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RESEARCH ARTICLE

Unveiling the link between ACR TI-RADS grading and Bethesda score of thyroid nodules in diabetic patients: A comprehensive analysis

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ABSTRACT

This study aimed to explores the factors influencing thyroid nodules (TNs) in individuals with type 2 diabetes mellitus (T2DM) and evaluates the consistency between different American College of Radiology Thyroid Imaging Reporting and Data System (ACR TI-RADS) grades and Bethesda scores. Total of 642 T2DM patients were divided into TN group (245) and control group (397) based on the presence or absence of TNs. TN patients were further categorized into ACR TI-RADS classification (TR) 1 to 4 and TR5 subgroups. Diabetes-related clinical and biochemical parameters were collected, and differences were analyzed using univariate analysis. Logistic regression analysis was utilized to pinpoint independent influencing factors for TN occurrence and different TN classifications. Consequently, age, body mass index (BMI), fasting plasma glucose level (FBGL), low density lipoprotein cholesterol (LDL-C), diabetic progression, and family history of TNs emerged as independent risk factors for TN development in T2DM patients. Additionally, glycosylated hemoglobin (HbA1c), nodule diameter, and family history of TNs were identified as independent risk factors for TR5 TN development in T2DM patients. All TR1 to 2 nodules had a Bethesda score of 2 and all showed benign pathological findings. In 97.10% of cases (67/69), nodules classified as TR3 exhibited a Bethesda score of 2, with all pathological results indicating benign findings, aligning with the Bethesda score. In addition, the concordance between TR4 nodules and Bethesda score was only 78.57% (88/112). In conclusion, TNs and their malignancy in T2DM patients are significantly linked to blood glucose and lipid metabolism indexes. TR3 classification in T2DM patients poses a low malignancy risk, suggesting caution when conducting Fine Needle Aspiration Cytology (FNAC) testing. **KEYWORDS:** Type 2 diabetes mellitus, thyroid nodules, ACR TI-RADS grading, Bethesda score, logistic regression analysis.

INTRODUCTION

The thyroid gland stands out as a pivotal player in the human endocrine system [1]. The thyroid gland is mainly regulated by the hypothalamus-pituitary gland, and its synthesized and secreted thyroid hormones play a vital role in human growth, development, and the regulation of glucose and lipid metabolism, among other functions[1]. Thyroid nodules (TNs), common maladies of the endocrine system, denote isolated anomalies characterized by localized abnormal growth of thyroid cells distinctly separated from surrounding tissue [2]. The occurrence and development of TNs are mainly caused by genetic predisposition, environmental factors, abnormal iodine intake, dietary habits, and other influences [3]. In the absence of prior imaging techniques, thyroid nodules can only be detected by palpation by experienced clinicians with an incidence between 4% and 7%, with a considerable rate of underdiagnosis [4]. Typically, thyroid nodules have no obvious clinical manifestations, appearing solely as palpable masses moving within the anterior cervical region upon swallowing [5]. However, as nodules expand, they may cause neck enlargement and compression symptoms like dysphagia and dyspnea [5]. With the development of imaging techniques, the diagnostic efficacy of TNs has markedly improved. The detection rate via color ultrasonography ranges from 20% to 76%, with malignancies accounting for 7% to 15% [6]. As per 2022 statistics from the Chinese Cancer Center, thyroid cancer ranked seventh among various cancers, and the prevalence was significantly increased compared with that five years ago [7]. Therefore, regular ultrasonography for thyroid nodules detection and preventative measures against malignant thyroid nodules are imperative.

Epidemiological investigations have unveiled a close association between type 2 diabetes mellitus (T2DM) and TN occurrence [8]. Studies have shown that the risk of TNs in patients with T2DM is 1.78-fold higher than that in healthy individuals [9]. Nonetheless, the underlying pathogenesis of

T2DM and TNs remains elusive. Presently, insulin resistance is the widely accepted mechanism by many researchers. Clinical studies reveal significantly higher insulin resistance (IR) levels in TN patients compared to non-TN patients, with a notable correlation between IR and TNs [10]. Further studies indicate that the size of TNs increases with elevated insulin resistance index (HOMA-IR) in patients with T2DM [11]. Moreover, findings from Blanc et al. suggest that higher glycosylated hemoglobin A1c (HbA1c) levels may serve as a risk factor for TN formation and tissue growth in elderly patients with metabolic syndrome, correlating with altered thyroid morphology [12]. Given the intricate relationship between diabetes mellitus and thyroid nodules, the influencing factors for TNs in the diabetic population are unclear.

Presently, the optimal utilization of ultrasound to discern clinically significant thyroid cancer remains a focal point of recent research. The American College of Radiology Thyroid Imaging Reporting and Data System (ACR TI-RADS), proposed by the American College of Radiology (ACR), represents the latest risk stratification criteria. ACR TI-RADS primarily assigns relative scores based on thyroid nodule composition, echogenicity, morphology, margins, and echogenic foci, thereby enhancing the diagnostic precision of thyroid nodules [13]. Additionally, Fine Needle Aspiration Cytology (FNAC) serves as the primary diagnostic tool to differentiate benign from malignant TNs, with cytopathological diagnoses classified by the Bethesda Reporting System. However, literature reports indicate that approximately 20% of FNAC results are inconclusive due to unsatisfactory specimens[14]. Currently, the gold standard for diagnosing benign and malignant thyroid nodules remains pathological biopsy following surgical resection. Moreover, FNAC represents an invasive procedure, and given that most nodules are benign and do not necessitate FNAC, unnecessary procedures should be minimized. To address this, we analyzed factors influencing thyroid nodules

across different ACR TI-RADS risk stratifications. Concurrently, this study aimed to assess the consistency between different ACR TI-RADS classification nodules and Bethesda scores in diabetic patients, thereby facilitating more accurate diagnosis of benign and malignant thyroid nodules and reducing unnecessary FNAC procedures.

MATERIALS AND METHODS

Study subjects

According to the inclusion and exclusion criteria, 642 patients with T2DM, aged 29 to 81 years, were selected from the General Practice Health Management Center of Zhejiang Provincial People's Hospital from June 2020 to June 2023. The patients' diagnoses of T2DM were consistent with the Chinese guidelines [15]. Inclusion criteria included (1) meeting the diagnostic criteria of T2DM; (2) undergoing thyroid color ultrasonography; (3) completing FNAC for nodules ranked 3 to 5 in the ACR TI-RADS system, and obtaining cytopathological diagnosis and classification by Bethesda reporting system; (4) all nodules with FNAC were found to have histopathological results; (5) patients were required to sign informed consent. Exclusion criteria included (1) patients with a history of thyroid surgery; (2) patients with thyroid metastasis; (3) patients with a history of neck radiation; (4) patients with other malignant tumors; (5) patients with severe heart, liver and kidney dysfunction.

Clinical data

Demographic and medical information, including age, sex, duration of diabetes, and family history of thyroid nodules, was collected for all participants. Height and weight were also measured to calculate body mass index (BMI). Blood samples were taken in the morning after a 10-hour fast to

114 determine levels of fasting plasma glucose (FBGL, mmol/L), fasting insulin (FINS, mIU/L),
115 glycosylated hemoglobin (HbA1c, %), triglycerides (TG, mmol/L), total cholesterol (TG, mmol/L),
116 high-density lipoprotein cholesterol (HDL-C, mmol/L), and low-density lipoprotein cholesterol (LDL-
117 C, mmol/L). Insulin resistance index (HOMA-IR) was calculated from FBGL and FINS. HOMA-
118 IR=(FBGL×FINS)/22.5[16]。
119
120 **Thyroid examination**
121 All patients underwent thyroid color ultrasonography using a 7.5 MHz probe and the HS-2000 color
122 Doppler ultrasound machine (Honda Electronics Co., Ltd.). The procedure was performed while the
123 patients were in a supine position with their anterior cervical region fully visible. All ultrasound
124 examinations were performed by a senior physician with more than 5 years of experience in ultrasound
125 diagnosis of the thyroid gland. If a thyroid nodule was detected, its size, boundary, location, echo,
126 morphology, and presence of calcification were noted. The nodules were then classified using the ACR
127 TI-RADS system [13]. ACR TI-RADS risk stratification interpretations were evaluated individually
128 by two experienced senior physicians in a double-blind manner. In cases of disagreement, a third senior
129 physician at the rank of deputy director or higher was consulted. The final conclusion was reached
130 through joint consultation. All thyroid nodules were measured in a three-dimensional manner and the
131 largest diameter was recorded to assess thyroid nodule size regardless of the number of nodules [17].
132
133 **Thyroid fine needle aspiration cytology**
134 The patient was instructed to take a supine position, place his shoulder and neck high so that it was
135 in an extended position to fully expose the anterior cervical region. The anterior cervical area is

routinely disinfected. After local anesthesia, a 22 G needle was punctured into the thyroid nodule under ultrasound guidance and the needle core was removed. Remove a few tumor cells by suction and collect cell debris by rapid lifting and inserting back and forth under negative pressure. After the operation, the puncture point was pressed for hemostasis. According to the classification criteria of thyroid cytopathology, Bethesda score was divided into 6 categories: 1 as not diagnostic value or dissatisfactory, 2 as benign, 3 as atypical hyperplasia of unclear significance or follicular hyperplasia of uncertain significance, 4 as follicular tumor or suspicious follicular tumor, 5 as suspicious malignant, and 6 as malignant [18]. Cytological aspirate samples with a Bethesda score of 1, indicating no value or unsatisfactory results, were not included in the study. Samples with a score of 3 or 4 were not included because they could not be confidently classified as either benign or malignant.

Statistical analysis

The data was analyzed using SPSS 27.0 statistical software. Measurement data with a normal distribution were expressed as Mean ± SD, while non-normal distribution data were presented as median (quartile). The independent sample T-test was used to compare normal distribution measurement data, and the Kolmogorov-Smirnov test was used for non-normal distribution data. Categorical data were compared using a $\chi 2$ test, and logistic regression was used for multivariate analysis of different groups. A P value of less than 0.05 was considered statistically significant.

RESULTS

Analysis of influencing factors of thyroid nodules in diabetic patients

This study included 642 patients with diabetes who underwent thyroid color ultrasonography, with 245 patients ultimately screened for thyroid nodules. Table 1 shows the analysis of risk factors for thyroid nodules in diabetic patients. Compared to controls, patients with thyroid nodules were significantly older ($P < 0.001$), but there was no significant difference in sex distribution ($P > 0.05$). In addition, BMI was significantly higher in patients with thyroid nodules than in controls ($P < 0.001$). The levels of FBGL, FINS, HOMA-IR and HbA1c were significantly higher in patients with thyroid nodules compared to controls (All $P < 0.01$). In terms of lipid metabolism, the levels of TG, TC and LDL-C in patients with thyroid nodules were significantly higher than those in the control group (All $P < 0.05$), while HDL-C levels were significantly lower than those in the control group ($P < 0.01$). Additionally, patients with diabetes for 10 years or more had a significantly higher incidence of thyroid nodules ($P < 0.001$), and there was a higher proportion of patients with thyroid nodules who had a family history compared to controls ($P < 0.001$).

Logistic regression analysis of influencing factors of thyroid nodules in diabetic patients

The 12 candidate variables with $P < 0.05$ in the univariate were included in the multivariate Logistic regression analysis and the results are shown in Table 2 and Figure 1. Age (OR = 1.149) and BMI (OR = 1.173) were independent risk factors for thyroid nodules in diabetic patients ($P < 0.001$). Specifically, for every 1-unit increase in age or BMI, there was a 14.9% and 17.3% increase in the risk of developing thyroid nodules in diabetic patients, respectively. While FINS, HOMA-IR, and HbA1c levels were included in the multivariate logistic regression analysis as metabolic indices of diabetes mellitus, their

impact on the risk of thyroid nodules was not statistically significant (All $P > 0.05$). This indicates that these factors were not independent risk factors for the development of thyroid nodules. However, higher FBGL levels were identified as an independent risk factor (OR = 2.504, P < 0.01), with each 1-unit increase corresponding to a 1.504-fold increase in the risk of developing thyroid nodules in diabetic patients. Among the indices of lipid metabolism, an elevated LDL-C level was also found to be an independent risk factor for the development of thyroid nodules in diabetic patients (OR = 1.951, P < 0.05). For every 1-unit increase in LDL-C, there was a 95.1% increase in the risk of developing thyroid nodules. Additionally, having a diabetes course of 10 years or longer or a family history of thyroid nodules were associated with 7.979 and 2.628 times higher likelihood, respectively, of developing thyroid nodules compared to diabetic patients with a diabetes course less than 10 years or no family history of thyroid nodules.

Analysis of influencing factors of thyroid nodules with different ACR TI-RADS classification in diabetic patients

Further risk determination was performed for all patients with thyroid nodules by the ACR TI-RADS risk stratification system, and the influencing factors for ACR TI-RADS = 5 (TR5) nodules were analyzed. As shown in Table 3, there were no statistically significant differences in age, sex distribution, and BMI levels between TR5 and TR1 to 4 thyroid nodules (All P > 0.05). The levels of FBGL, FINS, HOMA-IR and HbA1c in patients with TR5 thyroid nodules were significantly higher than those in patients with TR1-4 (All P < 0.05). In terms of lipid metabolism, LDL-C levels in patients with TR5 thyroid nodules were significantly higher than those in TR1-4 groups (P < 0.05). However, TG, TC, and HDL-C levels were not statistically different between patients with TR5 and TR1 to 4 thyroid

nodules (All P > 0.05). Furthermore, patients with TR5 thyroid nodules had larger nodule diameters than those with TR1-4 nodules (P < 0.001). The proportion of patients with a family history of thyroid nodules was also significantly higher in the TR5 group compared to the TR1-4 group (P < 0.05).

Logistic regression analysis of influencing factors of thyroid nodules with different ACR TI-RADS classification in diabetic patients

Seven candidate variables with P < 0.05 in the univariate were included in the multivariate Logistic regression analysis and the results are shown in Table 4 and Figure 2. When FBGL, FINS and HOMA-IR levels were included in multivariate Logistic regression analysis, the significant effect on the risk of TR5 thyroid nodules disappeared (All $P > 0.05$), suggesting that these factors were not independent risk factors for the development of TR5 thyroid. In addition, HbA1c was an independent risk factor for the development of TR5 thyroid nodules (OR = 1.566, $P < 0.05$). When HbA1c increased by 1, diabetic patients had an independent 56.6% increased risk of developing TR5 thyroid nodules. There was no significant independent effect of LDL-C on the occurrence of TR5 thyroid nodules ($P > 0.05$). In addition, nodule diameter was an independent risk factor for the development of TR5 thyroid nodules (OR = 1.433, $P < 0.01$). This indicates that diabetic patients with a family history of thyroid nodules have a 1.729-fold increased risk compared to those without a family history.

Consistency analysis of thyroid nodules with different ACR TI-RADS classification and Bethesda score in patients with diabetes mellitus

All 236 study participants underwent FNAC and results were analyzed concordantly using the ACR TI-RADS and Bethesda scoring systems. Table 5 displays the results for 211 patients. 28 nodules unable to be adequately classified as benign or malignant (Bethesda 1 = 4, Bethesda 3 = 10, Bethesda 4 = 11) were excluded from the analysis. Among the remaining nodules classified as TR3, only 2 had a Bethesda score of 5, while the others (n=67) were classified as Bethesda score 2. Of these TR3 nodules, 97.10% (67/69) were pathologically confirmed as benign, demonstrating 97.10% agreement with the Bethesda scoring system. Out of the 112 TR4 nodules, 15 were classified as Bethesda score 5 and 9 as Bethesda score 6. Of these, 88 were confirmed as benign, indicating that 78.57% (88/112) did not support the ACR TI-RADS recommendation. However, it should be noted that 5 nodules with a Bethesda score of 5 showed negative pathological findings. For TR5 nodules, which were recommended for FNAC, 12 had a Bethesda score of 5 and 18 had a Bethesda score of 6. All TR5 nodules were confirmed as malignant, supporting the ACR TI-RADS recommendation.

DISCUSSION

The thyroid gland is one of the target tissues that affected by metabolic disorders [19]. Among endocrine and metabolic system issues, type 2 diabetes mellitus and thyroid disease stand out as the most prevalent [20]. Diabetes mellitus has been shown to be closely related to the development of thyroid nodules, and there is a positive correlation between blood glucose and the formation of thyroid nodules [21]. Insulin resistance, characterized by hyperglycemia and high insulin levels, serves as the primary trigger in the onset of most type 2 diabetes cases. Excessive insulin can bind to insulin-like

growth factor binding proteins, thereby increasing levels of free insulin-like growth factor 1 (IGF-1) in the blood [22]. IGF-1 and its receptors have been shown to be expressed in follicular and C cells of the thyroid gland and involved in cell regulation and proliferation [23]. One of the target tissues for disturbance of glucose metabolism is the thyroid gland, and the statement that insulin resistance, hyperinsulinemia are associated with the development of thyroid nodules has been confirmed by Ayturk et al. [24]. In addition, Auchincloss et al. reported that insulin receptors are expressed in both thyroid cells and insulin, and that increased insulin levels may reduce production of IGF-1 binding proteins, leading to elevated levels of free IGF-1, which subsequently stimulates protein and DNA synthesis and promotes mitosis in thyroid cells [25]. Belfiore et al. found that insulin itself is a pro-cytokine that can induce the growth, differentiation and proliferation of thyroid cells and stimulate thyroid nodule formation [26]. In the present study, FBGL, FINS, HOMA-IR, HbA1c levels, and diabetes progression were significantly higher in patients with type 2 diabetes mellitus and thyroid nodules than in the non-nodular group. In addition, the results of logistic regression analysis showed that both FBGL level and diabetes progression were independent risk factors for the development of thyroid nodules. Currently, the exact mechanism linking disturbances in glucose metabolism to thyroid nodules remains unclear. However, we hypothesize that insulin not only acts as a glucose-lowering hormone but also promotes vascular endothelial cell proliferation. Prolonged exposure to high glucose levels in poorly controlled type 2 diabetes patients can lead to insulin resistance and mild inflammatory responses in cells and tissues, thereby promoting angiogenesis in thyroid nodules.

Currently, due to the widespread use of high-frequency ultrasound in thyroid nodule diagnosis, there has been a significant increase in nodule detection rates. The ACR TI-RADS grading system serves as a method for assessing the risk of thyroid malignancy based on ultrasonographic features. It is

generally accepted that TR1-3 nodules can be considered as benign nodules, while TR4-5 should be highly suspected of malignancy [27]. However, recent studies have revealed that the optimal diagnostic threshold on the ROC curve for distinguishing between benign and malignant thyroid nodules is > TR4, indicating that TR5 nodules are highly suspicious for malignancy. Therefore, we categorized all patients with thyroid nodules into TR1-4 and TR5 groups to further explore the factors influencing the malignancy of thyroid nodules. The results of this study showed that FBGL, FINS, HOMA-IR and HbA1c levels were significantly higher in patients with TR5 thyroid nodules than in patients with TR1 to 4. Furthermore, logistic regression analysis identified HbA1c levels as an independent risk factor for elevated TNs grade in patients with type 2 diabetes mellitus. This may be attributed to impaired glucose tolerance leading to insulin resistance, subsequently triggering a chronic inflammatory response and increasing TNs grade. Additionally, Yildirim et al. discovered that insulin resistance poses a risk factor for papillary thyroid cancer, indicating a significant link between insulin resistance and malignant thyroid lesions, which aligns with our findings [28].

In this study, no statistically significant difference was observed in the distribution of sexes between thyroid nodules and controls, nor between the different ACR TI-RADS groups. This finding contrasts with the research by Li et al., which suggested a higher likelihood of thyroid nodules in women [29]. This inconsistency could be attributed to the relatively small sample size of our study and the specific selection of diabetic patients. It's known that cellular hyperplasia and fibrosis in the thyroid gland increase with age, contributing to the formation of thyroid nodules [6]. However, it has also been suggested that the increased incidence of TNs in the elderly is largely attributable to more extensive thyroid ultrasonography in the elderly population [30]. The results of this study indicate that age independently acts as a risk factor for thyroid nodules in diabetic patients, with the risk increasing by

14.9% for each additional year of age. This finding is in line with Guth et al.'s research, which demonstrated a higher prevalence of thyroid nodules among the elderly, with nearly 80% incidence in individuals aged ≥ 60 years[30]. However, it has been shown that the incidence of malignant thyroid nodules decreases with age [31]. A study of thyroid fine-needle aspiration revealed that the prevalence of thyroid cancer was 17% to 23% in the 20 to 49-year-old group, compared to only 13% in patients aged 70 years (± 14 years), suggesting a reduced prevalence of malignant nodules in older patients [31]. Interestingly, our study found no statistically significant difference in age between patients with TR5 and those with TR1-4 thyroid nodules, suggesting that age may not play a significant role in the degree of thyroid malignancy.

In 2015, Bétry and colleagues found that individuals with higher BMI can stimulate abnormal proliferation and differentiation of individual thyroid tissues by inducing local systemic metabolic disturbances, causing abnormalities in the hypothalamic-pituitary thyroid axis Similarly, Sari et al. discovered that higher BMI and body fat content were associated with elevated concentrations of TSH and larger thyroid gland volumes [32]. Similarly, Sari et al. discovered that higher BMI and body fat content were associated with elevated concentrations of TSH and larger thyroid gland volumes. In addition, Kitahara et al conducted a prospective study of 434,953 men and 413,3979 women in the United States and demonstrated a significant positive association between BMI and thyroid cancer risk [33]. However, in our study, BMI levels did not differ statistically between TR5 and TR1-4 nodules, possibly due to the small sample size. Furthermore, our study demonstrated that levels of triglycerides (TG), total cholesterol (TC), and low-density lipoprotein cholesterol (LDL-C) were notably higher in diabetic patients with thyroid nodules compared to controls, with LDL-C levels being identified as independent risk factors for thyroid nodule development in diabetic patients. Lee et al. have shown a

close relationship between TC, LDL-C, and thyroid-stimulating hormone (TSH) levels in patients with hyperthyroidism, suggesting that lipid metabolism influences TSH levels, thereby influencing thyroid nodules[34]. The current "hypothalamic-pituitary-thyroid-adipose tissue balance" hypothesis may explain the mechanism by which lipids affect thyroid nodules [34]. Elevated blood lipids, which can induce leptin resistance, play a role in regulating the expression of thyrotropin-releasing hormone genes[34]. Clinically, dyslipidemia usually coexists with thyroid disorders, and both hypersecretion and hypothyroid hormone can cause dyslipidemia [35]. Hypersecretion of thyroid hormones enhances metabolism, leading to decreased lipid levels, while decreased thyroid hormone secretion slows metabolism, resulting in elevated lipid levels. Additionally, excessive fat deposition in individuals with hyperlipidemia can increase the autoinflammatory response and promote the overexpression of inflammatory factors such as IL-6 and MCP-1, potentially contributing to thyroid nodule formation [36].

At present, the treatment of thyroid nodules primarily falls into two categories. Benign nodules are typically managed through observation, with surgery or radiofrequency ablation performed electively if compression symptoms arise [37]. Conversely, if nodules exhibit malignant characteristics, surgical intervention is usually warranted [37]. Therefore, distinguishing between benign and malignant thyroid nodules remains a pivotal clinical concern[38]. At present, fine-needle aspiration cytology (FNAC) is the most effective method differentiating between benign and malignant thyroid nodules [39]. However, given that the majority of nodules are benign, and FNAC is an invasive procedure, not all nodules necessitate FNAC[40]. Hence, there is a need for an effective, noninvasive approach to identify which nodules require FNAC. ACR TI-RADS offers a set of simple, easily and standardized classification criteria, effectively mitigating diagnostic bias arising from varying levels of ultrasound

expertise among practitioners. Hoang et al utilized ACR TI-RADS classification to assess the diagnostic accuracy of thyroid nodules and found notable improvement in diagnostic precision[41]. The results of this study show that 97.10% of TR3 nodules in diabetic patients with thyroid nodules do not recommend further FNAC examination as their pathological findings were benign, contradicting the ACR TI-RADS recommendation of FNAC for TR3 to TR5 nodules. Additionally, nodule diameter emerged as an independent risk factor for the development of TR5 nodules (OR = 1.433, $P < 0.01$). Consequently, nodal malignancy risk increased by 86.6% when the nodule diameter reached 3 cm. Thus, we propose that TR3 nodules ≥ 3 cm in diameter should be considered for further FNAC examination.

Furthermore, among 112 TR4 nodules, 88 were benign, indicating that 78.57% (88/112) of these nodules did not align with the ACR TI-RADS recommendation. Hence, we suggest that the determination of TR4 nodules for further FNAC examination should be based on additional parameters such as nodule size, morphology, calcification, etc. Moreover, all TR5 nodules were malignant, affirming the ACR TI-RADS recommendation.

There are several limitations to this study: (1) It relies on a single data source, lacks a multicenter control analysis, and the sample size is small, potentially introducing bias and limit the generalizability of the results to other clinical settings and patient groups; (2) Due to space constraints, factors such as patient lifestyle, iodine status, occupational exposure, nodule characteristics, and other related environmental factors were not included in the analysis; (3) The distinction between benign and malignant subgroups within TR4 nodules remains unexplored and warrants further investigation.

CONCLUSION

In summary, thyroid nodules in patients with T2DM are linked to age, BMI, and metabolic factors like blood sugar and lipid levels. The risk of thyroid nodule malignancy is also associated with blood sugar and lipid metabolism indicators. Patients with T2DM generally exhibit a low risk of malignancy within the TR3 classification of thyroid nodules, thus further FNAC testing is typically not recommended. However, nodules classified as TR3 with a diameter of 3 cm or more may need further FNAC assessment. For nodules classified as TR4 to TR5, additional FNAC should be considered on an individual basis. When using the ACR TI-RADS risk assessment system, it may be necessary to clarify the nodule category, scoring criteria, etc. to accurately diagnose and distinguish between benign and malignant nodules, and guide clinical management more effectively.

Informed consent

Informed consent has been obtained from the guardians of all patients for publication.

Authors' contributions

Ying Wang, Xi Chen, Yu Chen, Fei Xie Zhuoyan Wang and Runyue Mao analyzed the data and drafted the manuscript, and Ligang Wang contributed to the study design and critical revision. All authors reviewed and approved the final version of the manuscript.

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481 **TABLES AND FIGURES WITH LEGENDS**

482 **Table 1.** Univariate analysis of thyroid nodules in diabetic patients.

Variable		Thyroid nodule (n = 245)	Control (n = 397)	t/Z/X2	*P*
Age		56.00 (51.00, 61.00)	47.00 (43.00, 52.00)	5.344	<0.001
Sex	Male	118	171	1.586	0.208
	Female	127	226		
BMI		26.42±2.53	24.96±2.83	6.771	<0.001
FBGL (mmol/L)		9.24 (8.27, 10.07)	8.31 (7.60, 9.30)	3.468	<0.001
FINS (mIU/L)		17.70 (12.66, 20.38)	14.48 (11.73, 16.98)	3.993	<0.001
HOMA-IR		7.13 (5.14, 8.56)	5.31 (4.32, 6.50)	4.841	<0.001
HbA1c (%)		7.61 (6.83, 8.48)	7.54 (6.33, 8.99)	1.886	0.002
TG (mmol/L)		2.04 (1.56, 2.56)	1.96 (1.70, 2.23)	2.388	<0.001
TC (mmol/L)		3.97 (3.01, 4.82)	3.86 (3.28, 4.50)	1.615	0.011
HDL-C (mmol/L)		0.97±0.16	1.01±0.26	-2.916	0.004
LDL-C (mmol/L)		2.76±0.43	2.67±0.48	2.409	0.016
Diabetic progression	<10 yrs	79	355	226.132	<0.001
	≥10 yrs	166	42		
Family history of thyroid nodules	Yes	55	23	39.376	<0.001
	No	190	374		

Table 2. Analysis of independent risk factors for thyroid nodules in diabetic patients.

Variable	B	SE	WaldX2	*P*	OR	95%CI
Age	0.139	0.017	64.382	<0.001	1.149	(1.111-1.189)
BMI	0.160	0.048	11.143	<0.001	1.173	(1.068-1.289)
FBGL	0.918	0.335	7.527	0.006	2.504	(1.300-4.824)
FINS	0.196	0.196	1.006	0.316	1.217	(0.829-1.785)
HOMA-IR	-0.152	0.477	0.101	0.750	0.859	(0.337-2.189)
HbA1c	0.000	0.070	0.000	1.000	1.000	(0.871-1.148)
TG	0.343	0.238	2.083	0.149	1.410	(0.884-2.247)
TC	-0.018	0.116	0.024	0.876	0.982	(0.782-1.233)
HDL-C	-0.572	0.527	1.175	0.278	0.565	(0.201-1.587)
LDL-C	0.668	0.275	5.925	0.015	1.951	(1.139-3.342)
Diabetes progression ≥ 10 yrs	2.195	0.271	65.741	<0.001	8.979	(5.282-15.263)
Family history of thyroid nodules = Yes	1.289	0.380	11.522	<0.001	3.628	(1.724-7.635)

Table 3. Univariate analysis of thyroid nodules by ACR TI-RADS classification in diabetic patients.

Variable		ACR TI-RADS =1~4 （n=211）	ACR TI-RADS =5 （n=34）	t/Z/X2	*P*
Age		56.00 (51.00, 61.00)	57.50 (50.00, 61.00)	0.536	0.936
Sex	Male	103	15	0.259	0.611
	Female	108	19		
BMI		26.16±2.42	27.03±2.37	1.949	0.052
FBGL (mmol/L)		9.28 (8.41, 10.23)	9.81 (9.36, 10.37)	2.031	<0.001
FINS (mIU/L)		17.24 (11.80, 20.18)	19.51 (16.07, 22.72)	1.455	0.029
HOMA-IR		7.05 (5.09, 8.39)	8.44 (7.03, 9.59)	1.763	0.004
HbA1c (%)		7.53 (6.76, 8.37)	7.95 (7.53, 9.09)	1.450	0.030
TG (mmol/L)		2.00 (1.52, 2.56)	2.07 (1.67, 2.57)	0.728	0.664
TC (mmol/L)		3.89 (2.97, 4.71)	4.61 (3.30, 5.14)	1.300	0.068
HDL-C (mmol/L)		0.96±0.16	0.99±0.16	1.010	0.314
LDL-C (mmol/L)		2.73±0.42	2.94±0.42	2.692	0.008
Nodal diameter		4.58 (2.30, 6.46)	6.04 (4.76, 6.71)	2.000	<0.001
Diabetic progression	<10 yrs	96	11	2.057	0.152
	≥10 yrs	115	23		
Family history of thyroid nodules	Yes	42	13	5.651	0.017
	No	169	21		

Table 4. Analysis of independent risk factors of thyroid nodules by ACR TI-RADS classification in diabetic patients.

Variable	B	SE	WaldX2	P	OR	95%CI
FBGL	-0.088	0.487	0.033	0.856	0.916	(0.353-2.376)
FINS	-0.149	0.260	0.330	0.566	0.861	(0.518-1.433)
HOMA-IR	0.590	0.580	1.033	0.309	1.803	(0.578-5.622)
HbA1c	0.448	0.182	6.084	0.014	1.566	(1.096-2.235)
LDL-C	0.969	0.531	3.336	0.068	2.637	(0.932-7.462)
Nodal diameter	0.360	0.108	11.049	0.001	1.433	(1.159-1.772)
Family history of thyroid nodules	1.004	0.460	4.765	0.029	2.729	(1.108-6.722)

494 **Table 5.** Consistency analysis of thyroid nodules and bethesda scores by ACR TI-RADS classification.

Bethesda score	ACR TI-RADS Classification									
	1		2		3		4		5	
	+	-	+	-	+	-	+	-	+	-
2	0	2	0	4	0	67	0	88	0	0
5	0	0	0	0	2	0	10	5	12	0
6	0	0	0	0	0	0	9	0	18	0
X2						185.003				
P						<0.001				

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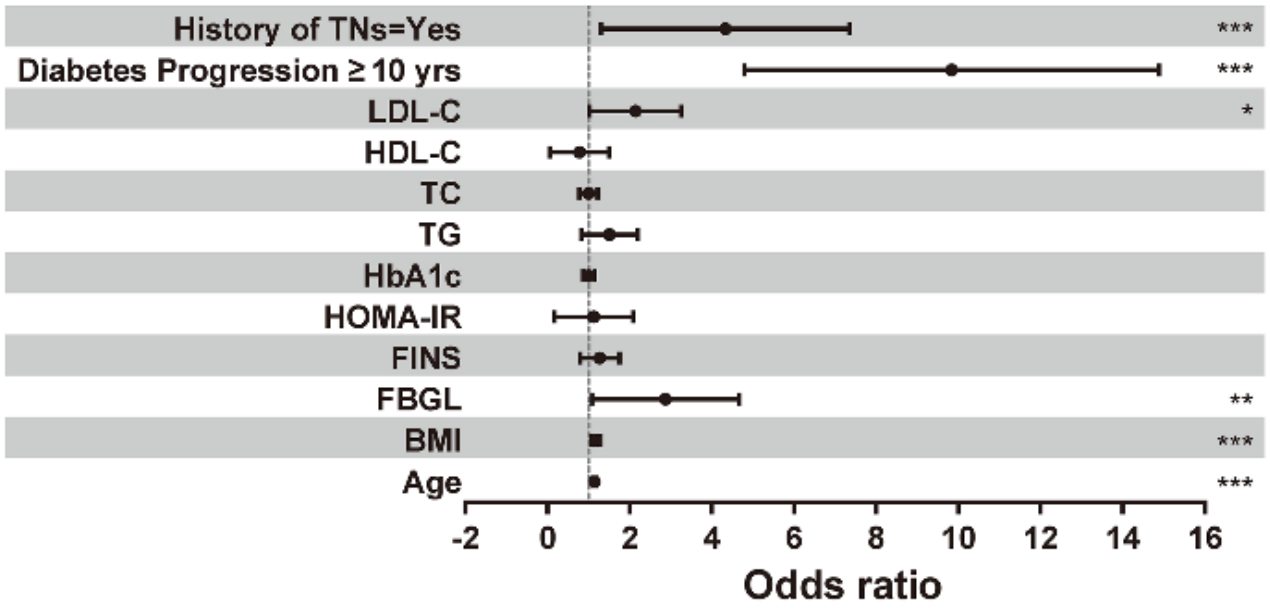

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498 **Figure 1. Logistic regression analysis of influencing factors of thyroid nodules in diabetic patients.**

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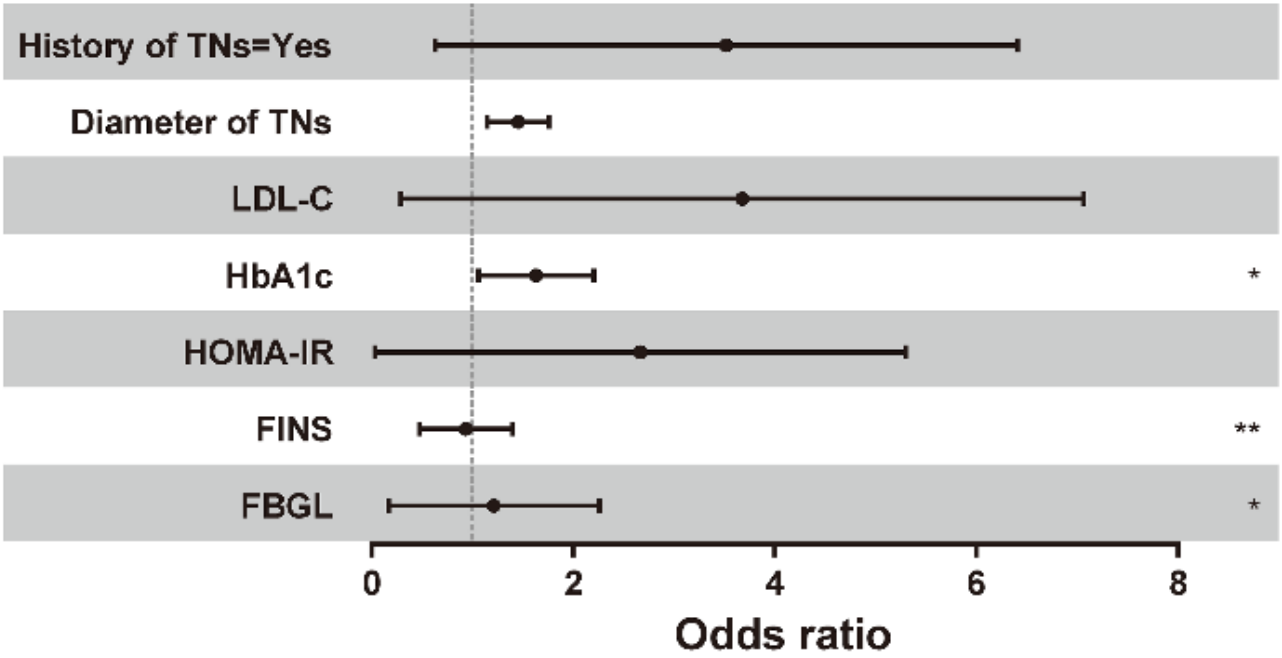

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501 **Figure 2. Logistic regression analysis of influencing factors of thyroid nodules with different**

502 **ACR TI-RADS classification.**