Am J Transl Res 2025;17(3):1938-1949
www.ajtr.org /ISSN:1943-8141/AJTR0160877

Original Article

Correlation between ultrasound characteristics of thyroid microcarcinoma and levels of thyroid-stimulating hormone and vascular endothelial growth factor

Jian Li[1], Miaoli Shi[1], Xiaobo Sun[2], Bihong Zhang[1], Yong Cao[1], Jian Su[1], Zhiqiang Chen[3]

[1]Department of Ultrasound, Boai Hospital of Zhongshan, Zhongshan 528403, Guangdong, China; [2]Department of Orthopedics, Ganzhou Hospital of Traditional Chinese Medicine, Ganzhou 341000, Jiangxi, China; [3]Department of Pathology, Boai Hospital of Zhongshan, Zhongshan 528403, Guangdong, China

Received September 30, 2024; Accepted January 25, 2025; Epub March 15, 2025; Published March 30, 2025

Abstract: Objectives: To investigate the role of thyroid-stimulating hormone (TSH) and vascular endothelial growth factor (VEGF) in the ultrasound characteristics of thyroid microcarcinoma (TMC). Methods: In this retrospective cohort study, data from 223 TMC patients (January 2018 - January 2023) were analyzed. Patients were grouped based on their baseline serum TSH and VEGF levels. Thyroid ultrasound images were evaluated for morphological features associated with TSH and VEGF concentrations. Results: A significant correlation was found between elevated TSH levels and increased nodule diameter (rho = 0.193, P = 0.004), clearer margins (rho = 0.196, P = 0.003), and microcalcifications (rho = 0.256, P < 0.001). Capsule invasion showed a negative correlation with TSH (rho = -0.180, P = 0.007). Similar associations were observed with higher VEGF levels, which correlated positively with larger nodule size (rho = 0.189, P = 0.005), clearer margins (rho = 0.186, P = 0.005), and microcalcifications (rho = 0.265, P < 0.001), but negatively with capsule invasion (rho = -0.169, P = 0.012). Conclusion: This study supports the hypothesis that elevated TSH and VEGF levels are associated with characteristic ultrasound features in TMC, which may serve as potential biomarkers for more accurate risk stratification.

Keywords: Correlation, thyroid microcarcinoma, ultrasound thyroid imaging characteristics, thyroid-stimulating hormone, vascular endothelial growth factor

Introduction

Thyroid microcarcinoma (TMC), defined as thyroid carcinoma with a maximum diameter of 1 cm or less, is a distinct subset of papillary thyroid carcinoma (PTC) [1]. Despite its small size, TMC represents a significant proportion of newly diagnosed thyroid cancers, with its incidence rising due to advancements in imaging techniques and increased surveillance [2]. Although TMC generally has a favorable prognosis, understanding its biological behavior is essential, as it may exhibit aggressive features, such as extrathyroidal extension and lymph node metastasis [3].

Among the available diagnostic tools, ultrasound imaging plays a crucial role in the evaluation, characterization, and monitoring of thyroid nodules, including TMC [4]. Key ultrasound features, such as nodule size, echogenicity, calcifications, and vascularity, provide valuable insights for distinguishing malignant from benign lesions [5]. However, the relationship between these imaging characteristics and underlying pathophysiological processes, especially the roles of hormonal and angiogenic factors, remains an active area of research [6].

Thyroid-stimulating hormone (TSH) is a major endocrine regulator in thyroid metabolism, and its role in the pathogenesis of thyroid malignancies has been well-documented [7]. Elevated TSH levels have been associated with an increased risk and progression of thyroid cancer, suggesting that TSH may promote tumor growth and transformation through direct effects on thyroid follicular cells [8]. The prognostic significance of serum TSH levels in patients with differentiated thyroid cancer highlights the

https://doi.org/10.62347/YRTV7362

importance of investigating its association with specific imaging characteristics, which could improve risk stratification and management protocols [9].

Similarly, vascular endothelial growth factor (VEGF), a key mediator of angiogenesis, plays an essential role in thyroid cancer biology by promoting neovascularization, which facilitates tumor growth and metastasis [10]. While elevated serum VEGF levels have been linked to poor prognosis in various malignancies, its specific role in TMC remains underexplored [11]. Understanding the relationship between serum VEGF levels and the ultrasound features of TMC could offer valuable insights into the tumor's biological behavior and open new avenues for therapeutic interventions. This study primarily aims to correlate ultrasound imaging characteristics with baseline serum levels of TSH and VEGF.

Materials and methods

Case selection

This retrospective cohort study included 223 patients diagnosed with TMC at Boai Hospital of Zhongshan between January 2018 and January 2023. Demographic data and thyroid ultrasound imaging characteristics were systematically collected from these patients.

The study utilized de-identified data, posing no risk to patient care, and therefore did not require informed consent. The exemption from informed consent, as well as the study itself, was approved by the Ethics Review Committee of Boai Hospital of Zhongshan and was conducted in accordance with applicable regulatory and ethical standards for retrospective research.

Inclusion and exclusion criteria

Inclusion criteria for this study were as follows: (1) Participants must be over 18 years of age, have no history of mental illness, exhibit normal cognitive function, and be capable of cooperating with various treatments and examinations [12]; (2) Participants must have a pathological diagnosis of TMC, characterized by a tumor diameter of ≤ 1 cm [13]; (3) Participants must have no other thyroid diseases, such as multinodular goiter or thyroid adenoma.

Exclusion criteria included: (1) Patients with other malignant tumors [12]; (2) Patients with severe liver or kidney dysfunction that may lead to abnormal serum levels of TSH or VEGF; (3) Patients with known autoimmune diseases that could influence TSH levels; (4) Pregnant or lactating patients; (5) Patients who had received radioactive iodine treatment or other thyroid-related therapies within the past six months.

Grouping method

This study used baseline serum levels of TSH and VEGF from the same cohort to form two distinct groups: one based on serum TSH levels and the other based on serum VEGF levels.

Ultrasound measurement

Ultrasound imaging was performed using a Canon Aplio 500 with a linear array probe operating at a frequency of 9-11 MHz. Patients were positioned supine with their heads tilted back for optimal exposure of the anterior neck. A multi-angle sectional scan of the bilateral thyroid and cervical lymph nodes was performed, and grayscale ultrasound findings, along with blood flow distribution characteristics, were documented. Image acquisition, recording, and analysis were managed by two professional physicians. Any discrepancies in analysis were resolved through discussion to reach consensus.

Serum TSH and VEGF levels were measured using immunohistochemistry with the UniCel DxI 800 fully automated chemiluminescence immunoassay analyzer (Beckman Coulter, Inc., USA).

Group division

Based on the average serum TSH level of 4.16 ± 1.52 mU/L, a threshold of 4.16 mU/L was established. Patients were divided into two groups: a high TSH group (n = 104) with TSH levels ≥ 4.16 mU/L, and a low TSH group (n = 119) with TSH levels < 4.16 mU/L.

Similarly, using the mean serum VEGF level of 26.32 ± 8.34 U/mL, a threshold of 26.32 U/mL was set. Patients were divided into a high VEGF group (n = 107) with VEGF levels ≥ 26.32

Table 1. General information of patients with different TSH levels

Parameters	Low TSH group (n = 119)	High TSH group (n = 104)	t/χ^2	P
Age (years)	45.32 ± 12.13	44.81 ± 12.52	0.309	0.758
Gender (male/female)	38/81	32/72	0.035	0.852
BMI (kg/m^2)	24.21 ± 3.41	24.01 ± 3.51	0.434	0.664
Education level (years)	12.48 ± 3.19	12.73 ± 3.17	0.568	0.571
Employment, work for pay [n (%)]	92 (77.31%)	79 (76.00%)	0.057	0.812
Smoking history [n (%)]	26 (21.85%)	20 (19.23%)	0.232	0.63
Drinking history [n (%)]	15 (12.61%)	14 (13.46%)	0.036	0.85
Family history of thyroid disease [n (%)]	13 (10.92%)	11 (10.58%)	0.007	0.933
Duration of illness (months)	24.12 ± 12.34	23.98 ± 12.45	0.085	0.932
Adverse reaction symptoms (present/absent)	88/31	76/28	0.022	0.883

Note: BMI: body mass index; TSH: thyroid-stimulating hormone.

U/mL, and a low VEGF group (n = 116) with VEGF levels < 26.32 U/mL.

Diagnostic criteria for ultrasound image analysis

The diagnostic criteria for TMC included the absence of normal thyroid tissue between the tumor nodule boundary and the thyroid capsule. This was characterized by indistinct boundaries between the capsule and surrounding thyroid tissue, as well as tumor invasion into the capsule or anterior cervical tissue. Microcalcifications are identified as scattered punctate strong echoes, with or without acoustic shadows, and are defined as having a diameter of ≤ 1 mm [14]. Blood flow levels within TMC masses are classified according to the standards established by Chakrabarty et al. [15]. These levels were divided into four categories:

Level 0: No blood flow.

Level I: 1-2 blood flow signals, indicating very low blood flow.

Level II: 3-4 punctate blood flow signals or a distinct blood vessel, indicating moderate blood flow.

Level III: Multiple or patchy blood flow signals, indicating very high blood flow.

Statistical methods

Measurement data were expressed as mean ± standard deviation or median with interquartile range, depending on whether the data followed a normal distribution. Categorical data were expressed as frequency and percentage. Continuous variables between two groups were compared using unpaired t-tests. Statistical significance was set at $P < 0.05$. All statistical analyses were performed using SPSS 19 software (SPSS Inc., Chicago, IL, USA) and R software package 3.0.2 (Free Software Foundation, Inc., Boston, MA, USA).

Results

Comparison of general information

In this study investigating the relationship between thyroid ultrasound imaging characteristics and serum levels of TSH and VEGF, participants were categorized into two groups based on TSH levels: low TSH (n = 119) and high TSH (n = 104) (**Table 1**). The mean age for the low and high TSH groups was 45.32 ± 12.13 years and 44.81 ± 12.52 years, respectively ($t = 0.309$, $P = 0.758$). The gender distribution was similar between the groups, with 38 males and 81 females in the low TSH group and 32 males and 72 females in the high TSH group ($\chi^2 = 0.035$, $P = 0.852$). Body mass index (BMI) values were 24.21 ± 3.41 kg/m^2 in the low TSH group and 24.01 ± 3.51 kg/m^2 in the high TSH group ($t = 0.434$, $P = 0.664$). The mean years of education were 12.48 ± 3.19 for the low TSH group and 12.73 ± 3.17 for the high TSH group ($t = 0.568$, $P = 0.571$). Other factors, such as employment rate, smoking history, drinking history, family history of thyroid disease, illness duration, and adverse reaction symptoms, were similar between the two groups (all $P > 0.05$).

Table 2. Comparison of thyroid ultrasound morphological characteristics in TMC patients with different TSH levels

Parameters	Low TSH group (n = 119)	High TSH group (n = 104)	χ^2	P
Number (unifocal/multifocal)	84/35	68/36	0.692	0.405
Ultrasound location (unilateral/bilateral)	84/35	71/33	0.141	0.707
Maximum diameter [n (%)]			8.319	0.004
- > 0.05 mm	38 (31.93%)	53 (50.96%)		
- ≤ 0.05 mm	81 (68.07%)	51 (49.04%)		
Aspect ratio [n (%)]			2.671	0.102
- A/T ≥ 1	54 (45.38%)	36 (34.62%)		
- A/T < 1	65 (54.62%)	68 (65.38%)		
Margin [n (%)]			8.579	0.003
- Clear	51 (42.86%)	65 (62.50%)		
- Indistinct	68 (57.14%)	39 (37.50%)		
Capsule invasion [n (%)]			7.187	0.007
- Absent	66 (55.46%)	39 (37.50%)		
- Present	53 (44.54%)	65 (62.50%)		
Regularity of margin [n (%)]			0.512	0.474
- Yes	42 (35.29%)	32 (30.77%)		
- No	77 (64.71%)	72 (69.23%)		

Note: A/T: anteroposterior to transverse diameter ratio; TSH: thyroid-stimulating hormone.

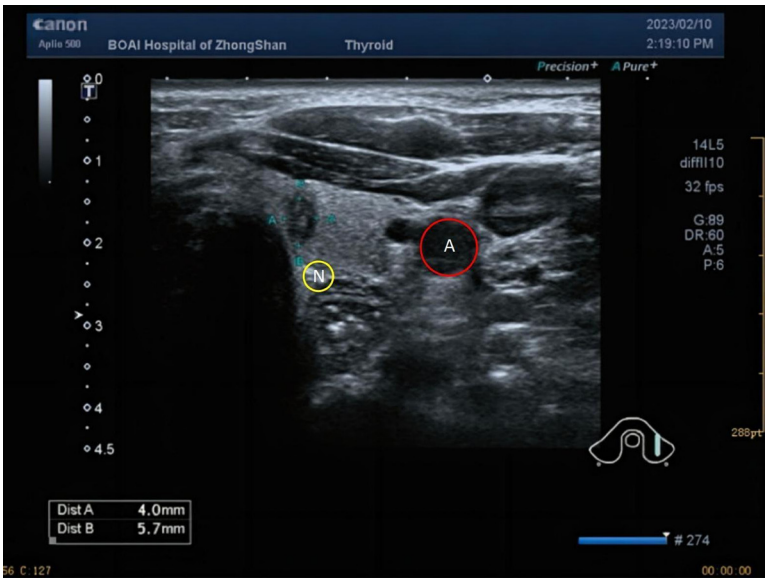

Figure 1. Typical and original figures of ultrasound thyroid imaging in TMC patients (A solid hypoechoic nodule in the left thyroid lobe of a 47-year-old male patient. The nodule measures 0.40 × 0.57 cm). Note: TMC: thyroid microcarcinoma.

Comparison of thyroid ultrasound morphological characteristics

Analysis of the thyroid ultrasound morphological characteristics showed significant differences in the maximum diameter, margin clarity, and capsule invasion of nodules (**Table 2**). **Figure 1** shows typical ultrasound images of TMC patients. A higher proportion of nodules in the high TSH group (50.96%) had a maximum diameter > 0.05 mm compared to the low TSH group (31.93%) (χ^2 = 8.319, P = 0.004). Margins were clearer in the high TSH group, with 62.50% of nodules demonstrating clear margins, compared to 42.86% in the low TSH group (χ^2 = 8.579, P = 0.003). Capsule invasion was present in a higher percentage of patients in the high TSH group (62.50%) compared to the low TSH group (44.54%) (χ^2 = 7.187, P = 0.007). No significant differences were found between the groups in terms of nodule number (unifocal vs. multifocal), ultrasound location (unilateral vs. bilateral), aspect ratio, or regularity of margins (P > 0.05). These findings suggest that higher TSH

Table 3. Comparison of thyroid ultrasound features in TMC patients with different TSH levels

Parameters	Low TSH group (n = 119)	High TSH group (n = 104)	χ^2	P
Halo sign [n (%)]			2.192	0.139
- Present	61 (51.26%)	43 (41.35%)		
- Absent	58 (48.74%)	61 (58.65%)		
Internal echo [n (%)]			1.937	0.164
- Hypoechoic	88 (73.95%)	68 (65.38%)		
- Hyperechoic	31 (26.05%)	36 (34.62%)		
Echo uniformity [n (%)]			2.377	0.123
- Uniform	46 (38.66%)	30 (28.85%)		
- Non-uniform	73 (61.34%)	74 (71.15%)		
Microcalcification [n (%)]			14.601	< 0.001
- Present	45 (37.82%)	66 (63.46%)		
- Absent	74 (62.18%)	38 (36.54%)		
Vascular flow Grading [n (%)]			4.505	0.212
- Grade 0	27 (22.69%)	15 (14.42%)		
- Grade I	27 (22.69%)	18 (17.31%)		
- Grade II	42 (35.29%)	46 (44.23%)		
- Grade III	23 (19.33%)	25 (24.04%)		

Note: TMC: thyroid microcarcinoma; TSH: thyroid-stimulating hormone.

levels are associated with specific ultrasound features that may be useful for the assessment and management of TMC.

Comparison of thyroid ultrasound features

Microcalcifications were more frequently observed in the high TSH group (63.46%) compared to the low TSH group (37.82%), with a statistically significant difference (χ^2 = 14.601, P < 0.001) (**Table 3**). No significant differences were found between the two groups for other ultrasound characteristics, including the presence of a halo sign, internal echo type, echo uniformity, and vascular flow grading (all P > 0.05). These results indicate that microcalcification prevalence is significantly associated with higher TSH levels in patients with TMC.

Correlation analysis of thyroid ultrasound imaging characteristics in TMC patients with different TSH levels

There was a positive correlation between TSH levels and the maximum diameter of thyroid nodules (rho = 0.193, P = 0.004), suggesting that higher TSH levels are associated with larger nodules (**Figure 2**). A positive correlation was also found between margin clarity and TSH levels (rho = 0.196, P = 0.003), indicating that higher TSH levels are associated with clearer nodule margins. Conversely, capsule invasion showed a negative correlation with TSH levels (rho = -0.180, P = 0.007), implying that higher TSH levels are linked to a lower occurrence of capsule invasion. The strongest correlation was observed with microcalcifications, which showed a significant positive association with TSH levels (rho = 0.256, P < 0.001).

Comparison of general information of patients with different VEGF levels

The mean age was similar between the low VEGF group (45.27 ± 12.23 years) and the high VEGF group (44.94 ± 12.49 years) (t = 0.199, P = 0.843) (**Table 4**). Gender distribution was consistent, with a male-to-female ratio of 36/80 in the low VEGF group and 34/73 in the high VEGF group (χ^2 = 0.014, P = 0.905). The mean BMI was 24.18 ± 3.45 kg/m^2 in the low VEGF group and 24.04 ± 3.53 kg/m^2 in the high VEGF group (t = 0.301, P = 0.764). Educational levels were comparable, with averages of 12.50 ± 3.20 years and 12.71 ± 3.15 years in the low and high VEGF groups, respectively (t = 0.498, P = 0.619). Other factors such as employment status, smoking and

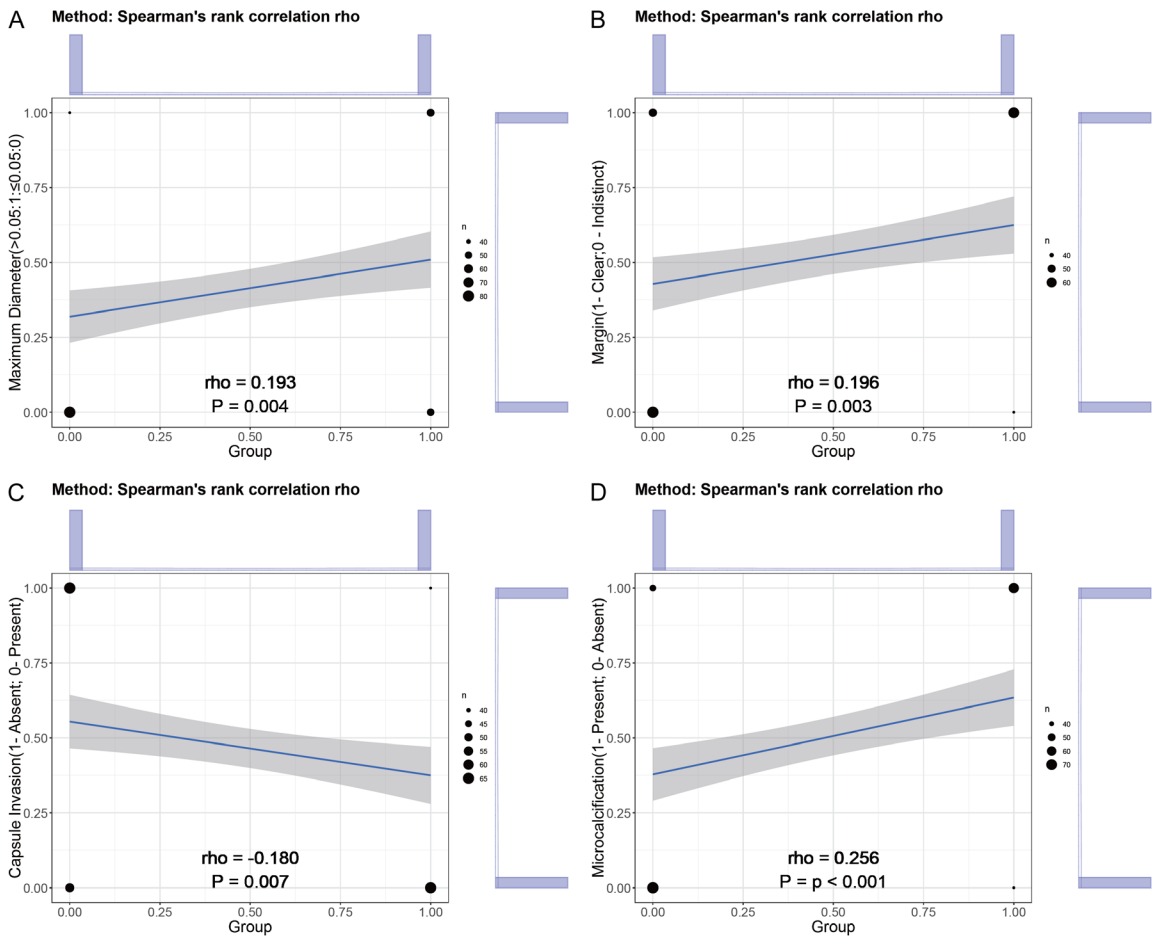

Figure 2. Correlation analysis of thyroid ultrasound imaging characteristics in TSH level TMC patients. A: Maximum diameter; B: Margin; C: Capsule invasion; D: Microcalcification. Note: TMC: thyroid microcarcinoma; TSH: thyroid-stimulating hormone.

Table 4. General information of patients with different VEGF levels

Parameters	Low VEGF group (n = 116)	High VEGF group (n = 107)	t/χ^2	P
Age (years)	45.27 ± 12.23	44.94 ± 12.49	0.199	0.843
Gender (male/female)	36/80	34/73	0.014	0.905
BMI (kg/m^2)	24.18 ± 3.45	24.04 ± 3.53	0.301	0.764
Education level (years)	12.50 ± 3.20	12.71 ± 3.15	0.498	0.619
Employment, work for pay [n (%)]	89 (76.72%)	82 (76.64%)	0	0.988
Smoking history [n (%)]	21 (18.10%)	25 (23.36%)	0.941	0.332
Drinking history [n (%)]	14 (12.07%)	15 (14.02%)	0.187	0.665
Family history of thyroid disease [n (%)]	12 (10.34%)	12 (11.21%)	0.044	0.834
Duration of illness (months)	24.07 ± 12.38	24.03 ± 12.49	0.024	0.981
Adverse reaction symptoms (present/absent)	85/31	79/28	0.009	0.925

Note: BMI: body mass index; VEGF: vascular endothelial growth factor.

drinking histories, family history of thyroid disease, disease duration, and the presence of adverse reaction symptoms were also similar between groups (all P > 0.05).

Table 5. Comparison of thyroid ultrasound morphological characteristics in TMC patients with different VEGF levels

Parameters	Low VEGF group (n = 116)	High VEGF group (n = 107)	χ^2	P
Number (unifocal/multifocal)	85/31	67/30	2.914	0.088
Ultrasound location (unilateral/bilateral)	83/33	72/35	0.477	0.490
Maximum diameter [n (%)]			7.947	0.005
- > 0.05 mm	37 (31.90%)	54 (50.47%)		
- ≤ 0.05 mm	79 (68.10%)	53 (49.53%)		
Aspect Ratio [n (%)]			0.757	0.384
- A/T ≥ 1	50 (43.10%)	40 (37.38%)		
- A/T < 1	66 (56.90%)	67 (62.62%)		
Margin [n (%)]			7.697	0.006
- Clear	50 (43.10%)	66 (61.68%)		
- Indistinct	66 (56.90%)	41 (38.32%)		
Capsule invasion [n (%)]			6.346	0.012
- Absent	64 (55.17%)	41 (38.32%)		
- Present	52 (44.83%)	66 (61.68%)		
Regularity of margin [n (%)]			2.457	0.117
- Yes	44 (37.93%)	30 (28.04%)		
- No	72 (62.07%)	77 (71.96%)		

Note: A/T: anteroposterior to transverse diameter ratio; TMC: thyroid microcarcinoma; VEGF: vascular endothelial growth factor.

Comparison of thyroid ultrasound morphological characteristics in TMC patients with different VEGF levels

In evaluating thyroid ultrasound morphological characteristics, significant differences were observed between the high and low VEGF groups in terms of maximum diameter, margin clarity, and capsule invasion (**Table 5**). The high VEGF group had a greater percentage of nodules with a maximum diameter > 0.05 mm (50.47%) compared to the low VEGF group (31.90%), which was statistically significant (χ^2 = 7.947, P = 0.005). The margin was clearer in the high VEGF group (61.68%) than that in the low VEGF group (43.10%) (χ^2 = 7.697, P = 0.006). Additionally, capsule invasion was more frequent in the high VEGF group (61.68%) compared to the low VEGF group (44.83%) (χ^2 = 6.346, P = 0.012). No significant differences were found for other parameters, such as nodularity (unifocal vs. multifocal), ultrasound location (unilateral vs. bilateral), aspect ratio, or margin regularity (all P > 0.05).

Comparison of thyroid ultrasound features in TMC patients with different VEGF levels

Patients in the high VEGF group exhibited a significantly higher prevalence of microcalcifications (63.55%) compared to those in the low VEGF group (37.07%) (χ^2 = 15.614, P < 0.001) (**Table 6**). No significant differences were found in other ultrasound characteristics, including the halo sign, internal echo pattern, echo uniformity, and vascular flow grading (all P > 0.05).

Correlation analysis of thyroid ultrasound imaging characteristics in TMC patients with VEGF levels

A positive correlation was observed between VEGF levels and maximum nodule diameter (rho = 0.189, P = 0.005), indicating that higher VEGF levels were associated with larger nodule sizes. Margin clarity also showed a positive correlation with VEGF levels (rho = 0.186, P = 0.005), suggesting that nodules with higher VEGF levels tend to have clearer margins (**Figure 3**). Conversely, capsule invasion demonstrated a negative correlation with VEGF levels (rho = -0.169, P = 0.012), indicating less frequent capsule invasion at higher VEGF levels. The strongest positive correlation was observed between VEGF levels and microcalcifications (rho = 0.265, P < 0.001), highlighting its strong association with elevated VEGF.

Discussion

This study examined the relationship between TMC ultrasound imaging characteristics and

Table 6. Comparison of thyroid ultrasound features in TMC patients with different VEGF levels

Parameters	Low VEGF group (n = 116)	High VEGF group (n = 107)	χ^2	P
Halo sign [n (%)]			2.514	0.113
- Present	60 (51.72%)	44 (41.12%)		
- Absent	56 (48.28%)	63 (58.88%)		
Internal echo [n (%)]			2.012	0.156
- Hypoechoic	86 (74.14%)	70 (65.42%)		
- Hyperechoic	30 (25.86%)	37 (34.58%)		
Echo uniformity [n (%)]			2.39	0.122
- Uniform	45 (38.79%)	31 (29.07%)		
- Non-uniform	71 (61.21%)	76 (70.93%)		
Microcalcification [n (%)]			15.614	< 0.001
- Present	43 (37.07%)	68 (63.55%)		
- Absent	73 (62.93%)	39 (36.45%)		
Vascular flow grading [n (%)]			3.018	0.389
- Grade 0	26 (24.14%)	16 (14.95%)		
- Grade I	24 (20.69%)	21 (19.63%)		
- Grade II	45 (38.79%)	43 (40.19%)		
- Grade III	21 (18.10%)	27 (25.23%)		

Note: TMC, thyroid microcarcinoma; VEGF, vascular endothelial growth factor.

serum levels of TSH and VEGF. One of the most notable findings was the significant association between higher TSH levels and specific ultrasound characteristics, including increased nodule size, clearer margins, higher prevalence of capsule invasion, and greater occurrence of microcalcifications. These results suggest that elevated TSH levels may contribute to more aggressive tumor characteristics, which are detectable on ultrasound imagings.

The relationship between TSH and thyroid tumor morphology can be partially explained by TSH's known role in stimulating thyroid follicular cells, which promotes the proliferation and growth of thyroid tumors [16]. Elevated TSH levels may exert a stimulatory effect on the tumor microenvironment, fostering tumor growth and potentially enhancing the structural changes that make nodules more distinguishable on ultrasound, as indicated by clearer margins and larger size [17]. This aligns with the established understanding that TSH plays a key role in thyroid cell growth and function, and its elevated levels may lead to the expansion of microcarcinomas, thus influencing imaging characteristics [18]. For example, a study by Mao et al. [19] found that higher TSH levels were associated with increased tumor size and a higher incidence of extrathyroidal extension in PTC patients, which supports our findings. Additionally, a meta-analysis by Liu et al. [20] reported a significant association between elevated TSH levels and an increased risk of lymph node metastasis in PTC, further substantiating the notion that TSH may play a crucial role in tumor aggressiveness.

Similarly, microcalcifications were more frequently observed in patients with higher TSH levels. Microcalcifications, often associated with psammoma bodies, are considered a hallmark of PTC and may reflect a pathophysiological process driven by increased TSH activity [21]. Calcification within the thyroid tissue could indicate both proliferative growth of neoplastic follicular cells and the subsequent degeneration of certain cellular components, a process potentially exacerbated by elevated TSH [22]. A study by Gao et al. [23] also reported a higher prevalence of microcalcifications in PTC patients with elevated TSH levels, supporting our findings.

Moreover, the significant negative correlation between TSH levels and capsule invasion is a surprising discovery, suggesting a complex interplay between TSH levels and tumor aggressiveness indicators. One plausible explanation for this inverse relationship is that increasing TSH levels might play a protective role in reduc-

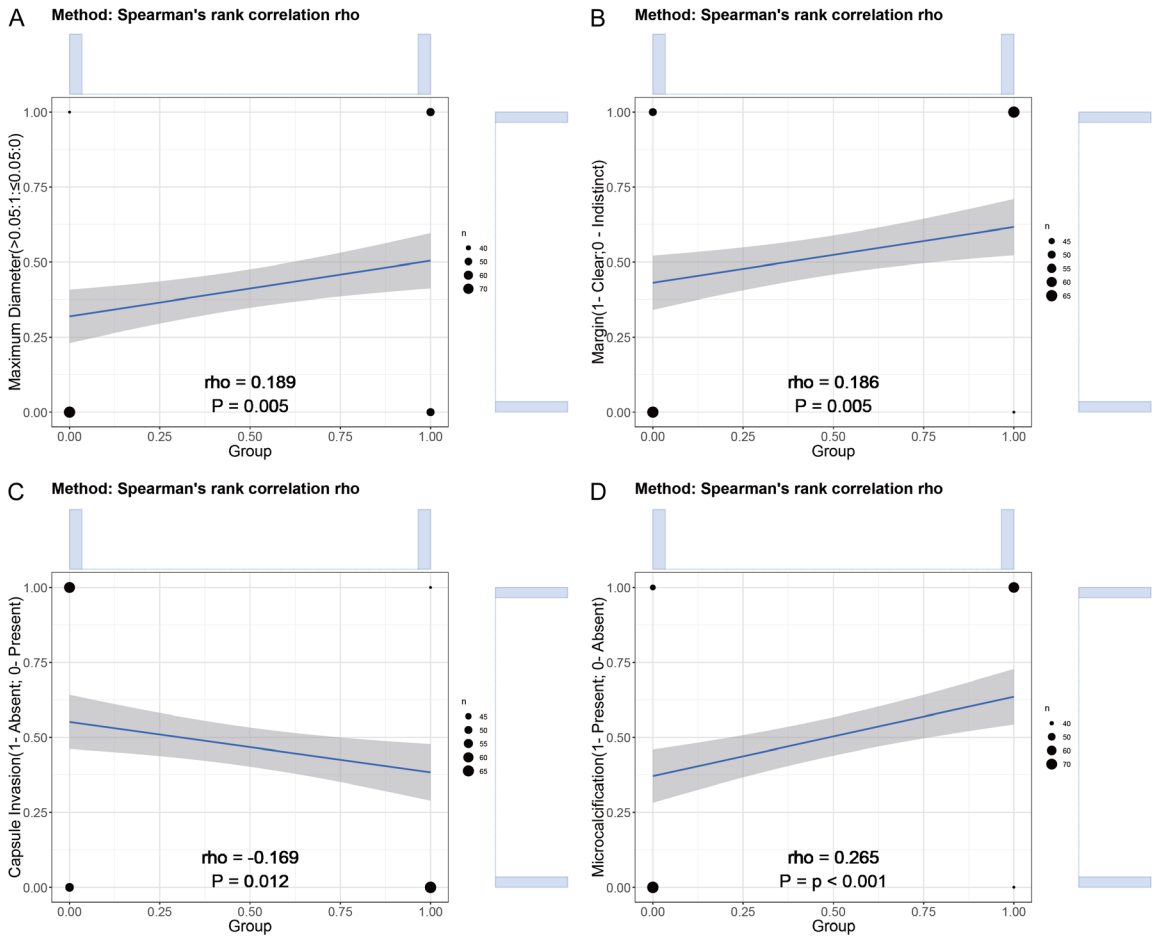

Figure 3. Correlation analysis of thyroid ultrasound imaging characteristics in TMC patients with VEGF levels. A: Maximum diameter; B: Margin; C: Capsule invasion; D: Microcalcification. Note: TMC: Thyroid microcarcinoma; VEGF: vascular endothelial growth factor.

ing local invasion [24]. However, this hypothesis requires further mechanistic studies to better understand its biological underpinnings.

Our analysis of VEGF provides equally compelling insights. As a key regulator of angiogenesis, VEGF's elevated serum levels in TMC patients were associated with specific ultrasound characteristics, including increased nodule diameter, clearer margins, and a higher incidence of capsule invasion and microcalcifications. These findings align with VEGF's role in promoting vascular growth within tumors, potentially leading to larger nodule sizes and more pronounced margins due to increased blood supply to the proliferating tumor [25-27].

The positive correlation between VEGF levels and microcalcifications may reflect the interplay between angiogenesis and mineral deposition within the tumor microenvironment. VEGF-driven angiogenesis can provide nutrients and growth factors, which support tumor expansion and structural changes, manifesting as microcalcifications [28]. This is consistent with the understanding that angiogenic inducers like VEGF not only remodel the vasculature but also influence the neoplastic pathways of dysplasia and calcification formation [29].

Interestingly, both TSH and VEGF levels showed a negative association with capsule invasion, indicating that higher levels of these factors might correlate with reduced invasiveness. This counterintuitive finding challenges the generally accepted view of these hormones promoting aggressive tumor behavior and suggests the activation of alternative biological routes or counterbalancing pathways in response to increased endocrine stimulation, potentially

limiting invasive growth. For instance, a study by Shi et al. [30] suggested that elevated VEGF levels might induce a compensatory downregulation of invasive enzymes, thereby reducing capsule invasion.

The combination of TSH and VEGF in predicting ultrasound characteristics supports the hypothesis of a synergistic interaction between endocrine disruption and angiogenic promoter activity within thyroid tumors [31]. The complex relationship between these factors and morphological changes may reflect underlying cellular and molecular processes that are not yet fully understood. This raises questions about how angiogenesis facilitators like VEGF might influence or interact with thyroid follicular responses to TSH, impacting cellular adaptations visible through non-invasive imaging modalities.

This study highlights the significance of biochemical markers like TSH and VEGF in enhancing the diagnostic and prognostic assessment of TMC. Their correlation with imaging characteristics opens the possibility of integrating serum biomarker evaluations with ultrasound features, offering a more comprehensive understanding of tumor dynamics. This could inform clinical management strategies and personalized patient care.

From a clinical perspective, our findings suggest that monitoring TSH and VEGF levels alongside traditional ultrasound evaluations could improve early detection of aggressive TMC phenotypes. Despite these insights, our study has limitations. First, as a retrospective analysis, it is constrained by its reliance on existing records, which may lack certain critical data or include inconsistencies in measurement techniques, potentially introducing bias and affecting the reliability of the findings. Additionally, the study sample, drawn from a single medical center, may not fully represent the broader population, limiting the generalizability of the results. The study also did not control for potential confounding variables, such as variations in patients' medical histories or environmental factors, which could independently influence serum TSH and VEGF levels or ultrasound findings. Furthermore, while correlations were observed, the causal mechanisms were not explored, highlighting the need for further prospective, longitudinal studies to validate these associations and clarify the underlying biological processes.

In conclusion, this study reveals a significant relationship between hormonal and angiogenic biomarkers and ultrasound imaging traits, providing insights into the biological behavior of TMC. It emphasizes the need for further mechanistic studies to explore the fundamental biological basis of these correlations, potentially leading to more effective management strategies for thyroid cancer.

Disclosure of conflict of interest

None.

Address correspondence to: Jian Li, Department of Ultrasound, Boai Hospital of Zhongshan, Zhongshan 528403, Guangdong, China. E-mail: masterlc98@163.com

References

[1] Kant R, Davis A and Verma V. Thyroid nodules: advances in evaluation and management. Am Fam Physician 2020; 102: 298-304.
[2] Pidchenko NS, Krasnoselskyi MV, Mitriaieva NA, Grebenik LV, Astapieva OM, Grushka GV, Paskevych OI, Fedulenkova YY and Myroshnychenk MS. Insulin-like growth factors in the serum of patients with papillary thyroid cancer. Wiad Lek 2021; 74: 1925-1930.
[3] Klain M, Hadoux J, Nappi C, Finessi M, Ambrosio R, Schlumberger M, Cuocolo A, Deandreis D and Salvatore D. Imaging medullary thyroid cancer patients with detectable serum markers: state of the art and future perspectives. Endocrine 2022; 75: 330-337.
[4] Trimboli P, Valderrabano P, Pitoia F, Piccardo A and Bojunga J. Appropriate and mindful measurement of serum calcitonin in patients with thyroid nodules. A white paper. Endocrine 2024; 83: 60-64.
[5] Ren B, Wan S, Liu L, Qu M, Wu H and Shen H. Distributions of serum thyroid-stimulating hormone in 2020 thyroid disease-free adults from areas with different iodine levels: a cross-sectional survey in China. J Endocrinol Invest 2021; 44: 1001-1010.
[6] Fan J, Fu S, Chen X, Li Y, Zhao Y, Lv F and Yao Y. Thyroid nodules and its association with vitamin D in centenarians. Exp Gerontol 2022; 161: 111730.
[7] Danzi S and Klein I. Thyroid abnormalities in heart failure. Heart Fail Clin 2020; 16: 1-9.
[8] Xia L, Lu J, Chen Z, Cui X, Chen S and Pei D. Identifying benign and malignant thyroid nod-

ules based on blood serum surface-enhanced Raman spectroscopy. Nanomedicine 2021; 32: 102328.
[9] Schlumberger M and Leboulleux S. Current practice in patients with differentiated thyroid cancer. Nat Rev Endocrinol 2021; 17: 176-188.
[10] Petranović Ovčariček P, Görges R and Giovanella L. Autoimmune thyroid diseases. Semin Nucl Med 2024; 54: 219-236.
[11] Giovanella L, Tuncel M, Aghaee A, Campenni A, De Virgilio A and Petranović Ovčariček P. Theranostics of thyroid cancer. Semin Nucl Med 2024; 54: 470-487.
[12] Freedman S and Wickramasekera IE 2nd. Review of the international hypnosis literature. Am J Clin Hypn 2020; 62: 159-165.
[13] Tan S, Sun PF, Xue H, Fu S, Zhang ZP, Mei F, Miao LY and Wang XH. Evaluation of thyroid micro-carcinoma using shear wave elastography: initial experience with qualitative and quantitative analysis. Eur J Radiol 2021; 137: 109571.
[14] Casaril A, Inama M, Impellizzeri H, Bacchion M, Creciun M and Moretto G. Thyroid follicular microcarcinoma. Gland Surg 2020; 9 Suppl 1: S54-S60.
[15] Chakrabarty N, Mahajan A, Basu S and D'Cruz AK. Comprehensive review of the imaging recommendations for diagnosis, staging, and management of thyroid carcinoma. J Clin Med 2024; 13: 2904.
[16] Leboulleux S, Bournaud C, Chougnet CN, Zerdoud S, Al Ghuzlan A, Catargi B, Do Cao C, Kelly A, Barge ML, Lacroix L, Dygai I, Vera P, Rusu D, Schneegans O, Benisvy D, Klein M, Roux J, Eberle MC, Bastie D, Nascimento C, Giraudet AL, Le Moullec N, Bardet S, Drui D, Roudaut N, Godbert Y, Morel O, Drutel A, Lamartina L, Schvartz C, Velayoudom FL, Schlumberger MJ, Leenhardt L and Borget I. Thyroidectomy without radioiodine in patients with low-risk thyroid cancer. N Engl J Med 2022; 386: 923-932.
[17] So S, Hashimoto K, Mori M, Endo S, Yamaguchi W, Miyano N, Murabayashi N and Tawara F. Serum thyroid-stimulating hormone receptor antibody levels and thyroid dysfunction after hysterosalpingography: a case-control study. Gynecol Endocrinol 2021; 37: 898-901.
[18] Li Y, Teng D, Ba J, Chen B, Du J, He L, Lai X, Teng X, Shi X, Li Y, Chi H, Liao E, Liu C, Liu L, Qin G, Qin Y, Quan H, Shi B, Sun H, Tang X, Tong N, Wang G, Zhang JA, Wang Y, Xue Y, Yan L, Yang J, Yang L, Yao Y, Ye Z, Zhang Q, Zhang L, Zhu J, Zhu M, Ning G, Mu Y, Zhao J, Shan Z and Teng W. Efficacy and safety of long-term universal salt iodization on thyroid disorders: epidemiological evidence from 31 provinces of mainland China. Thyroid 2020; 30: 568-579.
[19] Mao A, An N, Wang J, Wu Y, Wang T, Wang Z, Guan H and Wang J. Association between preoperative serum TSH and tumor status in patients with papillary thyroid microcarcinoma. Endocrine 2021; 73: 617-624.
[20] Liu XN, Duan YS, Yue K, Wu YS, Zhang WC and Wang XD. The optimal extent of lymph node dissection in N1b papillary thyroid microcarcinoma based on clinicopathological factors and preoperative ultrasonography. Gland Surg 2022; 11: 1047-1056.
[21] Ito M, Kawasaki M, Danno H, Kohsaka K, Nakamura T, Hisakado M, Yoshioka W, Kasahara T, Kudo T, Nishihara E, Fukata S, Nishikawa M, Nakamura H and Miyauchi A. Serum thyroid hormone balance in levothyroxine monotherapy-treated patients with atrophic thyroid after radioiodine treatment for graves' disease. Thyroid 2019; 29: 1364-1370.
[22] Sugisawa C, Narumi S, Tanase-Nakao K, Hoshiyama A, Suzuki N, Ohye H, Fukushita M, Matsumoto M, Yoshihara A, Watanabe N, Sugino K, Hishinuma A, Noh JY, Katoh R, Taniyama M and Ito K. Adult thyroid outcomes of congenital hypothyroidism. Thyroid 2023; 33: 556-565.
[23] Gao Y, Qu N, Zhang L, Chen JY and Ji QH. Preoperative ultrasonography and serum thyroid-stimulating hormone on predicting central lymph node metastasis in thyroid nodules as or suspicious for papillary thyroid microcarcinoma. Tumour Biol 2016; 37: 7453-7459.
[24] Gönülal M, Teker K, Öztürk A and Yaşar FY. Investigation of thyroid blood tests and thyroid ultrasound findings of patients with rosacea. Dermatol Ther 2021; 34: e14632.
[25] Goto M, Kimura N and Matsubara E. Association of serum thyroid hormone levels with positron emission tomography imaging in non-demented older adults. Psychogeriatrics 2022; 22: 373-381.
[26] Olejarz M, Szczepanek-Parulska E, Dadej D, Sawicka-Gutaj N, Domin R and Ruchała M. IgG4 as a biomarker in graves' orbitopathy. Mediators Inflamm 2021; 2021: 5590471.
[27] Li N, Zhang J, Meng X and Yao W. Clinical application value of high-frequency ultrasound combined with detection of serum high mobility group Box 1, soluble IL-2 receptor, and thyroglobulin antibody in diagnosing thyroid cancer. J Healthc Eng 2022; 2022: 7851436.
[28] Leimbach RD, Hoang TD and Shakir MKM. Diagnostic challenges of medullary thyroid carcinoma. Oncology 2021; 99: 422-432.
[29] Zhao J, Zheng X, Gao M, Zhang S, Yun X, Chi J and Xu G. Ultrasound features of medullary thyroid cancer as predictors of biological behavior. Cancer Imaging 2021; 21: 33.

[30] Shi C, Guo Y, Lv Y, Nanding A, Shi T, Qin H and He J. Clinicopathological features and prognosis of papillary thyroid microcarcinoma for surgery and relationships with the BRAFV600E mutational status and expression of angiogenic factors. PLoS One 2016; 11: e0167414.

[31] Fan H, Liu Z, Zhang X, Wu S, Shi T, Zhang P, Xu Y, Chen X and Zhang T. Thyroid stimulating hormone levels are associated with genetically predicted nonalcoholic fatty liver disease. J Clin Endocrinol Metab 2022; 107: 2522-2529.