

Original Article

Application and limitations of ultrasound for the early diagnosis of thyroid cancer: a systematic review and meta-analysis

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Abstract: Objective: To systematically evaluate the diagnostic performance of high-frequency ultrasound and its sonographic features in the early detection of thyroid cancer through a meta-analysis. Methods: A comprehensive search was conducted in PubMed, Embase, and Web of Science for studies published up to December 31, 2024. Studies assessing the diagnostic performance of high-frequency ultrasound and ultrasound-guided procedures for thyroid cancer were included based on predefined criteria. Extracted data included sensitivity, specificity, and the diagnostic relevance of sonographic features (e.g., nodule size, margin irregularity, echogenicity, calcifications, and vascularity). Study quality was assessed using the Quality Assessment of Diagnostic Accuracy Studies (QUADAS) tool. Meta-analytic methods were applied to pool diagnostic accuracy measures. Publication bias was evaluated using funnel plots. Results: A total of 14 studies were included. Combined diagnostic approaches, particularly high-frequency ultrasound combined with ultrasound-guided fine-needle aspiration biopsy (US-FNAB), demonstrated high sensitivity (ranging from 0.814 to 0.975) and specificity (ranging from 0.833 to 0.976). Key sonographic features significantly associated with malignancy included hypoechogenicity, microcalcifications, and irregular margins. Pooled analysis showed that microcalcifications and irregular margins were strong predictors for malignancy, with an overall Peto odds ratios (OR) of 39.47 [28.88, 53.94] for irregular margins ($P < 0.001$). Minimal publication bias was observed for most features, although mild asymmetry was noted in analyses involving microcalcifications. Conclusion: High-frequency ultrasound, particularly when combined with ultrasound-guided biopsy or contrast-enhanced ultrasound, provides high diagnostic accuracy for thyroid cancer. Specific features, such as hypoechogenicity, microcalcifications, and irregular margins, are valuable in differentiating malignant from benign thyroid nodules. Future studies should aim to standardize ultrasound-based diagnostic criteria and explore the use of multimodal imaging techniques to improve early thyroid cancer detection.

Keywords: Thyroid cancer, high-frequency ultrasound, early diagnosis, meta-analysis

Introduction

Thyroid cancer is the most prevalent malignant tumor of the endocrine system, with a steadily rising global incidence and public health significance. This upward trend places a dual burden on the patients' physical and psychological well-being, while simultaneously posing greater challenges to healthcare systems. Early-stage thyroid cancer typically refers to small, localized tumors confined to the thyroid gland without distant metastasis. At this stage, most patients are asymptomatic, and diagnoses are often incidental during routine check-ups or

examinations for other conditions. Early detection is critical for treatment and prognosis of thyroid cancer. Patients treated at early stages have significantly higher five-year survival rates and better quality of life compared to those diagnosed at later stages [1, 2].

High-frequency ultrasound, characterized by non-invasive procedure, operational simplicity, low cost, and high reproducibility, is a widely used diagnostic tool for thyroid cancer [3]. It enables detailed visualization of thyroid anatomy, facilitating the identification of small nodules and subtle lesions. Key ultrasound indices

include nodule size, shape, location, margin clarity, internal echogenicity, presence of calcification, and vascularity, which are essential for differentiating benign from malignant lesions [4]. Specific ultrasound findings, including poorly-defined margins, irregular contours, heterogeneous echogenicity, microcalcifications, and increased intranodular vascularity, are strongly associated with a greater risk of thyroid cancer [5].

With advancements in medical technology, high-frequency ultrasound has undergone continuous refinement. Emerging techniques like contrast-enhanced ultrasound and ultrasound elastography have further improved its diagnostic utility for thyroid cancer [6]. Contrast-enhanced ultrasound visualizes microvascular distribution within nodules through contrast agent perfusion, while ultrasound elastography evaluates tissue stiffness to differentiate benign from malignant nodules, providing more dimensional information for prognosis [7]. However, high-frequency ultrasound still faces several challenges in early thyroid cancer detection. Its diagnostic accuracy is affected by various factors, including nodule size, location, pathologic type, and operator expertise. In some cases, limited image resolution may lead to diagnostic ambiguity or misclassification [8]. Systematic reviews and meta-analyses are essential for objectively evaluating the diagnostic value and limitations of high-frequency ultrasound, optimizing diagnostic strategies, and improving patient outcomes.

Thyroid nodules are frequently encountered in clinical settings. Accurate differentiation between benign and malignant lesions is of paramount importance. Current ultrasound evaluation mainly relies on three key findings: microcalcifications, hypoechoic patterns, and irregular margins. Among these, microcalcifications are strongly associated with malignancy; however, their sensitivity is variable across studies and many malignant nodules do not exhibit this feature. Hypoechogenicity demonstrates poor discriminatory power when used alone, as some malignant nodules may present as isoechoic or even hyperechoic. Irregular margins provide additional diagnostic information but remain insufficient as an independent indicator. The diagnostic challenge lies in effectively integrating these features. Current

evidence suggests no single feature can reliably distinguish benign from malignant nodules. Microcalcifications, while highly specific, require contextual interpretation. Similarly, hypoechogenicity and irregular margins yield greater diagnostic value when considered in combination. Clarifying the collective diagnostic contribution of these features remains critical. Currently, there is no consensus on the optimal method for integrating them clinical decision-making. Further research is needed to clarify their combined diagnostic value and establish more reliable criteria for evaluating thyroid nodules.

This study systematically reviews current literature on the use of high-frequency ultrasound in early thyroid cancer detection, focusing on its diagnostic value and limitations. The meta-analysis evaluates the diagnostic performance of specific ultrasound features, aiming to establish an evidence-based foundation for clinical application.

Materials and methods

Literature search

A systematic search was conducted in PubMed, Web of Science, Excerpta Medica Database (Embase), Cochrane Library, and China National Knowledge Internet (CNKI), covering studies published up to December 2024. The search strategy included a combination of terms such as “ultrasonography”, “high-frequency ultrasound”, “thyroid cancer”, “diagnosis”, and “limitation”. The search formula was: (“ultrasonography” OR “high-frequency ultrasound” OR “ultrasound”) AND (“thyroid cancer” OR “thyroid carcinoma” OR “thyroid malignancy”) AND (“diagnosis” OR “detection” OR “diagnostic accuracy”) AND (“limitation” OR “challenges” OR “restrictions” OR “pitfalls”).

Literature selection

Inclusion criteria: (1) Only studies presenting original data and published in peer-reviewed journals were considered to ensure data reliability and traceability. (2) Study populations should include patients with a confirmed diagnosis of thyroid cancer, or suspected cases where the primary objective was to evaluate the diagnostic accuracy of high-frequency ultrasound. For confirmed cases, studies must

investigate its application in assessing tumor characteristics (e.g., size, shape, location, margins, internal echogenicity, calcification, and vascularity), lymph node metastasis, disease staging, or its role in guiding treatment decisions. (3) High-frequency ultrasound must be the principal imaging modality used, either alone or in combination with other diagnostic techniques, such as ultrasound-guided biopsy, contrast-enhanced ultrasound, elastography, or the Thyroid Imaging Reporting and Data System (TI-RADS). Studies must focus specifically on its role in the early diagnosis of thyroid cancer.

Exclusion criteria: (1) Duplicate studies or overlapping data, defined as multiple publications of the same or highly similar data from the same research group or authors, were excluded. In such cases, only the most representative or comprehensive study should be retained. (2) Non-original research including review articles, meta-analyses, case reports, letters, and conference abstracts were excluded. Review articles and meta-analyses are secondary studies that synthesize existing research rather than presenting original data. Case reports typically involve only a single case or a small sample size, which limits their generalizability. Letters and conference abstracts provide limited and preliminary information, failing to meet the rigorous data and comprehensive analysis standards required for systematic reviews and meta-analyses. (3) Literature with flawed experimental design or low quality was excluded. This includes studies with unscientific research methods, inappropriate sample selection, the absence of control groups, erroneous statistical analysis, incomplete data, or a significant risk of bias (e.g., selection bias, measurement bias, or confounding bias) that cannot be reasonably corrected. Such limitations would compromise the reliability and validity of the pooled results.

This study was registered with the International Prospective Register of Systematic Reviews (PROSPERO; No. CRD420251032366).

Data extraction

Two reviewers (Y. Liu and W. Xu) independently extracted key information from each included

study, including the first author, sample size, study design (type of study), diagnostic methods, and relevant ultrasound features.

Quality assessment

The same two reviewers independently screened the titles, abstracts, and full texts of potentially eligible studies according to the predefined inclusion and exclusion criteria. The results were cross-verified, and any disagreements were resolved through consultation with a third reviewer. The methodological quality of the included studies were assessed using the Quality Assessment of Diagnostic Accuracy Studies (QUADAS) tool.

Statistical analysis

All statistical analyses were performed using R software (version 4.3.2). Pooled diagnostic outcomes were expressed as odds ratio (OR) with 95% confidence interval (CI). A random-effect model was applied to account for possible clinical and methodological heterogeneity among included studies, which was anticipated due to differences in patient populations, diagnostic methods, and outcome measures. Heterogeneity was assessed using the I^2 statistic, with $I^2 > 50\%$ indicating substantial heterogeneity. In cases of low heterogeneity ($I^2 < 50\%$), a fixed-effect model was applied in sensitivity analyses to evaluate the robustness of the results. Both direct and indirect comparisons were incorporated within the network meta-analysis framework. All statistical tests were two-sided, and a P -value < 0.05 was considered significant.

Results

Study selection and quality assessment

According to the predefined search strategy, including manual screening of reference lists, a total of 432 records were initially identified. After removing duplicates, 321 records remained. Following title and abstract screening and full-text review using the inclusion and exclusion criteria, 14 studies [9-22] comprising 15334 patients were ultimately included in this meta-analysis (**Figure 1**). The basic characteristics of the included studies are summarized in **Table 1**. Study quality was assessed using the QUADAS system, and all studies were deter-

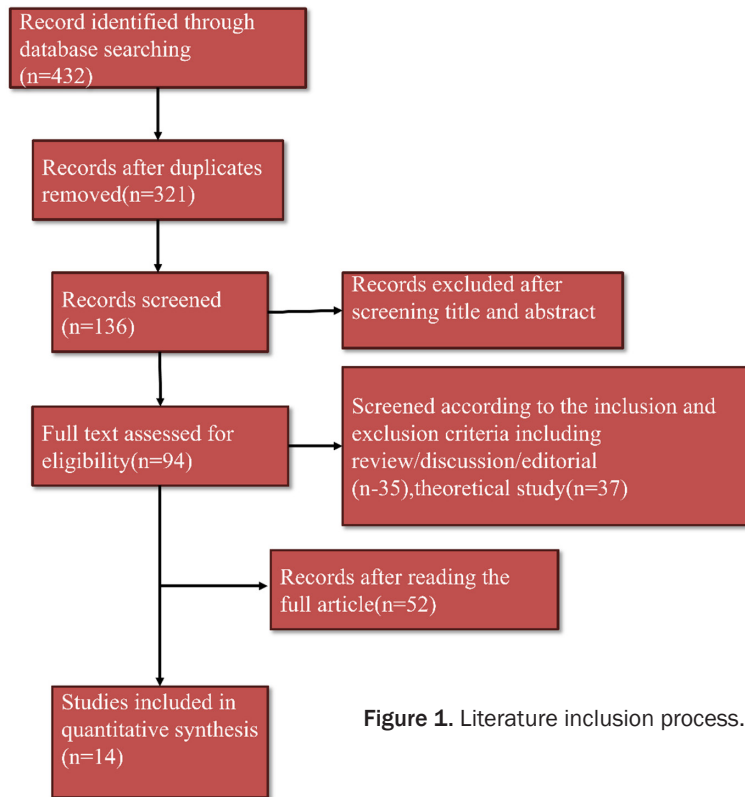


Figure 1. Literature inclusion process.

mined to be of relatively high methodologic quality (**Table 2**).

Diagnostic performance of various ultrasound-based methods for thyroid cancer

Substantial variability was observed in the sensitivity across different diagnostic modalities. In particular, combined diagnostic approaches demonstrated higher sensitivity compared to single techniques. For instance, Zheng et al. [9] reported a sensitivity of 0.975 for the combination of high-frequency ultrasound and ultrasound-guided biopsy; Fu et al. [10] documented a sensitivity of 0.942 for high-frequency ultrasound combined with contrast-enhanced ultrasound; Similarly, He et al. [11] reported a sensitivity of 0.952 for the integration of high-frequency ultrasound with ultrasound-guided fine-needle aspiration biopsy (US-FNAB), indicating that combined modalities may improve detection rates of thyroid cancer. However, this advantage was not uniformly observed in all studies. For instance, Yu et al. [12] reported lower sensitivity for high-frequency ultrasound (0.853) and US-FNAB (0.814), suggesting that

diagnostic efficacy may vary across different research contexts (**Table 3**).

Specificity also varied among studies. In several studies, ultrasound-guided biopsy, either alone or in combination with other modalities, demonstrated high specificity. For instance, Zheng et al. [9] reported a specificity of 0.917 for ultrasound-guided biopsy. Similarly, in the study by He et al. [11], the specificity of US-FNAB and in combination with high-frequency ultrasound were 0.917 and 0.944, respectively. These findings indicate that such approaches are effective in accurately identifying patients without disease, thereby reducing false positives. However, in Yu et al.' study [12], the specificity of high-frequency ultrasound was comparatively lower (0.583),

suggesting that this method may yield more false-positive results in certain cases, necessitating cautious judgment (**Table 3**).

Correlation analysis between ultrasound features and thyroid cancer

Table 4 summarizes the findings from multiple studies investigating the correlation between various ultrasound features and thyroid cancer. The results indicate that nodule size, margin characteristics, echogenicity, calcifications, and vascular patterns are key sonographic indicators in the diagnosis and risk assessment of thyroid cancer. Nodule size has been identified as a crucial factor in assessing thyroid cancer risk. He et al. [11] and Smith-Bindman et al. [13] reported that larger nodules (exceeding 1.5-2 cm) were likely to be malignant. Margin characteristics also served as important diagnostic markers. Irregular or poorly-defined margins were more common in malignant nodules, as demonstrated by He et al. [11], Qin et al. [14], and Luo et al. [15]. Echogenicity also contribute to diagnosis, with malignant nodules typically exhibiting hypoechoic or heterogeneous echotexture, as reported by Li et al. [16].

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Table 1. Summary of main information

Study	Study type	Sample size	Mean/median age of patients (years)	Proportion of male patients	Proportion of thyroid cancer patients	Ultrasound equipment and probe frequency	Primary observation indicators
Zheng et al. [9]	Case-control study	92 cases	36.4	39/92	80/92	SuperSonic Aixplorer V color Doppler ultrasound diagnostic system, 3-12 MHz	The consistency of high-frequency ultrasound, ultrasound-guided puncture, and their combination with the gold standard in diagnosing thyroid cancer. The accuracy and specificity of various diagnostic methods.
Fu et al. [10]	Observational study	98 cases	37.24±8.64	55/98	52/98	High-frequency ultrasound: Philips IU22 color Doppler ultrasound diagnostic system, 5-12 MHz high frequency line array probe; enhanced ultrasound: GE Logic E9 ultrasound diagnostic system, 3-12 Hz	Outcomes and diagnostic performance of high-frequency ultrasound (HFUS) and contrast-enhanced ultrasound (CEUS) alone and in combination in the diagnosis of papillary thyroid carcinoma and the detection rate of different types of thyroid carcinoma and lymph node metastases.
He et al. [11]	Observational study	100 cases	Metastasis group: 48.12±9.24; Non-metastasis group: 49.03±9.81	Metastasis group: 22/62; Non-metastasis group: 11/38	100%	Aplio400 (Toshiba), Affiniti 50 (Philips), EPIC7C color Doppler ultrasound diagnostic system (Philips), 4-12 MHz	Ultrasound features of cervical lymph node metastases (CLNM) in thyroid cancer, diagnostic performance parameters (e.g., sensitivity, specificity) of high-frequency ultrasound for the diagnosis of CLNM, and risk factors associated with CLNM.
Yu et al. [12]	Prospective study	172 cases (181 minute foci of thyroid glands)	44.1±13.4	54/172	109/123 (Numbers of pathologically confirmed PTMC lesions/Total numbers of pathological lesions)	Siemens Axiom Antares 5.0 and Hitachi VISION Preirus color Doppler ultrasound diagnostic system, 5-12 MHz	Accuracy of high-frequency color Doppler ultrasound and ultrasound-guided fine-needle aspiration biopsy in the diagnosis of thyroid microcarcinoma. Follow-up of thyroid remnant lobes and cervical lymph node recurrence.
Smith-Bindman et al. [13]	Retrospective case-control study	8806 cases (11618 thyroid ultrasound examination)	51.6±15.5	2277/8806	105/8806	Not mentioned	
Qin et al. [14]	Retrospective study	95 cases (152 nodules)	57.23±5.28	15/95	99/152	SSA - 370A color Doppler ultrasound diagnostic system, 7-12 MHz variable frequency line array probe	The application value of high-frequency ultrasound and ultrasound-guided fine-needle aspiration biopsy (US-FNAB) in the diagnosis of papillary thyroid microcarcinoma (PTMC), including diagnostic accuracy, sensitivity, specificity, and the correlation between ultrasound features of various nodules and PTMC.
Luo et al. [15]	Observational study	69 cases	47.48±5.03	28/69	47/69	IU22 color Doppler ultrasound diagnostic system, 5-12 MHz wideband line array probe	Accuracy, sensitivity, and specificity of high-frequency ultrasound in the diagnosis of thyroid cancer. Correlation between TCM syndrome and ultrasound manifestations in patients with thyroid cancer.
Li et al. [16]	Retrospective study	80 cases	73.51±2.62	10/80	100%	SXFL014LOGIQP, 7-10 MHz	The consistency between high-frequency ultrasound diagnosis and surgical pathological diagnosis. The ultrasound features of thyroid cancer (such as echogenicity, blood flow signals, tumor size, metastasis, etc.).

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Boris Brkljacic, 1994 [17]	Retrospective study	165 cases, 426 nodules	46.5	22/165	70/426	Aloka SSD 256 real time scanner, 5 MHz linear probe (142 cases); G.E. - CGR Radius CF real time scanner, 7.5 MHz convex array probe (23 cases)	Analysis of the correlation between the ultrasound features (echo structure, calcification, margins, cystic changes, nodule size, and location) of thyroid nodules in patients with multinodular thyroid glands and their pathological outcomes, and determination of the ultrasound features associated with the benign or malignant nature of the nodules.
Cappelli C, 2007[18]	Prospective observational study	5198 cases, 7455 nodules	Mean age not mentioned, nodule size 6-100 mm (mean 15.5±9.0 mm)	1377/4495	284/349 (nodules undergoing surgery)	Siemens Elegra or ATL 5000, 10-12 MHz linear probe (morphology study), 4.7 MHz probe (color Doppler evaluation)	Correlation of ultrasound features of thyroid nodules (nodule size, echo structure, echo intensity, calcification, margins, and vascular pattern) with histological malignancy, assessment of the predictive value of each ultrasound feature for the determination of the benign or malignant nature of thyroid nodules, and identification of criteria that are useful for clinical decision making.
Ousehal A, 1996 [19]	Retrospective study	100 cases	Not mentioned	7/100	Not mentioned	Not mentioned	The value of ultrasonography in the diagnosis and etiology of thyroid diseases, comparison of ultrasound findings and histological results, analysis of the ultrasound features of benign and malignant thyroid nodules (such as echo structure, presence of halo signs, calcification, nodule margins, and associated cervical lymphadenopathy) as well as the ultrasound manifestations of various thyroid conditions (e.g., Graves' disease).
T Rago, 1998 [20]	Prospective study	104 cases	42.3 (overall mean patient age)	34/104	30/104	AU 590 Asynchronous (Esaote Biomedica), 7.5 MHz linear probe	The role of conventional thyroid ultrasound and color Doppler ultrasound in assessing malignancy in "cold" thyroid nodules, and the analysis of correlation between ultrasound characteristics (such as halo sign, hypoechogenicity, microcalcifications, and blood flow patterns) and nodule malignancy.
Mustafa Sahin MD, 2006 [21]	Clinical study	207 cases, 472 nodules	51.5±13.1	37/207	31/145 (nodules undergoing surgery)	Siemens SI - 400 or Siemens Elegra, 7.5 - MHz linear transducer	Validity of ultrasound-guided fine-needle aspiration biopsy of small thyroid nodules, the correlation between ultrasound features of thyroid nodules and pathological findings, and the assessment of the risk of malignancy in thyroid nodules and the disease extent of micronodular carcinoma.
Shi et al. [22]	Observational study	48 cases	63.48±2.25	25/48	36/48	EPIQ7 and EPIQ7C ultrasound diagnostic system (Philips), wideband line array probe, 3-14 MHz	Diagnostic performance of high-frequency ultrasound, ultrasound elastography, and TI-RADS classification alone and in combination in the diagnosis of cervical lymph node metastases in elderly patients with thyroid cancer. Comparison of length diameter and cervical regions of benign and malignant lymph nodes.

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Table 2. Quality evaluation

Researchers	Spectral component	Selection criteria	Reference standard	Disease progression bias	Partial validation	Difference verification	Fusion bias	Index test execution	Reference standard execution	Test review bias	Reference standard review bias	Clinical review bias	Unexplained test results	Withdrawal	Total score
Zheng et al. [9]	Yes	Yes	Yes	Yes	Full sample	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	14/14
Fu et al. [10]	Yes	Yes	Yes	Yes	Full sample	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	13/14
He et al. [11]	No	Yes	Yes	Yes	Full sample	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	13/14
Yu et al. [12]	Yes	Yes	Yes	Yes	Full sample	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	13/14
Smith-Bindman et al. man [13]	Yes	Yes	Yes	Yes	Full sample	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	14/14
Qin et al. [14]	Yes	Yes	Yes	Yes	Full sample	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	14/14
Luo et al. [15]	Yes	Yes	Yes	Yes (maximum 4 weeks)	Full sample	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	13/14
Li et al. [16]	Yes	Yes	Yes	Yes	Full sample	Yes	Yes	No	Yes	Yes	Yes	No	Yes	Yes	12/14
Boris Brkljacic, 1994 [17]	Yes	Yes	Yes	Yes	Full sample	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	13/14
Cappelli C, 2007 [18]	Yes	Yes	Yes	Yes	Full sample	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	14/14
Ousehal A, 1996 [19]	Yes	Yes	Yes	Yes	Full sample	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	13/14
T Rago, 1998 [20]	Yes	Yes	Yes	Yes	Full sample	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	13/14
Mustafa Sahin MD, 2006 [21]	Yes	Yes	Yes	Yes	Full sample	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	13/14
Shi et al. [22]	Yes	Yes	Yes	Yes	Full sample	No	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	12/14

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Table 3. Efficacy of multiple diagnostic methods for thyroid cancer in different studies

Diagnostic methods	Studies	True positive (TP)	False positive (FP)	False negative (FN)	True negative (TN)	Sensitivity (Se)	Specificity (Sp)	Lower limit of 95% confidence interval (CI) (Se)	Upper limit 95% confidence interval (CI) (Se)	Lower limit of 95% confidence interval (CI) (Sp)	Upper limit 95% confidence interval (CI) (Sp)
High-frequency ultrasound	Zheng et al. 2022 [9]	66	2	14	10	0.825	0.833	0.73	0.91	0.683	0.983
Ultrasound-guided biopsy	Zheng et al. 2022 [9]	71	1	9	11	0.888	0.917	0.797	0.979	0.78	1
High-frequency ultrasound combined with ultrasound-guided biopsy	Zheng et al. 2022 [9]	78	2	2	10	0.975	0.833	0.909	1	0.683	0.983
High-frequency ultrasound	Fu et al. 2022 [10]	39	2	13	44	0.75	0.957	0.624	0.876	0.88	0.997
High-frequency ultrasound combined with contrast-enhanced ultrasound	Fu et al. 2022 [10]	49	3	3	43	0.942	0.935	0.863	0.999	0.847	0.997
High-frequency ultrasound	He et al. 2022 [11]	54	10	8	28	0.871	0.737	0.766	0.976	0.588	0.893
High-frequency ultrasound	Yu et al. 2022 [12]	93	30	16	42	0.853	0.583	0.775	0.931	0.464	0.702
Ultrasound-guided fine-needle aspiration biopsy (US-FNAB)	Yu et al. [12] 2022	48	3	11	49	0.814	0.942	0.702	0.926	0.857	1
High-frequency ultrasound	Qin et al. 2022 [14]	94	9	5	44	0.95	0.83	0.893	0.987	0.713	0.947
High-frequency ultrasound	Luo et al. 2022 [15]	46	1	1	21	0.979	0.955	0.917	1	0.846	1
High-frequency ultrasound	Li et al. 2021 [16]	78	2	2	20	0.975	0.909	0.917	1	0.804	1
High-frequency ultrasound	Shi et al. 2022 [22]	30	3	6	29	0.833	0.906	0.689	0.977	0.797	0.997
Ultrasound elastography	Shi et al. 2022 [22]	34	2	2	30	0.944	0.938	0.847	1	0.83	0.998
TI-RADS classification	Shi et al. 2022 [22]	34	6	2	36	0.944	0.857	0.847	1	0.746	0.97
High-frequency ultrasound combined with elastography and TI-RADS classification	Shi et al. 2022 [22]	35	1	1	41	0.972	0.976	0.902	1	0.914	1

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Table 4. Correlation analysis of ultrasound features (nodule size, margin, echogenicity, calcification, and blood flow signals) with thyroid cancer

Studies	Relationship between nodule size and thyroid cancer	Relationship between margin and thyroid cancer	Relationship between echogenicity and thyroid cancer	Relationship between calcification and thyroid cancer	Relationship between blood flow signals and thyroid cancer
Zheng et al. 2024 [9]	-	In high-frequency ultrasound examinations of patients with thyroid cancer, some nodules exhibit irregular margin shapes; however, the quantitative relationship between margin characteristics and thyroid cancer has not been compared with those of benign nodules.	In high-frequency ultrasound examinations of patients with thyroid cancer, some nodules present with ultrasound features such as hypoechogenicity; however, the quantitative relationship between echogenic characteristics and thyroid cancer has not been compared with those of benign nodules.	In high-frequency ultrasound examinations of patients with thyroid cancer, some nodules exhibit calcification and surrounding echogenicity; however, the quantitative relationship between calcification characteristics and thyroid cancer has not been compared with those of benign nodules.	In high-frequency ultrasound examinations of patients with thyroid cancer, some nodules exhibit blood flow signals both within and around them; however, the quantitative relationship between blood flow signals and thyroid cancer has not been compared with those of benign nodules.
Fu et al. 2024 [10]	-	The quantitative relationship between margin characteristics and thyroid cancer was not mentioned; only the description of the indistinct margin features of thyroid cancer nodules was provided.	The quantitative relationship between echogenic characteristics and thyroid cancer was not mentioned; only the description of the heterogeneous hypoechoic features within thyroid cancer nodules was provided.	The quantitative relationship between calcification characteristics and thyroid cancer was not mentioned; only the presence and types of calcification within thyroid cancer nodules were described.	The quantitative relationship between blood flow signals and thyroid cancer was not mentioned; only the blood flow signals around and within thyroid cancer nodules were described.
He et al. 2022 [11]	In the metastasis group, the incidence of nodules ≥ 1.5 cm in size (66.13%) was significantly higher than that in the non-metastasis group (42.11%). Nodule size ≥ 1.5 cm was identified as an independent risk factor for cervical lymph node metastasis in thyroid cancer (OR=3.425, $P<0.05$).	In the metastasis group, the incidence of indistinct margins (69.35%) was significantly higher than that in the non-metastasis group (39.47%). The presence of indistinct margins was identified as an independent risk factor for cervical lymph node metastasis in thyroid cancer (OR=3.747, $P<0.05$).	In the metastasis group, the prevalence of hypoechoic texture (69.35%) was markedly higher compared to the non-metastasis group (42.11%). Hypoechoic texture was identified as an independent risk factor for cervical lymph node metastasis in thyroid cancer (OR=4.899, $P<0.05$).	In the metastasis group, the incidence of microcalcifications (61.29%) was significantly higher than that in the non-metastasis group (31.58%). Microcalcification served as an independent risk factor for cervical lymph node metastasis in thyroid cancer (OR=5.387, $P<0.05$).	In the metastasis group, the incidence of abundant blood flow signals (77.42%) was significantly higher than in the non-metastasis group (15.79%). Abundant blood flow signals served as an independent risk factor for cervical lymph node metastasis in thyroid cancer (OR=5.392, $P<0.05$).
Yu et al. 2022 [12]	-	The typical ultrasonic signs of thyroid microcarcinoma include unclear margins and "crab-claw" infiltration; however, the quantitative relationship between margin characteristics and thyroid cancer has not been compared with those of benign nodules.	The typical ultrasound signs of thyroid microcarcinoma include solid hypoechoic nodules; however, the quantitative relationship between echogenic characteristics and thyroid cancer has not been compared with those of benign nodules.	The typical ultrasound signs of thyroid microcarcinoma include microcalcification in the nodules; however, the quantitative relationship between calcification characteristics and thyroid cancer has not been compared with those of benign nodules.	The blood flow within thyroid microcarcinoma nodules is notably abundant, significantly exceeding that of the surrounding tissue, and predominantly exhibits a high-resistance spectral pattern; however, the quantitative relationship between blood flow signals and thyroid cancer has not been compared with those of benign nodules.
Smith-Bindman et al. 2013 [13]	Nodule size >2 cm was associated with thyroid cancer, with an OR of 3.6 (95% CI: 1.7, 7.6), and it served as a significant influencing factor in multivariable analysis.	-	-	-	Microcalcifications were closely associated with thyroid cancer, with an OR of 8.1 (95% CI: 3.8-17.3), and it remained a significant influencing factor in multivariable analysis.

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Qin et al. 2023 [14]	-	The proportion of indistinct margins in Group A (PTMC nodules) (81/99) was significantly higher than in Group B (BTN nodules) (8/53), with a statistically significant difference ($P<0.05$). Indistinct margins are a crucial high-frequency ultrasound diagnostic feature of PTMC.	The proportion of hypoechoic nodules in Group A (86/99) was higher than in Group B (13/53), with a statistically significant difference ($P<0.05$). Hypoechoic nodules are a relatively important independent risk factor for the clinical diagnosis of PTMC.	The proportion of calcified nodules in Group A (63/99) was higher than that in Group B (10/53), with a statistically significant difference ($P<0.05$). PTMC is closely associated with calcification.	Group A exhibited 32 cases of blood flow signals, while Group B had 26 cases. Logistic multivariable analysis revealed significant differences between the two groups in high-frequency ultrasound imaging features, such as blood flow signals. However, the precise correlation between the abundance of blood flow signals and thyroid cancer remains unclear.
Luo et al. 2022 [15]	-	Thyroid cancer typically presents with well-defined or serrated, yet unclear margins, often exhibiting rough edges, distinct from benign nodules, though the quantitative relationship remains ambiguous.	Thyroid cancer typically presents as hypoechoic, isoechoic, or hyperechoic on imaging. Calcific foci and bright spots may be visible internally. There is a distinctive difference in echogenicity compared to benign nodules, but the proportion has not been specified.	The percentage of calcifications was not mentioned, but it was noted that microcalcifications are the most specific indicator of thyroid cancer diagnosed by high-frequency ultrasound.	The quantitative relationship between blood flow signals and thyroid cancer has not been thoroughly analyzed; only the characteristic of abundant blood supply within thyroid cancer nodules has been described.
Li et al. 2021 [16]	-	-	Among the cases, 25 (31.25%) exhibited uneven hypoechoic heterogeneity or isoechoic carcinoma, 15 (18.75%) presented with mildly hypoechoic lesions, well-defined margins, and favorable ultrasound hypoechogenicity, and 9 (11.25%) displayed nodules with irregular echo intensity and larger volumetric echoes; however, no comparison was made with benign nodules.	-	Among the cases, 67 (83.75%) exhibited abundant blood flow signals within and around the nodules, 10 (12.50%) showed no significant blood flow signals, and 3 (3.75%) displayed only minimal blood flow signals; however, no comparison was made with benign nodules.
Shi et al. 2024 [22]	-	In high-frequency ultrasound diagnostics, lymph node characteristics such as margins were evaluated to distinguish between benign and malignant conditions. The margins of malignant lymph nodes differ from those of benign ones, yet no similar studies have been conducted regarding the relationship between the margin characteristics of primary thyroid cancer lesions and thyroid cancer.	The relationship between the echogenicity of primary thyroid cancer lesions and thyroid cancer was not mentioned; only the echogenicity characteristics of the lymph nodes were analyzed to determine metastasis.	The relationship between calcification of the primary thyroid cancer lesions and thyroid cancer was not addressed; only the calcification characteristics of the lymph nodes were analyzed to determine metastasis.	High-frequency ultrasound was used to classify lymph nodes into distinct types based on blood flow distribution and assigns scores to determine the benign or malignant nature. While the characteristics of blood flow signals in malignant lymph nodes differ significantly from those in benign ones, no analogous research has been conducted to explore the relationship between blood flow signals in primary thyroid cancer lesions and thyroid cancer.

Ultrasound for early thyroid cancer

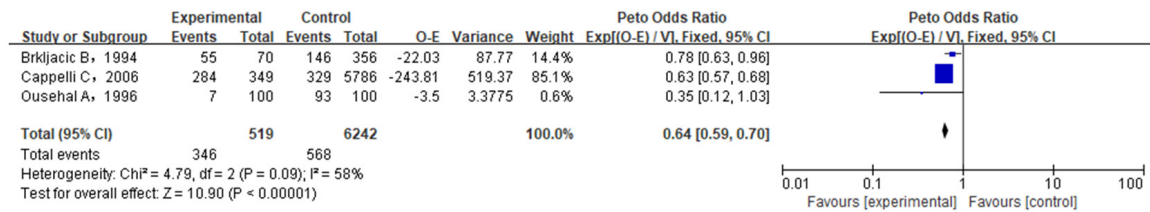


Figure 2. Diagnostic efficacy of hypoechogenicity in ultrasound features.

Table 5. Pooled results

Ultrasound feature	No. of studies	Peto fixed-effect OR	95% CI	I ² (%)	Random-effects OR*	95% CI
Hypoechogenicity	3	0.64	0.59-0.70	58	0.68	0.48-0.97
Microcalcification	4	18.50	14.65-23.36	100	15.12	6.87-33.30
Irregular margin	3	39.47	28.88-53.94	99	12.80	4.31-37.89

*DerSimonian-Laird random-effects model, used for I²>50%. Abbreviations: OR, odds ratio; CI, confidence interval. An OR>1 indicates that the ultrasound feature is more prevalent in malignant nodules; OR<1 indicates the opposite.

Microcalcifications remain a well-established sonographic hallmark of malignancy (He et al. [11] and Smith-Bindman et al. [13]. Additionally, vascular patterns may provide further diagnostic value. Increased vascularity within nodules has been associated with malignancy, as noted in studies by He et al. [11] and Li et al. [16].

Despite these findings, current research presents several limitations and inconsistencies. Some studies lack comparative analysis with benign nodules, particularly in terms of quantitative assessment. Furthermore, discrepancies in diagnostic criteria and ultrasound methodology persist across studies. To enhance diagnostic accuracy and clinical utility of ultrasound-based thyroid cancer detection, future research should focus on the standardization of sonographic criteria and methodological consistency.

Diagnostic efficacy of hypoechogenicity in ultrasound features

Three studies assessed the diagnostic value of hypoechogenicity in differentiating benign from malignant thyroid nodules, but the results were inconsistent. Brkljacic et al. [17] and Cappelli et al. [18] reported a correlation between hypoechogenicity and the malignancy of thyroid nodules, with the latter study contributing greater statistical weight. In contrast, Ousehal et al. [19] found no statistically significant correlation. Overall, the pooled Peto odds ratio was 0.64 (95% CI 0.59-0.70), indicating

that hypoechogenicity is significantly associated with malignant thyroid nodules (**Figure 2; Table 5**).

Diagnostic efficacy of microcalcifications in ultrasound features

Four studies reported the associations between microcalcifications and the malignancy of thyroid nodules, with conflicting results. Brkljacic et al. [17] suggested that microcalcifications may represent a risk factor for malignancy. Cappelli et al. [18] found a strong correlation between microcalcifications and the malignancy of thyroid nodules; however, the OR was unusually high, suggesting methodological anomalies or study-specific factors. Rago et al. [20] observed a positive correlation, whereas Sahin et al. [21] reported no significant association (**Figure 3**). The pooled Peto odds ratio was 18.50 (95% CI: 14.65-23.36; I² = 100%), indicating that microcalcifications are markedly more prevalent in malignant nodules (**Figure 3**). Sensitivity analysis using a random-effects model yielded a comparable result (OR=15.12, 95% CI: 6.87-33.30), confirming the robustness of this association.

Diagnostic efficacy of irregular margins in ultrasound features

Three studies examined the association between irregular margins and thyroid malignancy. In the study by Cappelli et al. [18], the experimental group included 349 cases, of whom

Ultrasound for early thyroid cancer

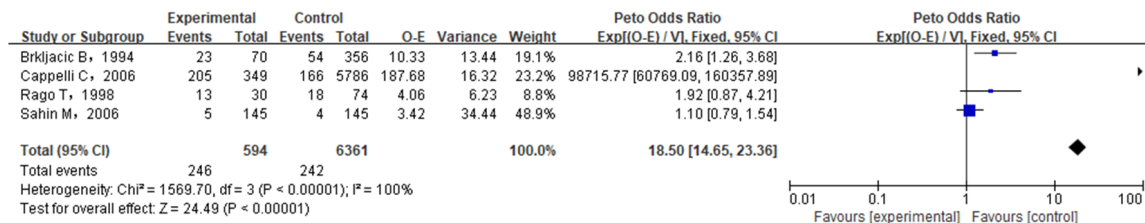


Figure 3. Forest plot of the association between micro-calcification and malignancy. Experimental = malignant nodules; Control = benign nodules; thus an OR>1 favours malignancy.

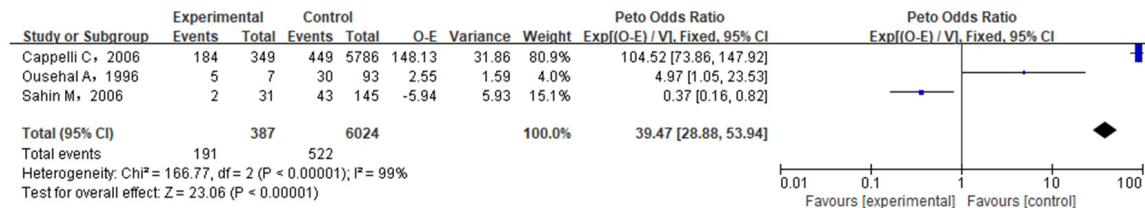


Figure 4. Diagnostic efficacy of irregular margins in ultrasound features. Experimental = malignant nodules; Control = benign nodules; therefore OR>1 denotes a higher prevalence of irregular margins in malignant nodules.

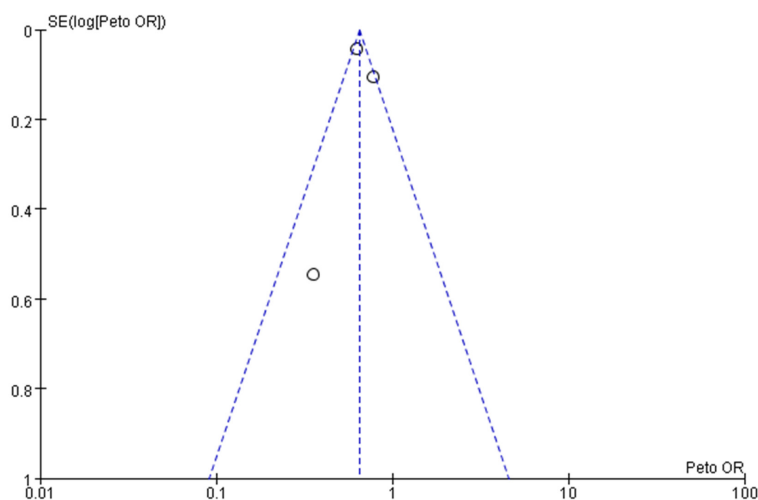


Figure 5. Funnel plot of diagnostic efficacy of hypoechogenicity in ultrasonic features.

184 had irregular margins, while the control group consisted of 5,786 cases, with 449 cases presenting irregular margins. The Peto OR was 104.52 [95% CI: 73.86-147.92], with a weight contribution of 80.9%, indicating a highly significant association between irregular margins and malignancy. Ousehal et al. [19] reported a certain correlation, whereas Sahin et al. [21] observed a negative correlation between irregular margins and malignancy. The pooled Peto OR was 39.47 (95% CI: 28.88-53.94; I² = 99%), confirming that irregular margins are markedly more frequent in malignant nodules (**Figure 4**). A random-effects sensitivity

analysis gave a similar estimate (OR = 12.80, 95% CI: 4.31-37.89) (**Figure 4**).

Publication bias

Funnel plots were generated to assess potential publication bias in studies evaluating the predictive value of different ultrasound features for thyroid cancer (**Figures 5-7**). The funnel plots for hypoechogenicity and irregular margins appeared relatively symmetrical, indicating minimal publication bias and high level of data reliability. In contrast, the funnel plot for microcalcifications was asymmetrical, suggesting possible publication bias. This may reflect under-reporting of studies with small sample sizes, non-publication of negative or inconclusive results, or limitations in literature retrieval. These findings indicate that the diagnostic value of microcalcifications may be overestimated in the current literature due to selective reporting.

Discussion

This systematic review and meta-analysis confirmed a high diagnostic value of high-frequency ultrasound in the early identification of thy-

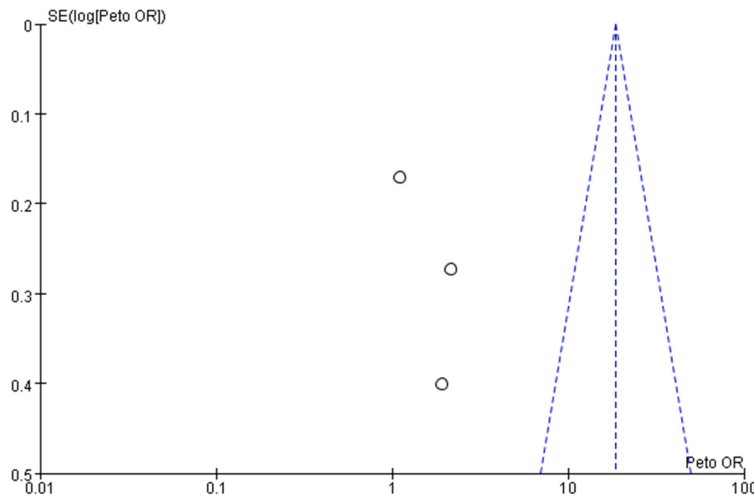


Figure 6. Funnel plot of diagnostic efficacy of microcalcifications in ultrasonic features.

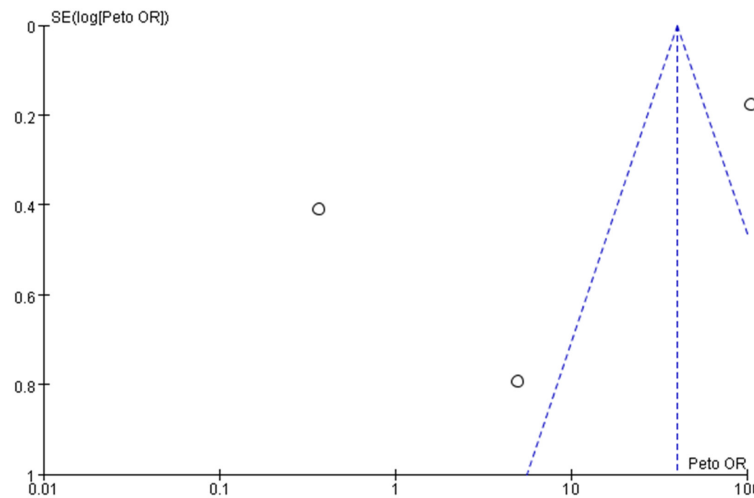


Figure 7. Funnel plot of diagnostic efficacy of irregular margins in ultrasonic features.

roid cancer. It enables detailed visualization of thyroid nodule characteristics, including morphology, margins, internal echogenicity, calcifications, and vascularity, thereby facilitating preliminary lesion assessment. The diagnosis of thyroid cancer is more accurate due to its great sensitivity to microcalcifications. High-frequency ultrasound is especially valuable in diagnosing papillary thyroid carcinoma, owing to its excellent soft tissue resolution, which allows for detailed observation of neck tissue architecture, tissue layers, and both intranodular and perinodular blood flow. In the evaluation of lymph node metastasis, particularly in elderly patients, high-frequency ultrasound plays a crucial role by providing multimodal evaluation

of lymph node size, number, morphology, margin definition, and vascular distribution. Its non-invasive nature, repeatability, and clinical practicality make it an ideal tool for both diagnosis and treatment planning. This imaging modality provides reliable data for treatment planning, as supported by previous meta-analyses [23, 24].

High-frequency ultrasound is commonly combined with complementary diagnostic techniques to improve early thyroid cancer detection. When integrated with ultrasound-guided biopsy, this approach demonstrates improved diagnostic accuracy and specificity, showing strong agreement with pathologic results. The integration of high-frequency ultrasound with contrast-enhanced ultrasound improves diagnostic sensitivity and detection rates for papillary thyroid cancer while reducing missed diagnoses, supporting more precise clinical decision-making. Shi et al. [22] found that combining elastography, high-frequency ultrasound, and the TI-RADS classification improved sensitivity and accuracy in detecting cervical lymph node metastases in elderly thyroid

cancer patients, compared to high-frequency ultrasound alone. This combined approach also showed higher specificity than TI-RADS alone. The combination of multimodal imaging compensates for the limitations of individual techniques, enhances diagnostic accuracy, and reduces misdiagnosis. This meta-analysis demonstrates that combining imaging techniques enhances early thyroid cancer detection compared to single-modality approaches. Clinicians are encouraged to tailor imaging strategies to individual patient characteristics to optimize diagnostic outcomes [25].

While high-frequency ultrasound remains a valuable tool for the early detection of thyroid

cancer, it is not without limitations [26, 27]. Its sensitivity is reduced in detecting micrometastases and may be compromised in cases of undifferentiated thyroid cancer, where tumors with intact capsules or well-defined margins can mimic benign lesions, leading to diagnostic misinterpretation. Furthermore, technique limitations can impact the success of ultrasound-guided fine-needle aspiration biopsy (US-FNAB). It is challenging to obtain adequate cytological samples from extremely small or densely calcified nodules, reducing diagnostic reliability. Equipment performance, operator expertise, and variability in tumor pathology also significantly influence diagnostic accuracy. As demonstrated in the included studies, these variables can contribute to both false-positive and false-negative results. Given these limitations, clinicians should be cautious in interpreting ultrasound findings and avoid relying only on a single diagnostic feature during early thyroid cancer detection [28].

The ultrasound characteristics evaluated in this study, including microcalcifications, hypoechogenicity, and uneven margins, are valuable for distinguishing benign from malignant thyroid nodules, though each has inherent limitations. These features have been previously investigated in numerous individual studies [29, 30]. The results of this study demonstrate the critical diagnostic value of microcalcifications, which exhibit high specificity for malignancy. However, when used alone, their sensitivity remains suboptimal. Similarly, hypoechogenicity is commonly associated with malignant thyroid nodules; however, when used in isolation, its diagnostic accuracy is low, which aligns with the low sensitivity observed in this study. This suggests that relying solely on hypoechogenicity may result in missed diagnoses. Previous research has also shown a correlation between irregular margins and malignancy [31], and the current study exhibits a comparable level of specificity. Nevertheless, when used in isolation, it is unable to reliably detect malignant nodules.

High-frequency ultrasound in thyroid cancer screening requires careful clinical consideration. Diagnostic accuracy relies on comprehensive evaluation of multiple sonographic features, including nodule size, margin, texture, echogenicity, microcalcifications, aspect ratio,

and blood flow signals, as overreliance on any single characteristic may lead to misinterpretation [32]. Detection of small or deep lymph nodes presents technical challenges. Combining high-frequency ultrasound with other modalities like elastography and contrast-enhanced ultrasound may improve diagnostic performance [33, 34]. For cases with atypical ultrasound findings, a comprehensive assessment should be made based on clinical symptoms, medical history, and other examination results. If necessary, a biopsy or routine follow-up can be performed to reduce the risk of incorrect diagnoses. Ongoing training for sonographers remains crucial to maintain diagnostic proficiency and optimize the clinical utility of high-frequency ultrasound [35].

A strength of this study was its large sample size, with all nodules confirmed by histopathology, enhancing the reliability of the diagnostic findings. Furthermore, the detailed evaluation of ultrasonographic features has further clarified their role in guiding clinical decision-making. However, the study has several limitations. First, some subgroup analyses were limited by small sample sizes, and key clinical data, including patient-specific malignancy risk factors and surgical indications, were not consistently reported across studies [36, 37]. Second, the included publications exhibited wide variations in sample size and study quality. Most statistical indicators were derived from only 3-4 of the 14 references, which may introduce publication bias and limit the generalizability of the findings. Additionally, the absence of long-term follow-up data in some studies restricts the ability to evaluate the effect of high-frequency ultrasound diagnostics on patient outcomes. Heterogeneity in study design, populations, and imaging protocols also contributed to variability in reported sonographic markers. Although random-effects models and sensitivity analyses were employed to address this heterogeneity, the restricted data source remains a limitation. In clinical settings, ultrasound findings should therefore be interpreted in conjunction with patient history, family history, and other relevant factors to enhance diagnostic accuracy. Future research should focus on improving study design quality, expanding sample sizes, and standardizing diagnostic criteria. Moreover, emerging technologies such as molecular ultrasound imaging, quantitative

elastography, and artificial intelligence-based image analysis hold promise for improving diagnostic precision and efficiency in early thyroid cancer detection. Multi-center prospective studies are necessary to systematically assess the clinical utility of these advantaged ultrasound techniques, representing an important direction for future investigation [38].

Conclusion

Thyroid cancer is the most prevalent endocrine malignancy, with early detection significantly improving treatment outcome and survival rate. High-frequency ultrasound is essential for thyroid cancer screening due to its high sensitivity in detecting suspicious nodular features in real time. This systematic review and meta-analysis evaluated the diagnostic value of various sonographic features, including hypoechogenicity, microcalcifications, margin irregularity, vascular patterns, and shape, in distinguishing malignant from benign thyroid nodules. Among these features, hypoechogenicity, microcalcifications, and irregular margins demonstrated the strongest association with malignancy. However, the diagnostic performance of high-frequency ultrasound is constrained by factors such as operator expertise, inter-observer variability, and the morphological similarities shared by benign and malignant lesions. Although high-frequency ultrasound is effective in detecting microstructural changes, its diagnostic performance differs among different thyroid cancer subtypes, making additional evaluation necessary in indeterminate cases.

To improve diagnostic certainty, standardized ultrasound criteria should be integrated with complementary techniques such as elastography, contrast-enhanced ultrasound, or fine-needle aspiration biopsy. A multidisciplinary approach involving radiologists, endocrinologists, and surgeons is essential to optimize imaging interpretation and clinical management. Future research should focus on AI-assisted ultrasound analysis to minimize interpretation variability and explore novel imaging biomarkers and molecular diagnostics for early detection. By improving diagnostic accuracy, these approaches may help clinicians identify thyroid cancer more effectively and reduce unnecessary procedures.

In conclusion, while high-frequency ultrasound remains indispensable in the diagnosis of thy-

roid cancer, its full potential can only be realized through standardization, multimodal integration, and continuous technical innovation.

Disclosure of conflict of interest

None.

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