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ORIGINAL RESEARCH

Association Between Triglyceride-Glucose Index and Malignant Risk in Thyroid Nodules: A Cross-Sectional Analysis

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Objective: The aim of this study is to investigate the association between the Triglyceride-Glucose (TyG) index and papillary thyroid carcinoma (PTC) risk, with a particular focus on metabolic, thyroid function, and immunological mechanisms.

Methods: A cross-sectional study involving 1,833 participants, including 823 individuals with benign thyroid nodules and 1,010 individuals with PTC, was conducted. The TyG index was calculated using the formula ln[fasting triglycerides (mg/dL) × fasting glucose (mg/dL)/2]. Multivariate logistic regression analyses were performed to evaluate the association between the TyG index and PTC risk, with adjustments made for potential confounders.

Results: The mean age of participants in the PTC group was 47.36 ± 12.12 years and the BTN group was 44.28 ± 10.95 years. In the unadjusted model, the TyG index demonstrated a positive correlation with PTC risk (OR = 1.67, 95% CI: 1.33–2.09, $p < 0.0001$); however, this association was no longer significant following adjustment (Adjusted OR = 0.94, 95% CI: 0.12–7.03, $p = 0.9495$), TYG is not a risk factor for benign and malignant thyroid nodules. Stratified analysis revealed that moderate TyG levels were linked to an increased PTC risk among middle-aged participants (OR = 1.45, 95% CI: 1.14–1.86, $p = 0.0027$). Elevated FT3 levels markedly increased PTC risk (OR = 9.13, 95% CI: 4.92–16.97, $p < 0.0001$), while reduced FT4 and TSH levels were inversely associated with PTC risk. Thyroid autoantibodies demonstrated complex associations. Proposed mechanisms indicate that insulin resistance may contribute to PTC development through inflammatory pathways and cellular proliferation.

Conclusion: The TyG index alone does not serve as an independent risk factor for PTC; however, the interaction between metabolic dysfunction, thyroid function, and immune markers contributes to thyroid carcinogenesis, providing valuable insights for future research and personalized screening strategies.

Keywords: triglyceride-glucose index, papillary thyroid carcinoma, thyroid function, thyroid carcinogenesi, thyroid nodule

Introduction

Thyroid nodules are a common endocrine disorder with a rising global incidence. Epidemiological studies indicate considerable variation in nodule detection rates, ranging from 19% to 68% in the general population, with notably higher prevalence in China (20%–50%). Women demonstrate significantly greater susceptibility compared to men.[1]

Although most thyroid nodules are benign, a significant subset—approximately 5% to 15%—has the potential for malignant transformation, possibly progressing to thyroid carcinoma.[2] Recent epidemiological trends highlight a concerning rise in thyroid cancer incidence, particularly among women, identifying it as one of the fastest-growing malignant neoplasms in this group.[3]

The complexity of thyroid nodule management is highlighted in the findings from surgical intervention cohorts, demonstrating a higher proportion of malignant lesions. These findings highlight the critical need for advanced early detection and comprehensive risk stratification strategies to improve patient outcomes and guide clinical interventions.

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The triglyceride-glucose (TyG) index is an innovative metabolic parameter calculated using a logarithmic formula that incorporates fasting triglyceride and glucose concentrations: ln[fasting triglycerides (mg/dL) × fasting glucose (mg/dL)/2].[4] Recognized as a practical surrogate marker for insulin resistance, the TyG index demonstrates strong associations with metabolic syndrome, type 2 diabetes, cardiovascular diseases, and other metabolic conditions.[5,6]

Recent research has demonstrated the multifaceted potential of the TyG index, indicating its role in carcinogenesis through mechanisms such as chronic inflammation and oxidative stress.[7] However, the exact relationship between the TyG index and thyroid nodule malignancy remains poorly understood, highlighting a critical gap in current research.

Existing literature has established strong associations between insulin resistance and thyroid nodules. Previous studies have consistently demonstrated higher Homeostatic Model Assessment of Insulin Resistance (HOMA-IR) values in patients with thyroid nodules, indicating a significant positive correlation.[8,9] Notably, Alkurt et al (2022) identified a positive association between elevated TyG index and papillary thyroid carcinoma (OR = 1.92, 95% CI: 1.15–3.21) in a single-center cohort of 892 participants. However, their analysis did not adjust for key confounders such as thyroid function markers or immune parameters, and the cohort lacked stratification by metabolic subgroups, limiting clinical generalizability.[10] In parallel, Zhang et al (2023) demonstrated that TyG index correlated with thyroid dysfunction (β = 0.34, $p < 0.001$) but focused primarily on its mediating role in diabesity and lipid profiles rather than malignancy risk. Their study also included participants with pre-existing metabolic disorders, potentially confounding thyroid-specific associations.[4] There are fewer articles investigating the association between TYG and thyroid nodules, and the sample size is small. Our sample size is large. The TyG index was selected as an innovative metabolic marker in this study based on its unique advantages over traditional HOMA-IR measures. Compared with HOMA-IR, TyG index not only can reflect insulin resistance more directly, but also has the characteristics of more convenient measurement and stronger clinical operability. Research objectives and significance: The aim of this cross-sectional study was to evaluate the association between the TyG index and the malignancy potential of thyroid nodules. Conducted at Longyan First Hospital from January 2020 to June 2024, the research focused on patients undergoing surgical intervention for thyroid nodules. The primary investigative goals encompass: 1. Quantifying the predictive capabilities of the TyG index for thyroid nodule malignancy. 2. Controlling for potential confounding variables. 3. Providing nuanced insights into metabolic risk assessment. The study's unique methodology combines high-quality clinical data with sophisticated multivariate statistical analysis, aiming to expand existing scientific literature.

The aim of this research is to offer novel perspectives in thyroid nodule risk stratification and potentially inform personalized clinical management strategies. By bridging existing knowledge gaps, the goal is to contribute substantive evidence that supports early diagnostic and interventional approaches in thyroid nodule management.

Methods

Study Participants

The patients undergoing thyroid nodule surgical resection were included in this cross-sectional study at Longyan First Hospital between January 2020 and June 2024. The total sample consisted of 1,833 participants, comprising 823 patients with benign thyroid nodules and 1,010 patients with papillary thyroid carcinoma (Figure 1).

Inclusion criteria: Surgical treatment for thyroid nodules at Longyan First Hospital, complete clinical and laboratory examination records.

Exclusion criteria: Concurrent endocrine system disorders (eg, diabetes, thyroid dysfunction), severe hepatic or renal dysfunction, recent hormonal therapy, history of malignant neoplasms, pregnant or lactating women, incomplete medical records, refusal to participate, severe cardiovascular diseases, long-term medication affecting insulin and glucose metabolism, and autoimmune disorders. Long-term use of corticosteroids, antipsychotics, immunosuppressants, and certain antidepressants can significantly impact insulin and glucose metabolism, particularly in patients with autoimmune diseases like systemic lupus erythematosus and rheumatoid arthritis. All thyroid nodule diagnoses were validated through postoperative pathological examination. Data sources included inpatient medical records, laboratory test results, and postoperative pathology reports. All information was extracted and entered into a database by professional medical personnel.

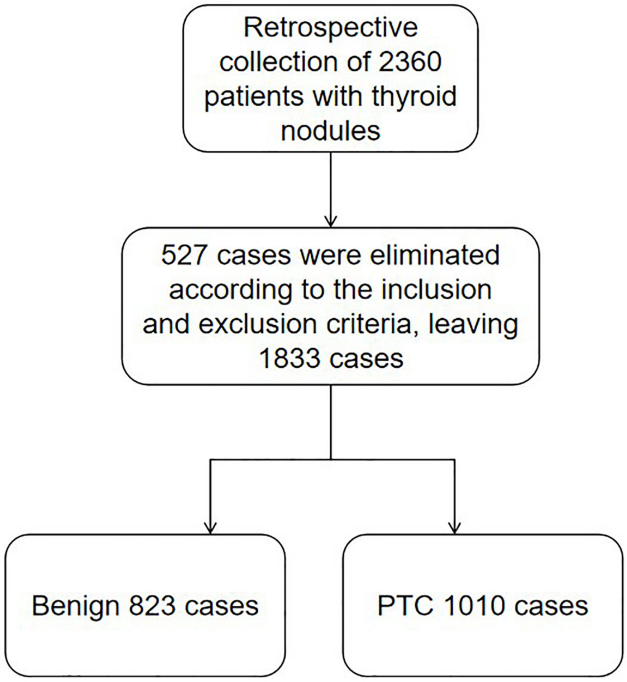

Figure 1 Study enrollment flowchart.

Variables

Exposure Variable

The TyG Index was calculated using the formula: ln[fasting triglycerides (mg/dL) × fasting glucose (mg/dL)/2] (Fasting for 8 hours). Blood samples were collected after fasting, and triglyceride and glucose levels were measured using a Roche automated biochemical analyzer. TyG was recorded as a continuous variable and stratified into low, medium, and high groups for categorical analysis. Measurements were taken within 24 hours of patient admission to maintain data timeliness and consistency.

Outcome Variable

The malignancy of thyroid nodules was confirmed through postoperative pathological diagnosis. Benign nodules included nodular goiter and thyroid adenoma, while malignant nodules consisted of papillary thyroid carcinoma. All pathological diagnoses were reviewed independently by two senior pathologists, and a third expert pathologist consulted in cases of discrepancy.

Covariates

Covariates included demographic characteristics (age, sex), high-density lipoprotein (HDL), blood glucose, triglycerides (TG), thyroglobulin antibodies (TGAb), thyroid peroxidase antibodies (TPOAb), and neutrophil, monocyte, and platelet counts. Missing data were controlled below 5% and handled using multiple imputation techniques to reduce bias and improve statistical power.

Ethical Statement

The study received approval from the Longyan First Hospital Ethics Committee (Approval No.: LYREC2024-K043-01) and adhered to the ethical principles outlined in the Declaration of Helsinki. As only anonymized historical data from medical records were analyzed, the Ethics Committee specifically waived the requirement for individual informed consent. The research team followed strict patient privacy protocols, storing data in an encrypted database with access restricted to research team members.

Statistical Methods

The relationship between metabolic indices, thyroid function parameters, hematological markers, and the risk of papillary thyroid carcinoma (PTC) were examined in this cross-sectional study. Continuous variables were expressed as mean ± standard deviation (SD) and compared using independent t-tests or Mann–Whitney *U*-tests for non-normally distributed data. Categorical variables were compared using Chi-square tests. Logistic regression analysis was employed to compute odds ratios (ORs) and 95% confidence intervals (CIs) for both univariate and multivariate analyses. Additionally, continuous variables were categorized into tertiles for subgroup comparisons.

Multivariate logistic regression analysis models were developed to account for confounders:

Model I: Adjusted for age and sex.

Model II: Further adjusted for metabolic, thyroid, and hematological parameters.

Stratified analyses were conducted based on age and other subgroups to assess potential effect modification. Sensitivity analyses were performed by excluding outliers and using alternative categorizations to ensure robustness. Statistical significance was defined as $p < 0.05$, and all analyses were executed using SPSS24 and EpoweRCH. Ethical approval was granted for this study.

These methods facilitated a thorough evaluation of the complex interactions among metabolic, thyroid, and immune factors in the development of PTC.

Potential collinearity among thyroid function markers (FT3, FT4, TSH) and antibodies (TPOAb, TGAb) was assessed using variance inflation factors (VIF); all VIF values were <5, indicating no significant collinearity.

Result

General Characteristics Comparison Between the PTC Group and the BTN Group

The age distribution included was 14–81 years. The general characteristics of the study population were compared between the PTC group and the BTN group. Notable differences were identified in several key parameters, as presented in Table 1.

Age subgroups were defined as: young (<45 years), middle-aged (45–60 years), and elderly (>60 years) based on clinical stratification standards.The study population was mainly composed of middle-aged people, with nearly half of the patients in the 45–60 age group. The gender distribution is relatively balanced, with a slight predominance of males. Body mass index for most patients suggests a tendency towards overweight. Compared with the BTN group, the PTC group showed a tendency toward higher total cholesterol, though differences in low-density lipoprotein levels were not apparent. Marked distinctions in thyroid function markers were observed, with the PTC group displaying increased free triiodothyronine but lower free

Table 1 Baseline Characteristics Comparison Between the PTC Group (Papillary Thyroid Carcinoma) and the BTN Group (Benign Thyroid Nodule)

Team	1(Benign Thyroid Nodule)	2(Papillary Thyroid Carcinoma)	P-value
Age (years)	44.28 ± 10.95	47.36 ± 12.12	<0.001
TC (mmol/L)	1.60 ± 0.24	1.64 ± 0.22	<0.001
LDL (mmol/L)	3.19 ± 0.84	3.26 ± 0.78	0.086
FT3 (pmol/L)	1.60 ± 0.22	1.67 ± 0.20	<0.001
GLU (mmol/L)	5.56± 1.06	5.76 ± 1.30	0.06
FT4 (pmol/L)	2.66 ± 0.34	2.49 ± 0.28	<0.001
TSH (mIU/L)	0.46 ± 0.96	0.11 ± 1.12	<0.001
TPOAB (IU/mL)	2.28 ± 2.06	0.91 ± 2.16	<0.001
TGAB (IU/mL)	2.31 ± 1.96	0.71 ± 1.66	<0.001
TRAB (IU/L)	−0.39 ± 0.72	−0.08 ± 0.67	<0.001
Neutrophil count	1.72 ± 0.62	1.37 ± 0.41	<0.001
Monocyte	2.07 ± 0.45	1.68 ± 0.49	<0.001
TyG	2.17 ± 0.27	2.48 ± 1.43	<0.001

thyroxine and thyroid-stimulating hormone. Additionally, thyroid autoantibodies were generally lower in the PTC group, except for thyroid receptor antibody, which tended to be elevated. Hematological parameters also varied, as the BTN group exhibited relatively higher neutrophil and monocyte counts. Notably, the TyG index, reflecting insulin resistance, was elevated in the PTC group, whereas glucose levels remained similar between groups.

These results demonstrate significant differences in thyroid function, metabolic parameters, and hematological markers between patients with papillary thyroid carcinoma and those with benign thyroid nodules. The observed changes in thyroid autoantibodies, thyroid function markers, and metabolic indices may reflect potential physiological and pathological mechanisms involved in the development and progression of papillary thyroid carcinoma, necessitating further research.

Association Between Various Exposure Factors and the Study Groups

We used a data-driven approach to triage the TyG metric based on sample distribution characteristics and clinical epidemiological studies. A univariate analysis was performed to explore associations between various exposure factors and study groups. As summarized in Table 2, a higher TyG index was linked to an increased likelihood of PTC, and this relationship remained suggestive when the TyG index was analyzed in categories. Older age was also associated with a greater risk of PTC, particularly among participants in the oldest group. Individuals with higher total cholesterol generally showed an increased risk of PTC compared to those with lower levels.

Notably, higher free triiodothyronine (FT3) levels were strongly related to a greater risk of PTC, whereas elevated free thyroxine (FT4) and thyroid-stimulating hormone (TSH) levels appeared to be protective, as higher values were

Table 2 Multivariate Analysis of the Association Between Variables and the Risk of Papillary Thyroid Carcinoma (PTC Group)

Exposure	Statistics	Team
TyG	2.30 ± 0.98	1.67 (1.33, 2.09) <0.0001
TyG Tertile		
Low	592 (33.28%)	1.0
Middle	594 (33.39%)	0.93 (0.74, 1.18) 0.5626
High	593 (33.33%)	1.21 (0.97, 1.53) 0.0957
Y	45.66 ± 11.59	1.02 (1.02, 1.03) <0.0001
Y Tertile		
Low	570 (31.15%)	1.0
Middle	616 (33.66%)	0.88 (0.70, 1.11) 0.2857
High	644 (35.19%)	1.88 (1.50, 2.37) <0.0001
TC	1.62 ± 0.23	2.18 (1.40, 3.39) 0.0005
TC Tertile		
Low	589 (33.05%)	1.0
Middle	598 (33.56%)	1.42 (1.13, 1.79) 0.0031
High	595 (33.39%)	1.63 (1.29, 2.05) <0.0001
LDL	3.22 ± 0.81	1.11 (0.99, 1.24) 0.0862
LDL Tertile		
Low	591 (33.18%)	1.0
Middle	596 (33.46%)	1.24 (0.99, 1.57) 0.0621
High	594 (33.35%)	1.21 (0.96, 1.52) 0.1038
FT3	1.63 ± 0.21	9.13 (4.92, 16.97) <0.0001
FT3 Tertile		
Low	593 (33.17%)	1.0
Middle	592 (33.11%)	2.27 (1.79, 2.89) <0.0001
High	603 (33.72%)	3.25 (2.56, 4.14) <0.0001

(*Continued*)

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Table 2 (Continued).

Exposure	Statistics	Team
GLUmg/dl	106.73 ± 257.37	1.00 (1.00, 1.00) 0.6425
GLUmg/dl Tertile		
Low	608 (33.19%)	1.0
Middle	613 (33.46%)	0.90 (0.72, 1.13) 0.3810
High	611 (33.35%)	1.12 (0.90, 1.41) 0.3119
FT4	2.58 ± 0.33	0.08 (0.06, 0.13) <0.0001
FT4 Tertile		
Low	595 (33.28%)	1.0
Middle	597 (33.39%)	0.88 (0.70, 1.10) 0.2634
High	596 (33.33%)	0.16 (0.12, 0.21) <0.0001
TSH	0.30 ± 1.05	0.71 (0.64, 0.78) <0.0001
TSH Tertile		
Low	586 (33.01%)	1.0
Middle	597 (33.63%)	0.54 (0.43, 0.68) <0.0001
High	592 (33.35%)	0.38 (0.30, 0.49) <0.0001
TPOAB	1.81 ± 2.19	0.73 (0.69, 0.77) <0.0001
TPOAB Tertile		
Low	495 (32.52%)	1.0
Middle	519 (34.10%)	0.38 (0.29, 0.49) <0.0001
High	508 (33.38%)	0.19 (0.14, 0.25) <0.0001
TGAB	1.77 ± 2.01	0.59 (0.54, 0.63) <0.0001
TGAB Tertile		
Low	5 (0.33%)	1.0
Middle	1006 (66.23%)	0.43 (0.07, 2.59)0.3577
High	508 (33.44%)	0.21 (0.03,1.28)0.0901
TRAB	−0.28 ± 0.72	1.90 (1.60, 2.25) <0.0001
TRAB Tertile		
Low	507 (33.33%)	1.0
Middle	507 (33.33%)	5.18 (3.82, 7.01) <0.0001
High	507 (33.33%)	4.31 (3.18, 5.84) <0.0001
Neutrophil count	1.57 ± 0.56	0.28 (0.23, 0.35) <0.0001
Neutrophil count Tertile		
Low	599 (33.02%)	1.0
Middle	609 (33.57%)	1.29 (1.03, 1.63) 0.0261
High	606 (33.41%)	0.26 (0.20, 0.33) <0.0001
Monocyte	1.90 ± 0.51	0.12 (0.09, 0.16) <0.0001
Monocyte Tertile		
Low	598 (32.97%)	1.0
Middle	610 (33.63%)	0.81 (0.64, 1.01) 0.0652
High	606 (33.41%)	0.18 (0.14, 0.23) <0.0001

associated with a reduced likelihood of PTC. Increased levels of thyroid autoantibodies, including TPOAb and TGAb, were related to a decreased risk, while higher concentrations of TRAB were associated with elevated PTC risk.

With respect to hematological parameters, higher neutrophil and monocyte counts were generally linked to a lower risk of PTC.

Together, these findings underscore complex and multifaceted relationships among metabolic, endocrine, immunological, and hematological markers in relation to the development of papillary thyroid carcinoma, highlighting the need for further in-depth investigation (Table 2).

Association Between Various Variables and the Risk of Papillary Thyroid Carcinoma

A comprehensive stratified analysis was conducted to explore the nuanced relationships between various parameters and papillary thyroid carcinoma (PTC) risk across different subgroups, as detailed in Table 3.

The TyG index demonstrated a particularly notable association with PTC risk among middle-aged participants, with more modest relationships observed in younger and older age groups. Total cholesterol and low-density lipoprotein showed significant associations primarily in the lowest tertile, suggesting potential metabolic influences on PTC risk that are most pronounced in specific population segments.

Blood glucose levels exhibited an interesting pattern, with a significant relationship to PTC risk primarily evident in the highest tertile. This finding hints at potential metabolic mechanisms underlying thyroid carcinogenesis, particularly at elevated glucose levels.

Hematological parameters revealed a complex picture. Both neutrophil count and monocyte levels demonstrated significant associations with PTC risk at the lowest and highest tertiles. This biphasic relationship suggests that extreme variations in these inflammatory markers may be intimately linked to thyroid cancer development.

The stratified analysis unveils the intricate and nuanced relationships between metabolic, hematological, and thyroid-related parameters across different population subgroups. These findings underscore the importance of comprehensive, multi-dimensional approaches in understanding the complex mechanisms underlying papillary thyroid carcinoma risk.

The results emphasize that disease risk is not uniformly distributed but varies significantly across different population strata, highlighting the need for personalized risk assessment and targeted screening strategies.

All candidate independent variables were screened for multicollinearity using a stepwise VIF (Variance Inflation Factor) approach. Only those variables with VIF less than 5 were retained. Finally, two variables (FT3 TRAB) were included for further multivariate analysis, both with VIF values of 1, indicating no collinearity.

Table 3 Association Between Variables and the Risk of Papillary Thyroid Carcinoma (PTC Group) in Stratified Analysis

Variable	Sub-Group	(N)	OR (95% CI)	P (P-value)
TyG	Low	556	2.45 (0.93, 6.48)	0.0712
	Middle	602	1.45 (1.14, 1.86)	0.0027
	High	620	1.99 (0.90, 4.40)	0.0871
TC	Low	589	1.45 (1.13, 1.85)	0.0032
	Middle	596	2.56 (0.83, 7.96)	0.1029
	High	594	2.29 (0.67, 7.86)	0.1888
LDL	Low	591	1.43 (1.12, 1.82)	0.0038
	Middle	594	2.66 (0.76, 9.31)	0.1270
	High	593	2.28 (0.75, 6.91)	0.1438
FT3	Low	586	1.47 (0.70, 3.07)	0.3064
	Middle	574	2.99 (0.41, 21.98)	0.2817
	High	581	2.23 (0.35, 14.10)	0.3955
GLU	Low	559	2.64 (0.79, 8.83)	0.1155
	Middle	610	2.98 (0.62, 14.35)	0.1733
	High	610	1.40 (1.12, 1.75)	0.0032
FT4	Low	577	1.32 (0.70, 2.49)	0.3920
	Middle	577	1.84 (0.39, 8.65)	0.4411
	High	587	8.33 (0.58, 120.50)	0.1201
Neutrophil count	Low	574	1.56 (1.13, 2.15)	0.0072
	Middle	594	4.62 (0.62, 34.69)	0.1366
	High	599	1.66 (1.20, 2.31)	0.0024
Monocyte	Low	576	1.46 (1.03, 2.06)	0.0334
	Middle	592	3.01 (0.58, 15.74)	0.1914
	High	599	1.74 (1.27, 2.40)	0.0006

Table 4 Association Between TyG and Its Tertiles With Disease Risk in Multivariate Regression Analysis

	Non-adjusted	Adjust I	Adjust II
TyG	1.67 (1.33, 2.09) <0.0001	1.59 (0.26, 9.74) 0.6187	0.94 (0.12, 7.03) 0.9495
TyG Tertile			
Low	1.0	1.0	1.0
Middle	0.93 (0.74, 1.18) 0.5626	1.18 (0.83, 1.67) 0.3632	1.24 (0.84, 1.85) 0.2801
High	1.21 (0.97, 1.53) 0.0957	1.18 (0.82, 1.68) 0.3707	1.09 (0.73, 1.62) 0.6789

Notes: Adjust I adjust for: GLUmg/dl; FT3; FT4; TSH; TPOAB; TGAB; TRAB; Neutrophils; white blood cells; Monocytes; Platelet; Total protein; Albumin; High density lipoprotein; Total bilirubin; Hemoglobin Adjust II adjust for: GLUmmol/L (smooth); FT3 (smooth); FT4 (smooth); TSH (smooth); TPOAB (smooth); TGAB (smooth); TRAB (smooth); neutrophils (smooth); leukocytes (smooth); monocytes (smooth); platelets (smooth); total protein (smooth); albumin (smooth); HDL (smooth); total bilirubin (smooth); hemoglobin (smooth).

Association Between the Tyg Index and the Risk of Disease

A multivariate regression analysis was conducted to assess the relationship between the TyG index and disease risk (Table 4).

In the unadjusted model, the TyG index was significantly associated with an increased risk of disease (OR = 1.67, 95% CI: 1.33, 2.09, $p < 0.0001$). However, after adjusting for potential confounders in Model I (OR = 1.59, 95% CI: 0.26, 9.74, $p = 0.6187$) and Model II (OR = 0.94, 95% CI: 0.12, 7.03, $p = 0.9495$), the association was no longer significant. These findings indicate that the observed association in the unadjusted model may be influenced by confounding factors, and TyG alone may not serve as an independent risk factor for the disease.

When the analysis was stratified by TyG tertiles, no significant association with disease risk was observed in the middle tertile across all models (unadjusted: OR = 0.93, 95% CI: 0.74, 1.18, $p = 0.5626$; Adjust I: OR = 1.18, 95% CI: 0.83, 1.67, $p = 0.3632$; Adjust II: OR = 1.24, 95% CI: 0.84, 1.85, $p = 0.2801$). Likewise, a slight trend toward an increased risk was found in the high tertile in the unadjusted model (OR = 1.21, 95% CI: 0.97, 1.53, $p = 0.0957$), though this association was attenuated and became non-significant following adjustment (Adjust I: OR = 1.18, 95% CI: 0.82, 1.68, $p = 0.3707$; Adjust II: OR = 1.09, 95% CI: 0.73, 1.62, $p = 0.6789$).

The results indicate that although TyG may initially seem to be associated with disease risk, its effect is likely influenced by confounding factors. Additional studies are required to examine the role of TyG in conjunction with other metabolic markers or within specific subpopulations to gain a clearer understanding of its potential contribution to disease development.

The Diagnostic Performance of the TyG Index for Discriminating Between the Positive and Negative Actual Status Groups Was Evaluated Using Receiver Operating Characteristic (ROC) Curve Analysis

The area under the curve (AUC) for the TyG index was 0.476 (standard error = 0.014), with a 95% confidence interval ranging from 0.449 to 0.504. The difference between the observed AUC and the null hypothesis value of 0.5 was not statistically significant (P = 0.088). This suggests that the TyG index did not demonstrate discriminative power for the outcome of interest in this cohort. It is noteworthy that at least one tie occurred between the positive and negative actual status groups, which may introduce some degree of bias in the statistical estimation of AUC. Nonetheless, these findings collectively indicate that the TyG index was not an effective classifier for the studied endpoint in this population (Figure 2).

Discussion

The association between the TyG index and the risk of thyroid diseases was examined through a large-scale cross-sectional study involving 1,823 participants. A significant positive correlation between the TyG index and the risk of PTC in unadjusted models was found ($p < 0.0001$), indicating that metabolic dysfunction may play a substantial role in the

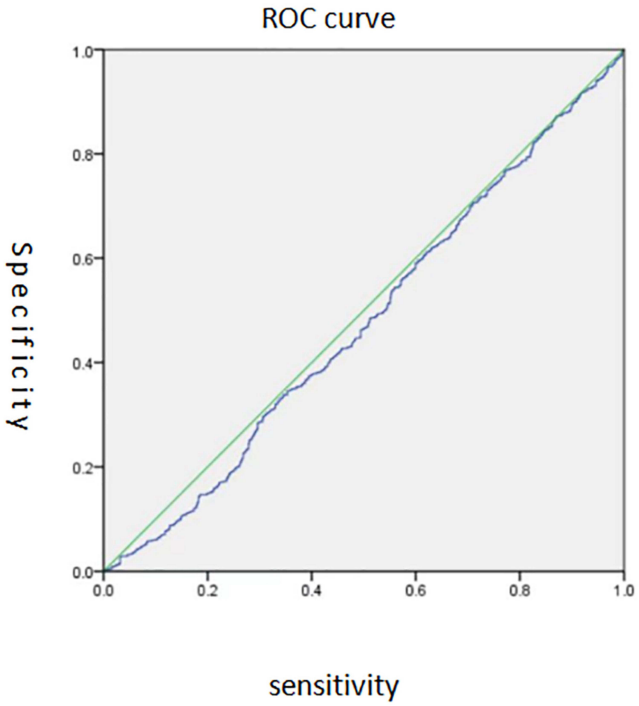

Figure 2 Diagnostic performance of TyG index for papillary thyroid carcinoma.

development of PTC. We acknowledge the reviewer's point. While these p-values indicate strong statistical significance, they do not, in isolation, imply clinical significance or importance. The clinical relevance of the associations should be interpreted cautiously alongside the effect sizes (ORs) and confidence intervals.

The TyG index, a marker of insulin resistance, may impact the risk of PTC through multiple mechanisms. First, insulin resistance can lead to persistent low-grade inflammation, enhancing the secretion of pro-inflammatory cytokines such as IL-6 and TNF-α.[11] These cytokines activate the NF-κB signaling pathway, which promotes thyroid cell proliferation and carcinogenesis.[12] Second, in the presence of insulin resistance, elevated insulin levels stimulate the release of insulin-like growth factor-1 (IGF-1), which encourages cell proliferation and inhibits apoptosis through the PI3K/AKT and MAPK signaling pathways, thus increasing the risk of cancer.[13,14]

Moreover, a significant association between elevated TC levels and an increased risk of PTC (p = 0.0005) was identified in this study. Cholesterol, a crucial component of cell membranes and a precursor for steroid hormones and bile acids, may play a role in the development of PTC through several mechanisms: (1) Cholesterol metabolites, such as oxidized cholesterol, can activate the LXR/RXR signaling pathway, which modulates immune cell function in the tumor microenvironment, promoting immune evasion by tumor cells;[15,16] (2) Elevated cholesterol levels may enhance the stability of lipid rafts in cell membranes, facilitating the signaling of receptor tyrosine kinases like EGFR, which subsequently activates tumor-related pathways, such as the RAS/RAF/MEK/ERK cascade.[15,17]

However, after adjusting for covariates, changes in effect estimates were observed, which partially align with the findings of Zhang et al.[4] They also reported the complexity of the relationship between the TyG index and thyroid disease risk. In contrast to their study, a larger clinical cohort (1,825 participants) was involved in this research, while Alkurt et al included only 892 participants and did not perform multivariable adjustments.[10] These differences may arise from variations in population characteristics, genetic backgrounds, and metabolic states. From a physiological standpoint, insulin resistance might influence thyroid function through inflammatory cytokines and oxidative stress, though the exact mechanisms remain unclear.[18] The non-linear and complex relationship between the TyG index and thyroid disease risk observed in this study provides a foundation for future research. While we employed various methods to mitigate the potential impact of collinearity, such as retaining only variables with a variance inflation factor (VIF) of less than 5 in the multivariable models, we cannot entirely rule out its potential influence. Moreover, in certain subgroup analyses (eg,

TGAb tertiles), model estimates may be unstable due to smaller sample sizes. Future research with larger cohorts and more sophisticated methods is needed to validate these findings and enhance model stability. Specifically, stratified analysis by TyG tertiles revealed that moderate TyG levels were significantly associated with increased PTC risk (OR 1.45, 95% CI: 1.14–1.86, $p = 0.027$), but this association became non-significant after adjustment. This indicates that the TyG index may not be an independent risk factor for thyroid diseases but may interact with other metabolic or demographic factors to jointly influence thyroid disease risk. Our findings carry potential clinical significance for the risk stratification and management of thyroid nodules. Although the TyG index alone cannot serve as an independent risk factor, our study underscores the combined impact of metabolic dysfunction, thyroid function abnormalities, and immune system changes. Future development of thyroid nodule risk assessment models could incorporate these factors to enhance the precision of risk prediction, thereby facilitating personalized screening and prevention strategies for individuals at high risk of thyroid cancer.

A significant association between elevated FT3 levels and an increased risk of PTC ($p < 0.0001$), with an OR of 9.13 (95% CI: 4.92–16.97) was also found in this study. FT3, the active form of thyroid hormone, may contribute to PTC development through the following mechanisms: (1) FT3 binds to thyroid hormone receptors (TRα and TRβ), regulating cellular metabolism and proliferation. Elevated FT3 levels may lead to hyperactive thyroid cell metabolism, increasing the risk of DNA damage and mutations;[17,19] (2) High FT3 levels may enhance mitochondrial activity and oxidative phosphorylation, resulting in elevated reactive oxygen species (ROS) levels, which induce DNA damage and genomic instability, thereby promoting carcinogenesis.[20,21]

Furthermore, a significant association between decreased FT4 levels ($p < 0.0001$) and TSH levels ($p < 0.0001$) with increased PTC risk was observed. As the primary regulator of thyroid function, TSH may indicate abnormal thyroid states when reduced. Mechanistically, TSH activates the cAMP/PKA signaling pathway via the TSH receptor (TSHR), regulating thyroid cell proliferation and differentiation.[8,19] Reduced TSH levels may indicate increased autonomous proliferation of thyroid cells, potentially linked to carcinogenesis. Decreased FT4 levels may reflect thyroid hormone metabolic dysregulation, potentially promoting PTC development by influencing tumor cell energy metabolism and proliferation capacity.[22,23]

The elevated TPOAB and TGAB levels were associated with a reduced risk of PTC, while elevated TRAB levels were linked to an increased risk of PTC ($p < 0.0001$) as discovered in this study. These findings indicate that thyroid autoimmunity may play a dual role in PTC development: (1) Elevated TPOAB and TGAB levels may indicate the presence of thyroid autoimmune inflammation, potentially enhancing immune surveillance against tumor cells and reducing PTC risk;[23–25] (2) Elevated TRAB levels may stimulate excessive thyroid cell proliferation and hyperfunction, thereby increasing the risk of carcinogenesis.

Additionally, it was observed that the neutrophil counts and monocyte levels were negatively associated with PTC risk ($p < 0.0001$). Neutrophils, as a critical component of innate immunity, may indicate impaired anti-tumor immune function when reduced, potentially promoting tumor development.[26] Monocytes, as precursors of tumor-associated macrophages (TAMs), may reflect an immunosuppressive state within the tumor microenvironment when reduced, which could inhibit anti-tumor immune responses and facilitate PTC progression.[26,27] Recent work by Montaser et al (2024) indicates that which has demonstrated that continuous glucose monitoringderived dynamic markers can detect early metabolic shifts more sensitively than static measures like the TyG index, highlighting the potential value of real-time data in refining disease risk stratification.[28]

Variations in the associations between metabolic, thyroid function, and hematological parameters with PTC risk across different subgroups were revealed in the stratified analysis. For instance, the TyG index exhibited a significant association with PTC risk in the middle-aged group but only marginal significance in the younger and older age groups. This indicates that age may play a crucial role in moderating the relationship between metabolic markers and PTC risk. Furthermore, TC and LDL demonstrated a significant association with PTC risk in the low-level group, but not in the medium or high-level groups, highlighting the heterogeneity of metabolic dysfunction across various populations.

The potential contributions of metabolic dysfunction, thyroid function abnormalities, and immune system changes to PTC development is emphasized in this study, offering valuable insights for early screening and prevention strategies. Further investigation is necessary to confirm these mechanisms. First, large-scale prospective cohort studies are essential to establish causal relationships between metabolic, thyroid function, and hematological parameters with PTC risk.

Second, mechanistic studies involving cellular and animal models are required to examine the molecular pathways that link metabolic dysfunction, thyroid abnormalities, and immune system changes to PTC development. Lastly, integrating metabolic, thyroid function, and hematological parameters may enhance the development of multi-factorial PTC risk prediction models, enabling personalized screening and intervention strategies for high-risk populations. Future research could explore combining these advanced metabolic monitoring technologies (eg, continuous glucose monitoring-derived dynamic markers) with conventional biomarkers to further refine thyroid cancer risk prediction models.[28]

Despite its scientific significance, this study has several limitations. First, since this was a single-center cross-sectional study, its findings may have limited external validity and require confirmation through multi-center, large-sample prospective studies. Second, the study participants predominantly comprised individuals of Chinese Han ethnicity, which may restrict the generalizability of the results to other ethnicities and regions. Future research should include more diverse populations. Third, as an observational study, only associations could be identified instead of establishing causal mechanisms in this research. Although multi-model adjustment strategies were applied, unmeasured confounders, such as genetic background and lifestyle factors, may still have influenced the findings. Lastly, the absence of long-term follow-up data limits the ability to assess how changes in the TyG index may affect the long-term risk of thyroid diseases, underscoring the need for further investigation. The non-linear and complex relationship between the TyG index and thyroid disease risk observed in this study provides a foundation for future research.Lastly, integrating metabolic, thyroid function, and hematological parameters may enhance the development of multi-factorial PTC risk prediction models.

Conclusion

The significant associations between metabolic dysfunction, thyroid function abnormalities, and immune system changes with PTC risk is underscored in this study. Identified contributors to PTC development include the TyG index, total cholesterol, FT3, FT4, TSH, and immune markers such as neutrophil and monocyte counts. While the TyG index alone did not demonstrate independent predictive value for PTC after adjustment for confounders, it may still hold potential utility as a component within multi-factorial risk assessment models or in specific subpopulations (eg, middle-aged individuals), warranting further investigation. These findings offer valuable insights into the multifactorial mechanisms driving PTC and highlight the importance of further research to confirm these associations and develop personalized screening and prevention strategies for high-risk populations. Clinically, markers such as elevated FT3, reduced TSH and FT4, and elevated TRAB levels could be integrated into refined risk stratification tools to identify individuals requiring closer monitoring or earlier diagnostic evaluation. Future prospective longitudinal studies are essential to establish causal relationships and validate the clinical utility of these markers and their combinations in predicting PTC risk.

Abbreviations

TyG, Triglyceride Glucose; PTC, Papillary thyroid carcinoma; HOMA-IR, Homeostatic model assessment of insulin resistance; HDL, High-density lipoprotein; TG, Triglycerides; TGAb, Thyroglobulin antibodies; TPOAb, Thyroid peroxidase antibodies; CIs, Confidence intervals; BTN, Benign thyroid nodule; TC, Total cholesterol; LDL, Low-density lipoprotein; TGAB, Thyroglobulin antibody; TRAB, Thyroid receptor antibody; GLU, Blood glucose; IGF-1, Insulin-like growth factor-1; TSHR, TSH receptor; TAMs, Tumor-associated macrophages.

Data Sharing Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Ethics Approval and Consent to Participate

The study was conducted in accordance with the Declaration of Helsinki (as was revised in 2013). The study was approved by Ethics Committee of the Longyan First Hospital (No.LYREC2024-K043-01). As only anonymized historical data from medical records were analyzed, the Ethics Committee specifically waived the requirement for individual informed consent. The research team followed strict patient privacy protocols, storing data in an encrypted database with access restricted to research team members.

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Disclosure

The authors declare that they have no competing interests.

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