Original Article

Ultrasound features as predictive markers of *BRAFV600E* mutation in thyroid cancer: a systematic review and meta-analysis

Rongwei Liu[1,2], Haiyuan Li[1], Xiumei Bai[1], Hong Yang[1], Yun He[1]

[1]Department of Medical Ultrasound, The First Affiliated Hospital of Guangxi Medical University, Nanning, China; [2]Department of Medical Ultrasound, The First Affiliated Hospital of Gannan Medical University, Ganzhou, China

Contributions: (I) Conception and design: R Liu, Y He; (II) Administrative support: H Yang, Y He; (III) Provision of study materials or patients: R Liu, H Li; (IV) Collection and assembly of data: R Liu, H Li, X Bai; (V) Data analysis and interpretation: R Liu, H Li, X Bai, H Yang; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Yun He, MM. Department of Medical Ultrasound, The First Affiliated Hospital of Guangxi Medical University, No. 6 Shuangyong Road, Qingxiu District, Nanning 530021, China. Email: heyun@stu.gxmu.edu.cn.

Background: Conflicting evidence exists on the predictive value of ultrasound characteristics for *BRAFV600E* gene expression in thyroid cancer. This study aimed to determine the predictive value of ultrasound features for *BRAFV600E* gene expression status in thyroid cancer.

Methods: A systematic review of studies published before December 31, 2023, was conducted in the PubMed, Web of Science, and Cochrane Library databases. Studies evaluating the ultrasonographic features for predicting *BRAFV600E* gene mutations in thyroid cancer were included. The relevant data were extracted, and the quality of eligible studies was independently assessed by two reviewers. Statistical analysis was performed using RevMan 5.4 and Stata 12.0 software.

Results: The meta-analysis included 13 studies involving a total of 2,250 thyroid cancer patients. Ultrasound features significantly associated with *BRAFV600E* gene expression status in thyroid cancer ($P<0.05$) comprised hypoechogenicity, absence of halo, irregular borders, and vertical orientation. Contrastingly, no significant differences were observed in solid composition, irregular shape, and microcalcifications ($P>0.05$). Among the seven ultrasound features, the ones with superior combined sensitivity for nodules were hypoechogenicity, solid composition, absence of halo, and irregular borders, with sensitivities of 0.93 [95% confidence interval (CI): 0.87–0.96], 0.93 (95% CI: 0.86–0.97), 0.83 (95% CI: 0.72–0.91), and 0.74 (95% CI: 0.64–0.83), respectively. Finally, the areas under the summary receiver operating characteristic (SROC) curve with the highest diagnostic performance were the absence of halo and hypoechogenicity, with area under the curve (AUC) of 0.84 (95% CI: 0.80–0.87) and 0.81 (95% CI: 0.77–0.84), respectively.

Conclusions: The expression status of the *BRAFV600E* gene in thyroid cancer correlates with nodules exhibiting hypoechogenicity, absence of halo, irregular borders, and taller-than-wide shape. Notably, the absence of a halo and hypoechogenicity were identified as the most predictive ultrasonic features. However, due to the limited sample size, there may be bias in the meta-analysis results, and more extensive research is necessary.

Keywords: Thyroid cancer; ultrasound features; *BRAFV600E*; meta-analysis

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Introduction

The past few years have witnessed a considerable increase in thyroid carcinoma cases (1,2). Papillary thyroid carcinoma (PTC), the most prevalent histological variant, constitutes about 80–90% of all thyroid cancer instances, and its incidence continues to increase annually (3). While the majority of thyroid cancers are associated with a favorable prognosis and low mortality rates, a minority of high-risk patients face extrathyroidal invasion, recurrence, and metastasis, especially in advanced stages. Thus, accurate preoperative evaluation of the lesion's characteristics and its invasiveness is critical for surgical decision-making and planning.

Earlier research indicates that the *BRAFV600E* mutation can serve as a valuable biomarker and therapeutic target for the diagnosis, risk stratification, and prognosis prediction of PTC (4,5). Of note, the *BRAFV600E* mutation plays a crucial role in regulating cell proliferation, differentiation, and apoptosis (6). Moreover, it is frequently observed in thyroid carcinoma cases and is connected with PTC.

Hence, preoperative prediction of the *BRAFV600E* mutation holds significant clinical value for the diagnosis and treatment of PTC. Previous studies have actively explored preoperative prediction of the presence of *BRAFV600E* mutations in thyroid cancer based on conventional ultrasound imaging (7). Some studies reported that conventional ultrasound features could predict *BRAFV600E* mutations in PTC (8-14), whereas others have reached opposite conclusions (7,15,16), leading to significant discrepancies in the field. Currently, there are no published meta-analyses on the use of ultrasound features to predict *BRAFV600E* mutations preoperatively in thyroid cancer patients, which are significant prognostic factors and would assist in the diagnosis and differentiation of the disease.

Therefore, this study aimed to conduct a meta-analysis to determine the predictive value of ultrasound features for *BRAFV600E* gene expression status preoperatively, laying a theoretical reference to potentially mitigate unnecessary invasive procedures such as fine-needle biopsies. We present this article in accordance with the PRISMA reporting checklist (available at https://gs.amegroups.com/article/view/10.21037/gs-24-134/rc).

Highlight box

Key findings

- This meta-analysis about the predictive value of ultrasonographic features for the *BRAFV600E* gene mutation in thyroid cancer has shown encouraging results. Certain ultrasonographic features can predict the *BRAFV600E* gene expression status in thyroid cancer patients.

What is known and what is new?

- The value of ultrasonographic features in predicting the *BRAFV600E* gene mutation in thyroid cancer is controversial and has not yet reached a consensus.
- In response to the current focus of controversy, our meta-analysis included the latest literature to explore the value of ultrasonographic features in predicting the *BRAFV600E* gene mutation in thyroid cancer.

What is the implication, and what should change now?

- If ultrasonographic features could predict the *BRAFV600E* gene mutation in thyroid cancer, it would help to reduce the rate of unnecessary biopsies.
- Further research may focus on using radiomics techniques to explore the value of ultrasonographic features in predicting the *BRAFV600E* gene mutation in thyroid cancer.

Methods

Literature search

Literature searches were conducted in PubMed, Web of Science, and Cochrane Library using the terms "thyroid cancer" and "ultrasonography", or "sonography", or "ultrasonic", or "ultrasound", and "*BRAF*" until December 2023.

A total of 214 articles was yielded by our search algorithm: 138 from PubMed, 74 from Web of Science, and 2 from Cochrane Library. EndNote X8 was used for literature management, and duplicates were manually excluded.

The inclusion criteria for this study were: (I) research on the ultrasound characteristics of thyroid cancer; (II) histopathology or fine needle aspiration (FNA) cytology as the standard reference; (III) evaluation of ultrasound features for predicting *BRAFV600E* mutation status; and (IV) studies with retrospective or prospective designs.

Exclusion criteria were: (I) studies not focusing on thyroid cancer; (II) unavailable data in 2×2 diagnostic tables; and (III) studies containing duplicated data or instances where patients may have overlapped across studies.

Data extraction

Data extracted from the selected studies comprised (I)

study details such as first author, publication year, design, and inclusion period; and (II) patient demographics such as gender, age, and number of malignant nodules. Two reviewers independently screened the literature and extracted data into a standardized Microsoft Excel spreadsheet to ensure consistency.

Literature evaluation criteria

Study quality was assessed using the Quality Assessment Tool for Diagnostic Accuracy Studies-2 (QUADAS-2) tool. Each article was evaluated for quality and categorized as "yes", "no", or "unclear". Literature was rated "yes" if the criteria were met, "no" if the criteria were unmet or unspecified, and "unclear" if the provided information was incomplete.

Furthermore, the included studies underwent risk of bias and applicability evaluation relative to the research question, with "low", "high", or "unclear" ratings denoting their applicability and bias risk levels. Disagreements were resolved via discussion.

Statistical analysis

Statistical analyses were performed using RevMan 5.4 and Stata 12.0. The risk of bias in the included studies was assessed using bias risk graphs. The sensitivity and specificity of different ultrasound features in predicting the expression status of the *BRAFV600E* gene in thyroid cancer were analyzed, and the summary receiver operating characteristic (SROC) curves were plotted. The area under the curve (AUC) was calculated with 95% confidence intervals (CIs). Heterogeneousness among studies was evaluated using the Q test and I^2 statistics. An I^2 inconsistency index was calculated to determine heterogeneity's level; high heterogeneousness was indicated by an $I^2 \geq 50\%$, and the random-effects model was adopted. In heterogeneity's absence, the fixed-effects model was applied. Funnel plots with different diagnostic indicators were used to detect potential publication bias, and sensitivity analyses were conducted. Forest plots generated by the software provided 95% CIs and P values for evaluating meta-analysis outcomes, with $P<0.05$ considered statistically significant.

Results

Literature search results and characteristics of included studies

The extensive search across the three databases yielded 214 relevant articles. Among them, 68 were found to be duplicates and thus excluded. A detailed review of the titles and abstracts led to the exclusion of 116 articles for their lack of relevance. Further scrutiny of the full texts resulted in the exclusion of 15 additional articles due to their insufficient relevance to the research topic. Moreover, two articles were excluded during the full-text assessment, given that it was not feasible to derive a 2×2 table from the data. Ultimately, 13 articles met the criteria and were incorporated into the systematic review and meta-analysis (8-20) (*Figure 1*).

This study consisted of 13 studies involving 2,250 patients with thyroid cancer, published between 2012 and 2022. Of these, eight were retrospective, three were prospective, and two were unspecified. The research was conducted across four countries: Poland, the United States, South Korea, and China. Sample sizes varied from 34 to 438 patients, with *BRAFV600E* mutation rates ranging from 47.7% to 86.5%. Notably, lower mutation rates were observed in European and American countries, while higher rates were found in East Asian countries (*Table 1*).

Quality assessment

Two reviewers independently conducted the quality assessment of the articles included in the study. In case of discrepancies between their evaluations, the decision was made following a thorough discussion. Based on the QUADAS-2 questionnaire outcomes, each study was characterized by a low risk of bias and qualified as high quality. This assessment is clearly reflected in both the literature risk of bias evaluation graph and the summary graph in *Figure 2*.

Evaluation of the diagnostic performance of ultrasound features

Notably, the combined sensitivity of the seven ultrasonographic features (as shown in Appendix 1) for

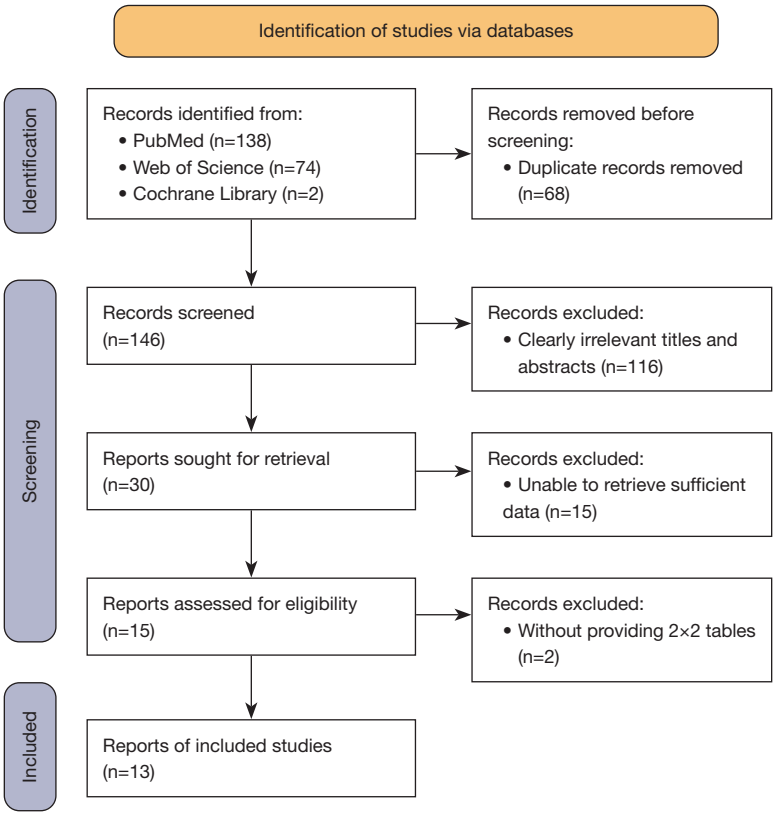

Figure 1 PRISMA flowchart of the study selection process. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-analyses.

Table 1 The basic information of the included literatures

First author	Year	Country	Design	Sex (M/F)	Thyroid cancer (n)	No. of *BRAF* (+) (n)	Rate of *BRAF* (+) (%)	Period of enrollment
Li H (8)	2022	China	Retrospective	25/78	103	72	69.9	2020–2021
Skubisz K (9)	2021	Poland	NA	8/36	44	21	47.7	2015–2016
Shangguan R (10)	2019	China	Retrospective	101/296	397	323	81.4	2016
Zhang Q (11)	2017	China	Retrospective	100/338	438	379	86.5	2015–2016
Wang S (12)	2017	China	Retrospective	NA	64	44	68.8	2014–2015
Hahn SY (13)	2017	Korea	NA	26/124	150	115	76.7	1994–2004
Kakarmath S (14)	2016	USA	Prospective	NA	81	56	69.1	NA
Kwon MR (15)	2020	Korea	Retrospective	18/78	96	48	50.0	2012–2013
Li Q (16)	2017	China	Retrospective	6/28	34	18	52.9	2009–2010
Tang J (17)	2022	China	Retrospective	57/175	232	168	72.4	2019–2021
Lee DY (18)	2017	Korea	Prospective	60/272	332	192	57.8	2011–2014
Moon WJ (19)	2012	Korea	Prospective	35/129	164	141	86.0	2006–2008
Kabaker AS (20)	2012	USA	Retrospective	23/83	115	60	52.2	2007–2009

M, male; F, female; NA, not available.

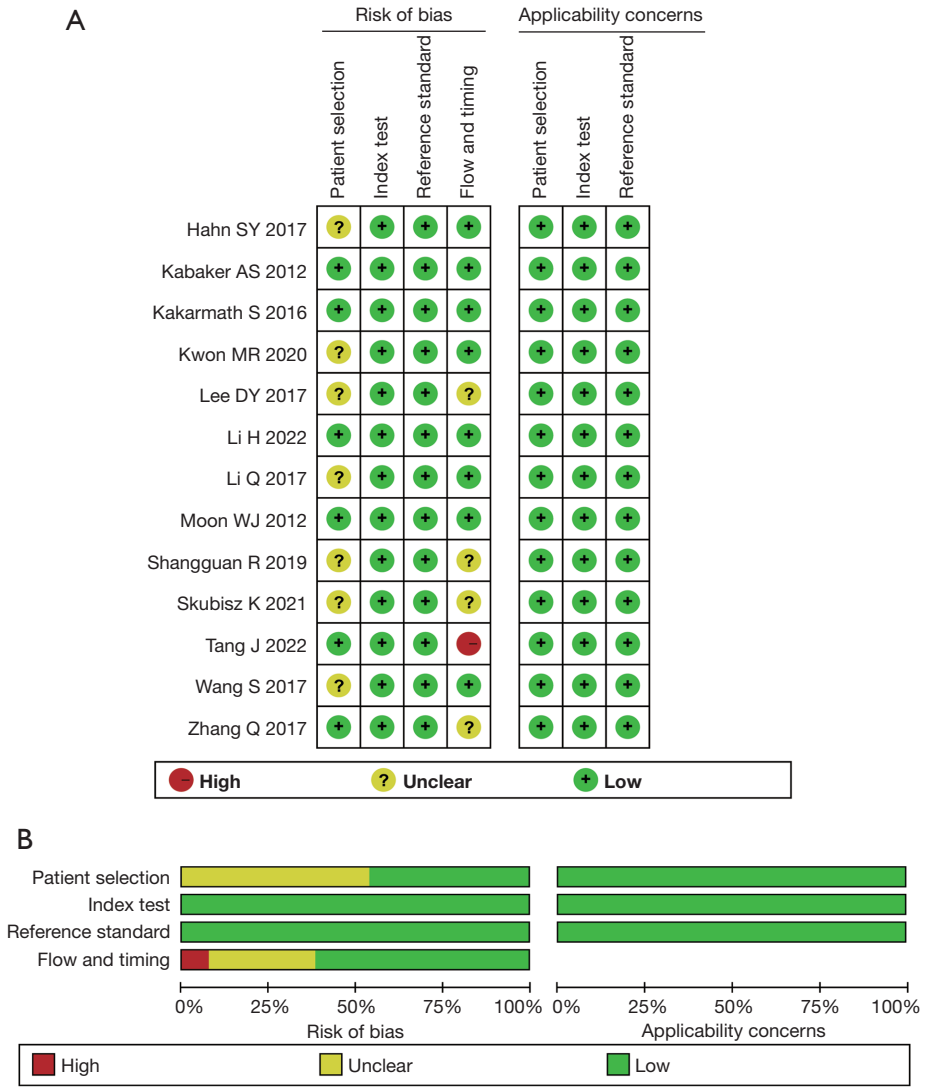

Figure 2 Outcomes of QUADAS-2 for included studies. (A) Risk-of-bias summary. (B) Risk-of-bias graph. Symbols: (+), low risk of bias; (?), unclear risk of bias; (–), high risk of bias. QUADAS-2, Quality Assessment Tool for Diagnostic Accuracy Studies-2.

predicting *BRAFV600E* gene expression in thyroid cancer was satisfactory. The ultrasonographic features with high combined sensitivity included hypoechogenicity, solid composition, absence of halo, and ill-defined borders, with sensitivities of 0.93 (95% CI: 0.87–0.96), 0.93 (95% CI: 0.86–0.97), 0.83 (95% CI: 0.72–0.91), and 0.74 (95% CI: 0.64–0.83), respectively (*Figure 3* and *Table 2*). Additionally, the SROC curve displayed that features with high AUC were the absence of halo and hypoechogenicity, with AUC values of 0.84 (95% CI: 0.80–0.87) and 0.81 (95% CI: 0.77–0.84), respectively (*Figure 4*).

Subgroup analysis and sensitivity analysis

High heterogeneousness was displayed by the forest plot in the pooled specificity and sensitivity of ultrasonographic features for predicting *BRAFV600E* gene expression in thyroid cancer. To address heterogeneousness and assess the results' robustness, the random-effects model was used to calculate combined outcomes, whilst subgroup analysis was conducted to explore heterogeneity's sources. The heterogeneity was addressed and homogenized following the exclusion of the study undertaken by Wang *et al.* using a leave-one-out approach (12), suggesting this study might

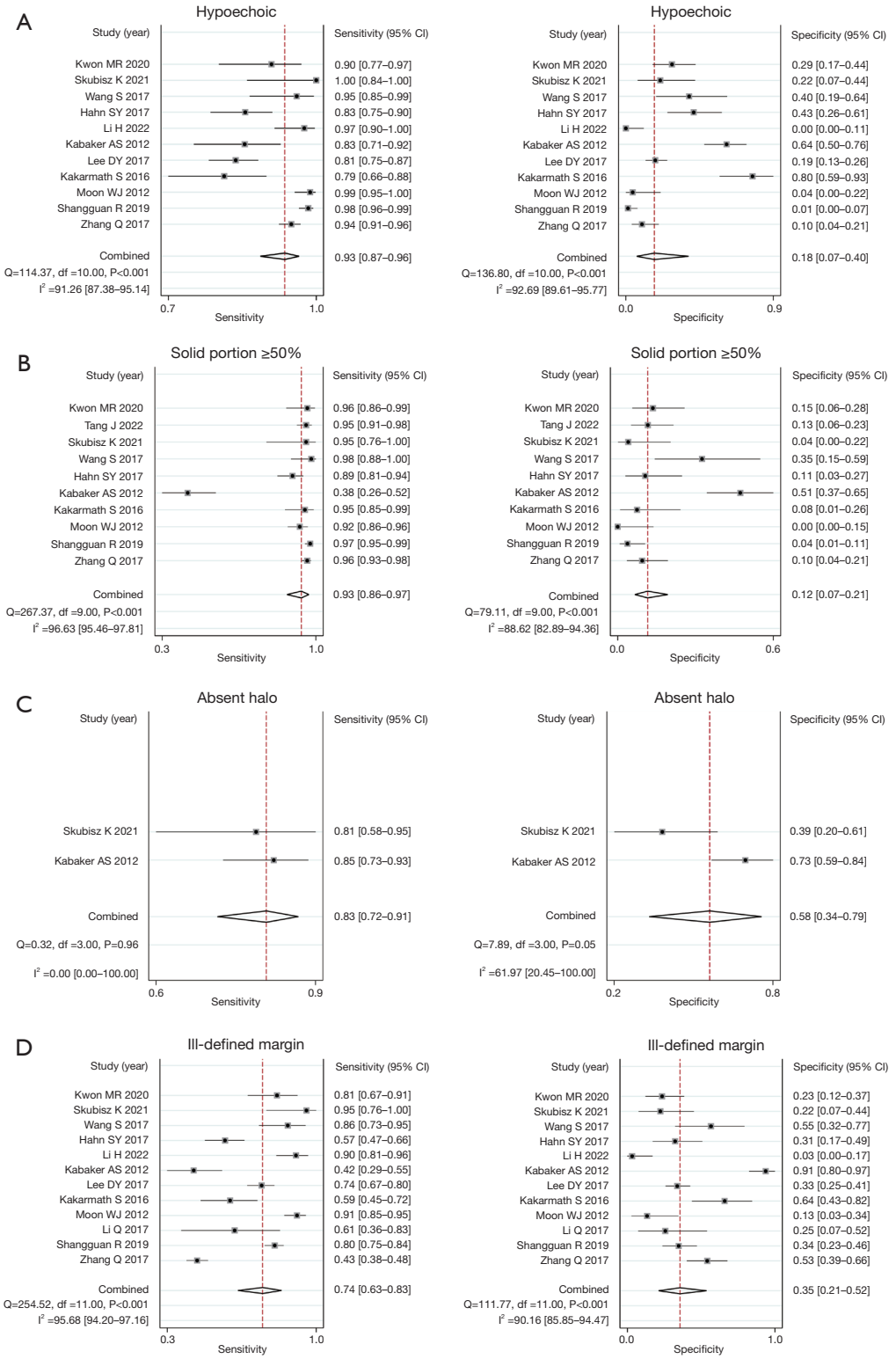

Figure 3 Forest plot of sensitivity and specificity among studies. (A) Hypoechoic; (B) solid composition; (C) absent halo; (D) ill-defined margin. Each horizontal line represents an individual study with the result plotted as a box and the 95% CI displayed as the line. The diamond at the bottom of each plot shows the result of the individual studies combined and averaged. The horizontal lines of the diamond are the limits of the 95% CIs. CI, confidence interval.

Table 2 Predicting performance of each sonographic features

Sonographic features	SROC AUC		Sensitivity		Specificity	
	Value	95% CI	Value	95% CI	Value	95% CI
Solid portion ≥50%	0.48	0.43–0.52	0.93	0.86–0.97	0.12	0.07–0.21
Taller-than-wide	0.62	0.57–0.66	0.55	0.43–0.65	0.63	0.51–0.73
Ill-defined margin	0.61	0.56–0.65	0.74	0.64–0.83	0.35	0.21–0.52
Absent halo	0.84	0.80–0.87	0.83	0.72–0.91	0.58	0.34–0.79
Hypoechoic	0.81	0.77–0.84	0.93	0.87–0.96	0.18	0.07–0.40
Microcalcification	0.57	0.53–0.62	0.67	0.57–0.76	0.42	0.31–0.54
Irregular shape	0.50	0.46–0.54	0.57	0.23–0.86	0.48	0.34–0.62

SROC, summary receiver operator characteristic; AUC, area under the curve; CI, confidence interval

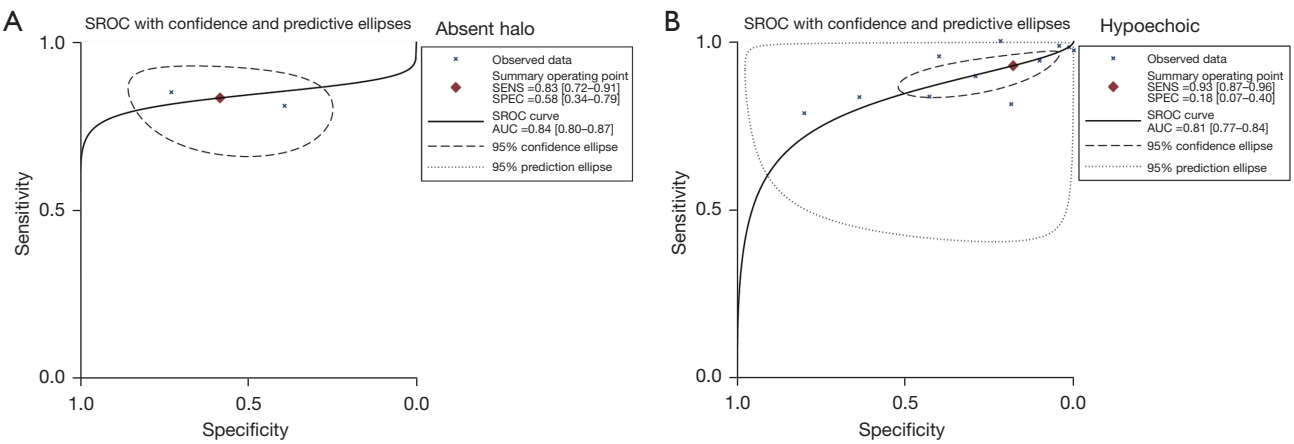

Figure 4 SROC curve with AUC of two sonographic features in predicting *BRAF* gene expression status in thyroid cancer. (A) Absent halo; (B) hypoechoic. SROC, summary receiver operator characteristic; SENS, sensitivity; SPEC, specificity; AUC, area under the curve.

have been a potential source of heterogeneity. Subgroup analysis of the seven ultrasonic features revealed that hypoechogenicity, absence of halo, ill-defined margins, and vertical orientation were statistically significant (P<0.05) predictors of *BRAFV600E* gene expression in thyroid cancer, with odds ratio (OR) values ranging from 1.02 to 36.91. However, solid nodule composition, irregular shape, and microcalcifications were not statistically significant (P>0.05) (*Figure 5*).

Publication bias

Additionally, the Deeks funnel plot analysis revealed no significant publication bias across the ultrasound characteristics (P>0.05) (*Figure 6*).

Discussion

To the best of our knowledge, this is the first meta-analysis summarizing the prognostic value of ultrasound features in preoperatively predicting *BRAFV600E* gene expression status in thyroid cancer. Prior research (21-23) documented that *BRAFV600E* gene expression is a critical prognostic factor in thyroid cancer, especially in advanced stages. Hence, this systematic review and meta-analysis were carried out to evaluate the predictive value of ultrasound characteristics. Based on the results of the included studies, the absence of halo and hypoechogenicity in thyroid nodules exhibited superior predictive efficacy for preoperative *BRAFV600E* gene expression status in thyroid carcinoma compared to the remaining ultrasonographic features.

In this meta-analysis, we included 13 studies involving

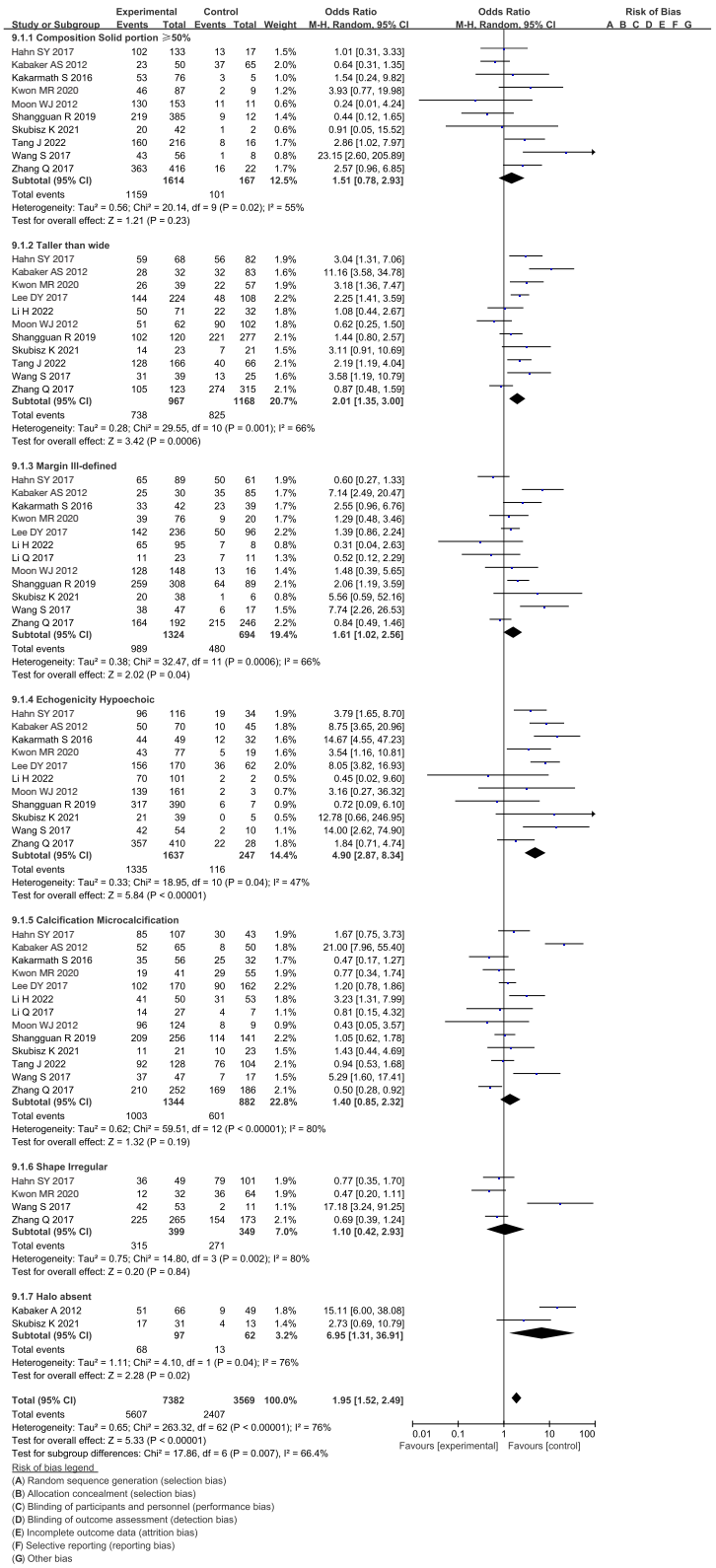

Figure 5 Odds ratio and its 95% confidence intervals of ultrasound features in predicting *BRAF* gene expression status in thyroid cancer. M-H, Mantel-Haenszel; CI, confidence interval.

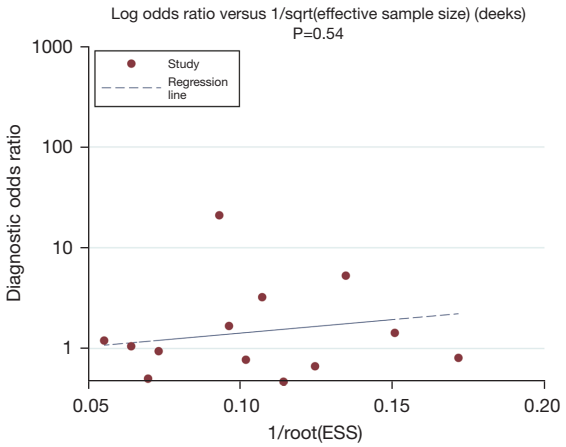

Figure 6 Deeks funnel plot to assess the publication of bias. ESS, effective sample size; sqrt, square root.

2,250 patients with thyroid carcinoma to examine the value of ultrasonographic features in predicting the *BRAFV600E* gene expression status in thyroid carcinoma. Herein, a SROC curve was constructed for each ultrasound feature, and the AUC value was used as an indicator of the diagnostic efficacy. A larger AUC corresponds to a greater diagnostic accuracy. The findings revealed that the AUC for the absence of a halo and hypoechogenicity was notably high, at 0.84 (95% CI: 0.80–0.87) and 0.81 (95% CI: 0.77–0.84), respectively. The findings implied that the absence of halo and hypoechogenicity were strongly predictive of *BRAFV600E* gene expression status in thyroid cancer. Likewise, ultrasonographic features such as hypoechogenicity, absence of halo, blurred margins, and vertical orientation were all significantly associated (P<0.05) with *BRAFV600E* gene expression in thyroid carcinoma, consistent with international studies' findings (9,14,24). This may be ascribed to the invasiveness of thyroid cancer, enhanced heterogeneity of cancer cells, and alterations in the tumor microenvironment associated with the *BRAFV600E* gene mutation (25,26). Increased invasiveness results in tumor cells penetrating the surrounding thyroid tissue and capsule, while increased heterogeneity reflects a complex cellular composition within the tumor, contributing to indistinct margins and heterogeneous internal echoes on ultrasonography. The presence of hypoechogenicity in nodules is commonly attributed to interstitial edema, which is the buildup of fluid between follicles and within the lobules, resulting in mild to moderate hypoechogenicity. Malignant nodules are often characterized by hypoechogenic or markedly hypoechogenic appearances. A nodule with a taller-than-wide shape is usually associated with malignancy and serves as an independent risk factor. The halo observed around thyroid nodules typically stems from blood vessels encircling the periphery. Some research suggests that this halo may also result from additional pathological changes, including compressive atrophy of the thyroid tissue outside the capsule, inflammatory exudate from adjacent tissues, and interstitial edema. A thin halo may indicate benign tumors, while malignant nodules often lack a halo or present with a thick halo. However, our meta-analysis noted that the differences in solid composition, irregular shape, and microcalcifications of nodules were not statistically significant (P>0.05), discrepant from the observations of previous studies wherein microcalcifications were significantly associated with *BRAFV600E* mutations in thyroid cancer and considered an independent predictive factor (8,11,12,20). These discrepancies may be attributed to differences in the studied populations, with reports documenting a significant association of microcalcifications being predominantly observed in East Asian populations. Variability in interpreting ultrasound imaging features among different physicians can significantly influence these findings.

The analysis of different ultrasonographic features across the 13 included studies exposed that while the combined sensitivity of the included features was satisfactory, their specificity was relatively poor. Although this collectively enhances screening capability, it may simultaneously lead to an increase in the rate of misdiagnosis. The high sensitivity but low specificity of these predictive outcomes can be attributed to the non-specific nature of the ultrasound features and their indirect correlation with *BRAFV600E* mutation. Ultrasound characteristics such as internal echoes, microcalcifications, blurred margins, and the absence of a halo are notably more prevalent in nodules with *BRAFV600E* mutations. Nevertheless, these features might also manifest in nodules without *BRAFV600E* mutations, leading to reduced specificity. The *BRAFV600E* mutation is also associated with certain characteristics of PTC and a more aggressive tumor phenotype. Nonetheless, this association is likely indirect. Moreover, heterogeneity among the included studies was relatively high; hence, the random-effects model was adopted, and subgroup sensitivity analyses were performed using the leave-one-out approach. The significant decrease in heterogeneity observed after excluding one particular study signals that it might have been the primary contributor to the heterogeneity (12). After conducting an exhaustive review, it was determined that the current study, which exclusively focused on patients

with PTC undergoing total thyroidectomy and central lymph node dissection, applied more stringent inclusion criteria compared to the remaining 12 studies, thereby accounting for the observed heterogeneity.

This study found that the prevalence of *BRAFV600E* mutations is lower in Western countries and higher in East Asian countries. This could be tied to genetic predispositions within the population, as well as variations in lifestyle and dietary choices. In addition, it is plausible that certain genetic traits in East Asian populations may increase their susceptibility to *BRAFV600E* mutations. Furthermore, disparities in iodine consumption could be linked to the frequency and variation of mutations observed in patients with thyroid cancer.

There are limitations to this study that cannot be overlooked. To begin, the patient demographic largely consisted of Asians in the included studies, with limited representation from Western populations, thereby limiting the generalizability of the findings across different ethnicities. In addition, not all studies reported data on the seven ultrasound features, and there was a lack of uniformity in their criteria across the studies. Furthermore, the exclusion of non-English language articles could have introduced inherent biases, as potentially relevant studies in other languages were not considered.

Conclusions

This meta-analysis evaluated ultrasonographic features for predicting the expression status of the *BRAFV600E* gene in thyroid cancer to determine their predictive value for *BRAF* expression status, which could mitigate the reliance on invasive diagnostic methods such as FNA biopsies and ultimately reduce the financial burden for patients. Our results collectively indicated the expression of the *BRAFV600E* gene in thyroid cancer was associated with hypoechoic nodules, the absence of halos, unclear margins, and a taller-than-wide shape. Notably, the absence of a halo and hypoechogenicity were identified as superior predictors of *BRAFV600E* gene status.

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Footnote

Reporting Checklist: The authors have completed the PRISMA reporting checklist. Available at https://gs.amegroups.com/article/view/10.21037/gs-24-134/rc

Peer Review File: Available at https://gs.amegroups.com/article/view/10.21037/gs-24-134/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://gs.amegroups.com/article/view/10.21037/gs-24-134/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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