer (L40, RAMZED RZ-VD6, China). The ENG group comprised 103 individuals with nodules ≥5 mm, classified according to the European Thyroid Imaging Reporting and Data System (EU-TIRADS) (grades 2–5). Those with suspicious features underwent fine-needle aspiration biopsy to exclude TC [13]. The control group included 109 participants with normal thyroid parenchyma.

Blood samples were obtained between 7:30 AM and 10:00 AM following a 12-hour fast. Thyroid function was assessed via thyroid-stimulating hormone (TSH; 0.4–4.0 μIU/mL), free thyroxine (fT4; 9.0–24.7 pmol/L), and thyroid peroxidase antibodies (TPOAb; <35 mIU/mL) using an immunoluminescent analyzer (IMMULITE 2000, Siemens Corporation, Germany). CRP (mg/L) was measured photometrically on the Abbott Alinity ci analyzer (Abbott Corporation, China). Complete blood counts, including neutrophils (NE), lymphocytes (LY), monocytes (MO), and platelets (PLT), were obtained with an automated hematology analyzer SYSMEX XP-300 (Japan/Germany). The following inflammatory indices were calculated: NLR=NE/LY, LMR=LY/MO, PLR=PLT/LY, SIRI=(NE×MO)/LY, and SII=(NE×PLT)/LY.

Statistical analysis

Statistical analysis was performed using MedCalc Statistical Software version 22.002 (MedCalc Software Ltd, Ostend, Belgium). Data normality was determined with the Kolmogorov–Smirnov test. Continuous variables are reported as mean±standard deviation (SD), and categorical variables as counts and percentages. Group comparisons were conducted using the independent samples t-test for normally distributed data or the Mann–Whitney U test for normally distributed data, and the Pearson chi-squared (χ^2) test for categorical variables. Associations between variables and thyroid nodule presence were evaluated using Spearman's correlation coefficient (ρ). Due to right-skewed distribution, SIRI was logarithmically transformed [log (SIRI)], and SII was square root transformed [sqrt (SII)] to reduce skewness and meet assumptions for parametric analysis. Variables associated with ENG at $P<0.6$ were entered into a multivariate logistic regression to identify independent predictors while minimizing multicollinearity. To reduce age-related confounding, groups were age-matched, and residual regression was applied to age-adjusted inflammatory markers before their inclusion in the logistic regression model. ROC curve analysis assessed optimal cut-off values and predictive performance (AUC, sensitivity, specificity,

Youden index) of age and inflammatory markers for ENG, including gender-specific ROC analyses for log (SIRI) compared with sqrt (SII). Statistical significance was set at $P<0.05$.

Results

Participants had a mean age of 43.43±9.08, with 83% female. The ENG group comprised 89.3% females, compared with 77.1% in the control group, with males markedly predominant in the control group (P=0.018). Elevated TPOAb above 35 mIU/mL was observed in 12 participants per group (11.7% *vs.* 11.0%; P=0.883). The mean nodule size was 10.38±5.75 mm, with 54.4% having a single nodule, 12.6% two, 19.4% three, and 13.6% four or more (up to eight).

As presented in Table 1, the groups were age-matched with no significant differences in thyroid function, blood counts, or SIMs (all $P>0.05$). Age showed a significant positive correlation with nodule presence ($\rho=0.148$, P=0.032), whereas thyroid function and SIMs exhibited no significant associations (ρ range: –0.078 to 0.058; all $P>0.05$).

The logistic regression model presented in Table 2 identified log (SIRI) and sqrt (SII) as independent predictors of ENG, with log (SIRI) positively and sqrt (SII) inversely associated with nodule presence. CRP showed borderline significance (P=0.054), while age and NLR were non-significant.

Table 1: Comparison and correlation of age, thyroid function tests, blood cell counts, and systemic inflammatory markers between the study groups.

Variables	Nodule group (n=103)	Control group (n=109)	Comparison	Correlation	
			P-value	ρ	P-value
Age (years)	44.54±9.67	42.38±8.39	0.082	0.148	0.032
TSH (mIU/L)	1.74 (1.14 to 2.66)	1.94 (1.42 to 2.56)	0.258	-0.078	0.259
fT4 (pmol/L)	13.10 (12.20 to 14.90)	13.40 (11.80 to 15.10)	0.858	-0.012	0.860
Neutrophils ($\times10^9$/L)	3.37 (2.80 to 4.62)	3.50 (2.71 to 4.51)	0.980	-0.002	0.980
Lymphocytes ($\times10^9$/L)	2.03 (1.72 to 2.33)	2.07 (1.79 to 2.45)	0.330	-0.066	0.335
Monocytes ($\times10^9$/L)	0.46 (0.39 to 0.60)	0.50 (0.40 to 0.61)	0.345	-0.066	0.341
Platelets ($\times10^9$/L)	257 (225 to 318)	269 (229 to 317)	0.616	-0.035	0.615
CRP (mg/L)	1.40 (0.70 to 3.20)	1.40 (0.60 to 2.95)	0.591	0.036	0.598
NLR	1.75 (1.29 to 2.23)	1.60 (1.30 to 2.14)	0.409	0.057	0.412
LMR	4.22 (3.36 to 4.98)	4.33 (3.53 to 4.96)	0.859	-0.012	0.857
PLR	128.93 (108.24 to 170.62)	128.18 (101.29 to 157.84)	0.401	0.058	0.405
SIRI ($\times10^9$/L)	0.84 (0.56 to 1.26)	0.86 (0.55 to 1.20)	0.940	0.005	0.942
SII ($\times10^9$/L)	479.13 (331.30 to 595.58)	439.36 (329.38 to 640.08)	0.710	0.025	0.718

Note: The results are expressed as: mean±standard deviation (SD); median; interquartile range (25^{th} to 75^{th} percentile). ρ – Spearman correlation coefficient; TSH – thyroid-stimulating hormone; fT4 – free thyroxine; CRP – C-reactive protein; NLR – neutrophil-to-lymphocyte ratio; LMR – lymphocyte-to-monocyte ratio; PLR – platelet-to-lymphocyte ratio; SIRI – systemic inflammation response index; SII – systemic immune-inflammation index.

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Table 2: Multivariable logistic regression analysis of age, CRP, and systemic inflammatory indices in the detection of predictors for the occurrence of thyroid nodules.

Variable	B	SE	Wald	Odds ratio	95% CI for OR	P-value
Age	0.028347	0.0158	3.2171	1.0288	0.09974 to 1.0611	0.073
Log (SIRI)	13.19395	5.7301	5.3017	5.37E+05	7.1193 to 40.5E+009	0.021
Sqrt (SII)	-0.42859	0.1907	5.0493	0.6514	0.4482 to 0.9467	0.025
CRP	0.023516	0.0384	0.3745	1.0238	0.9495 to 1.1039	0.054
NLR	0.30937	0.4548	0.4627	1.3626	0.5587 to 3.3229	0.496

Note: B – regression coefficient; SE – standard error; OR – odds ratio; CI – confidence interval; CRP – C-reactive protein; NLR – neutrophil-to-lymphocyte ratio; log (SIRI) – logarithmically-transformed Systemic inflammation response index; sqrt (SII) – square root-transformed Systemic immune-inflammation index.

ROC analysis depicted in Figure 1, showed log (SIRI) as the strongest predictor of thyroid nodules (AUC=0.675, P<0.001; cut-off >0.76; Youden index=0.328), with moderate accuracy. Age was a weaker predictor, while other markers were non-predictive. Gender-stratified analysis revealed comparable accuracy in males (AUC=0.696) and females (AUC=0.687; P=0.937), confirming the gender-independent value of log (SIRI).

As shown in Figure 2, log (SIRI) showed the highest predictive accuracy for thyroid nodule presence (AUC=0.675, P<0.001), whereas sqrt (SII) demonstrated limited discrimination (AUC=0.514, P=0.718). The AUC

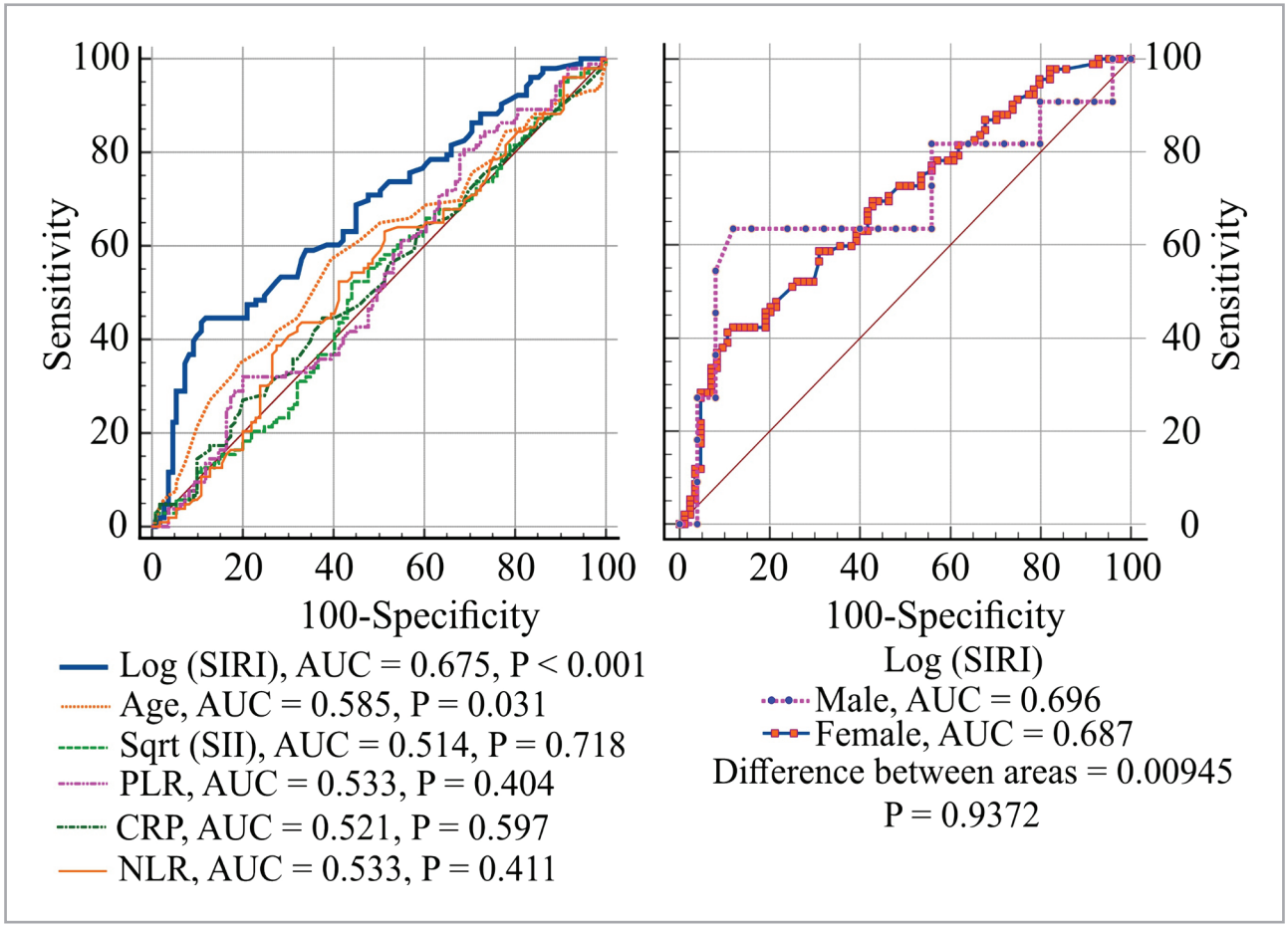

Figure 1: Receiver operating characteristic curve analysis of age and systemic inflammatory markers for predicting thyroid nodule presence with gender-specific analysis of log (SIRI). Log (SIRI) – logaritmically-transformed Systemic inflammation response index; NLR – Neutrophil-to-Lymphocyte Ratio; PLR – Platelet-to-Lymphocyte Ratio; CRP – C-reactive protein; Sqrt (SII) – square root-transformed Systemic immune inflammation index; AUC – Area Under the Receiver Operating Characteristic Curve.

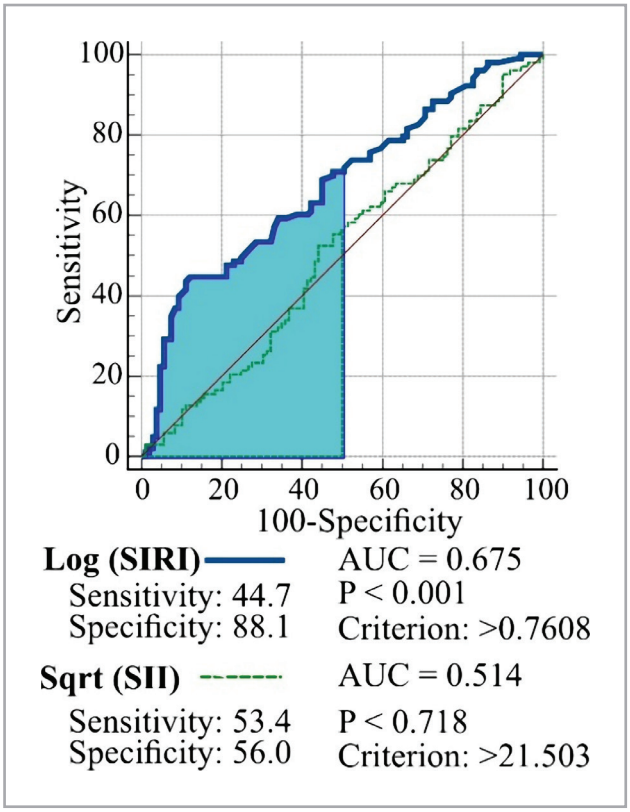

Figure 2: Receiver operating characteristic (ROC) curve analysis of log (SIRI) and sqrt (SII) for predicting thyroid nodule presence. Log (SIRI) – logaritmically-transformed Systemic inflammation response index; Sqrt (SII) – square root-transformed Systemic immune inflammation index; AUC – Area under the curve.

difference between log (SIRI) and sqrt (SII) was significant (P=0.039), confirming the superior predictive value of log (SIRI) for ENG occurrence.

Discussion

This study is among the few to evaluate SIMs in relation to ENG in an age-matched, iodine-sufficient population. Women outnumbered men by 8.36:1, consistent with previous findings, [1, 4] likely reflecting estrogen's influence on estrogen receptors (ER) α and β. Differences in their expression and the ER-α/ER-β ratio influence thyrocyte proliferation [14]. Estrogen-driven signaling pathways further contribute to the development of thyroid nodules [15].

The groups were age-matched, but rising age within this middle-aged cohort remained positively associated with ENG, consistent with evidence that thyroid nodule prevalence increases with advancing age [1–3]. This trend may reflect environmental influences and previous iodine deficiency, which may elevate TSH levels and stimulate thyrocyte proliferation [4, 6] through p70S6K-mediated p27 modulation and increased cyclic adenosine monophosphate (cAMP) – protein kinase A (PKA) - cAMP response element binding protein (CREB) signaling [15].

The average nodule size was around 10 mm, aligning with the results reported by Moon *et al.* [16]. More than half of the ENG patients presented with a solitary thyroid nodule, similar to the 49.7% prevalence documented by Xu *et al.* (49.7%) [17]. Multinodular goiter occurred in 46.5% of cases, mainly among females, consistent with the observations of Yan *et al.* [18].

TSH and fT4 were not associated with the presence of ENG. Conversely, Liu *et al.* reported higher TSH levels in individuals with nodules [19]. Reduced fT4 in ENG group aligns with Li *et al.* [20]. Thyroid autoimmunity showed no link to nodules consistent with Chen *et al.* [20]. Variations in findings may reflect differences in sample size, iodine intake, environmental risks, or diagnostics, warranting further research.

Blood cell counts and SIMs showed no relationship with ENG presence (all P>0.05). In contrast, Li *et al.* report a positive association between systemic inflammation, reflected by higher NE, LY, MO, LMR, and monocyte-to-/HDL cholesterol ratio (MHR), and thyroid nodules, suggesting inflammation may reduce thyroid hormone synthesis and indirectly raise TSH, promoting thyrocite growth [21]. Similarly, Liu *et al.* reported MHR strongly associated with nodule presence and size, independent of gender [22].

CRP, a classic inflammatory marker raised in infections, rheumatic disease [22], and vascular calcification [23], showed only borderline prognostic value for ENG (P=0.054), consistent with Pearce *et al.* [24]. Although Czarnywojtek *et al.* reported higher CRP in thyroid dysfunction [25], and Zhang *et al.* identified it as a preoperative inflammatory marker in DTC [10], our findings suggest limited diagnostic value of CRP for ENG.

NLR showed no significant association with ENG and restricted diagnostic performance. In contrast, Kocer *et al.* proposed NLR for differentiating benign from malignant nodules, with elevated NLR in cancer patients reflecting systemic inflammation or immune suppression [6]. Teketelew *et al.* found NLR superior to PLR in distinguishing benign from malignant thyroid lesions (AUC: 0.75) [26]. Conversely, Liu *et al.* reported no link with DTC progression or age-related differences in NLR values [27]. PLR and LMR were unrelated to ENG in our cohort, though Offi *et al.* identified LMR as predictive of malignancy in indeterminate nodules [28]. These findings underscore the inconsistent role of inflammatory indices in benign ENG.

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SIRI was linked to poor overall survival in various cancers with potential as a universal prognostic biomarker [11]. Riza *et al*. found SIRI, NLR, PLR, LMR, SII, and the systemic inflammation–activation index (SIAI) linked to multifocality, tumor growth, and metastasis in DTC, showing significant differences between nodules with atypia of undetermined significance (AUS) with benign *versus* malignant histopathology (P<0.001) [29]. These findings suggest such markers have potential in predicting malignancy in indeterminate thyroid nodules.

For clarity, in the following discussion, SIRI and SII refer to the original variables, although logarithmic and square root transformations were applied for data normalization. Logistic regression identified SIRI and SII as independent predictors of ENG, with SIRI showing the strongest diagnostic performance. Elevated SIRI increased nodule risk, linking systemic inflammation to tumorigenesis, whereas higher SII was inversely related, reflecting the complex role of immune balance in benign ENG. Similarly, Cao *et al*. reported SII and the aggregate index of systemic inflammation (AISI) as independent risk factors for nodules, particularly in diabetic males, possibly via tumor necrosis factor-alpha (TNF-α) and IL-6-mediated thyroid inflammation and proliferation, which could reveal new therapeutic targets and guide personalized prevention and management [30]. Deng *et al*. found SII, PLR, leukocyte count, and age to predict malignancy in TI-RADS 3 nodules [7]. These findings suggest that inflammation-based indices may serve as biomarkers for ENG, warranting further study into their underlying mechanisms.

ROC analysis identified SIRI as the most reliable SIM for detecting ENG (AUC=0.675, P<0.001; cut-off >0.76; specificity 88.1%), indicating moderate diagnostic value typical for benign conditions, while other markers were non-predictive. SIRI outperformed SII (P=0.039) with consistent, gender-independent accuracy. Age showed weak significance (AUC=0.585, P=0.031), suggesting a limited effect, possibly due to the study's age range (20–60 years), unlike prior studies [1]. Overall, SIMs showed modest, age-independent diagnostic value for ENG in iodine-sufficient individuals, warranting multicenter validation.

The crucial limitations of the study include the single-center design, small sample size, and potential ultrasound bias from a single examiner, limiting generalizability. Genetic, dietary, and environmental factors, and specific inflammatory mediators like cytokines or ILs were omitted, restricting insight into underlying mechanisms and precluding causal conclusions.

The study provides rare, region-specific insights into the relationship between SIMs and ENG in an iodine-sufficient population. By including euthyroid, non-diabetic, age-matched participants and evaluating a broad marker panel with standardized diagnostics and ROC analysis, it minimized confounding and enhanced clinical relevance despite modest predictive accuracy.

SIRI was an independent predictor of ENG, reflecting low-grade inflammation, typical of benign thyroid conditions, though modest predictive power suggests other factors contribute. Larger longitudinal studies should assess the prognostic value of SIMs and explore genetic, environmental, lifestyle, and cultural influences, while routine ultrasound and preventive strategies may aid early detection and management.

Conclusion

Subclinical inflammation contributes to ENG in iodine-sufficient population, with SIRI as the strongest independent, gender-independent predictor, and SII is inversely associated. Age also showed a positive correlation. However, limited sensitivity and insignificance of other SIMs indicate they are insufficient alone for risk assessment. Larger multicenter studies incorporating genetic, environmental, and lifestyle factors, alongside routine ultrasound, are needed to clarify mechanisms and improve ENG management.

Conflict of interest

The authors declare no conflicts of interest.

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