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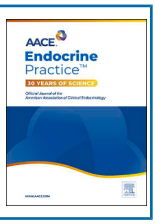

Review Article

Prognostic Value of BRAF V600E Mutation in Papillary Thyroid Carcinoma: A Meta-Analysis of Nodal Involvement, Distant Metastases, Recurrence, and Mortality

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A B S T R A C T

Objective: To investigate the prognostic value of the B-type Raf kinase (BRAF) V600E mutation in papillary thyroid carcinoma.
Methods: A comprehensive search of PubMed/MEDLINE, Scopus, and Web of Science up to August 31, 2025 identified 46 eligible studies including 20,570 patients, following Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines and Quality Assessment of Diagnostic Accuracy Studies version 2 quality assessment. Random-effects models were applied to evaluate associations between BRAF status and major oncological outcomes.
Results: BRAF V600E mutation was significantly associated with lymph node metastasis (odds ratios [OR] = 1.38; 95% confidence interval [CI], 1.17-1.61) and showed a borderline association with recurrence risk (OR = 1.56; 95% CI, 1.00-2.41). In contrast, no significant associations were observed for distant metastases (OR = 0.75; 95% CI, 0.48-1.17) or cancer-related mortality (OR = 0.97; 95% CI, 0.64-1.49). Sensitivity analyses confirmed the robustness of all pooled estimates. Meta-regressions revealed an inverse relationship between BRAF mutation prevalence and its prognostic impact, suggesting that the higher the mutation prevalence in a population, the lower its discriminative prognostic power. Funnel plot inspection and Egger's tests indicated no major publication bias.
Conclusion: Overall, these findings confirm that BRAF V600E mutation is associated with an increased risk of nodal metastasis and recurrence in papillary thyroid carcinoma. However, its lack of impact on distant metastases and disease-specific mortality limits its role as an independent prognostic marker in clinical decision-making.
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Introduction

Papillary thyroid carcinoma (PTC) represents the most frequent histological subtype of thyroid malignancies, accounting for approximately 80% of all cases. It is generally considered a relatively indolent neoplasm, characterized by excellent outcomes. Indeed, disease-specific survival rates exceed 90% at 10 years, reflecting the favorable prognosis associated with this malignancy.[1] Among the well-established traditional prognostic factors, molecular biology has gained increasing attention in recent years. The identification of reliable molecular markers has emerged as a key research priority to improve risk stratification and to personalize management strategies.[2]

Among these, the B-type Raf kinase (BRAF) mutation has received particular attention. First reported in thyroid carcinoma

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in 2003, the BRAF V600E substitution—a single nucleotide change at codon 600 leading to a valine-to-glutamate replacement—represents the most frequent genetic alteration in PTC, occurring in approximately 45% of cases.[3,4] Its high prevalence underscores both its biological relevance and potential clinical significance. Functionally, this mutation results in constitutive activation of the mitogen-activated protein kinase signaling cascade, which plays a central role in thyroid tumorigenesis and disease progression.[5] Given these mechanisms, the prognostic impact of BRAF V600E has been widely investigated. Several studies have linked it to adverse clinicopathological features, including extrathyroidal extension, lymph node metastasis, and recurrence, although results remain inconsistent. Importantly, the most recent American Thyroid Association guidelines emphasize that, despite the biological rationale and high frequency of this mutation, its independent prognostic value is still uncertain, and it should not be used in isolation to guide treatment decisions.[1]

This systematic review and meta-analysis aimed to clarify the prognostic significance of the BRAF V600E mutation in PTC, updating previously available meta-analysis.[6,7] Specifically, we evaluated its association with major oncological outcomes—namely lymph node metastasis, distant metastasis, disease recurrence, and disease-specific mortality—to determine whether the presence of this mutation provides clinically meaningful prognostic information beyond established pathological and clinical risk factors.

Highlights

- The B-type Raf kinase (BRAF) V600E mutation is significantly associated with an increased risk of lymph node metastases in papillary thyroid carcinoma
- Patients carrying the BRAF V600E mutation show a higher risk of disease recurrence compared with wild-type cases
- No significant association was found between BRAF V600E and distant metastases or cancer-related mortality
- The prognostic role of BRAF V600E should not be considered in isolation but integrated with established clinicopathological factors

Clinical Relevance

B-type Raf kinase V600E mutation predicts nodal metastasis and recurrence but not mortality in papillary thyroid carcinoma, limiting its independent value in clinical decision-making.

Materials and Methods

Search Strategy and Inclusion Criteria

A wide literature search of the PubMed/MEDLINE, Scopus, and Web of Science databases was made.

The review questions were defined based on the "Population, Intervention, Comparator, Outcome" framework: what is the prognostic value of BRAF V600E mutation (exposure) in predicting lymph node metastasis, recurrence, distant metastasis, and disease-specific mortality (outcomes) in patients with PTC (population)?

The algorithm used for the research was the following: (BRAFV600E) AND (papillary thyroid cancer).

The search was updated until August 31, 2025. Only articles in English were considered, and preclinical studies, conference proceedings, reviews, or editorials were excluded. To expand our search, the references of the retrieved articles were also screened for additional papers; moreover, other studies were identified by looking through all the articles that cite the papers included in the review ("snowballing"). All eligible studies were exported and managed in EndNote 20.3.

Eligibility Criteria

The eligibility criteria were chosen taking into account the review question. Studies addressing the review questions defined according to the Population, Intervention, Comparator, Outcome framework were included. Exclusion criteria for the systematic review (qualitative analysis) were reviews, letters, comments, editorials on the topic of interest, case reports, or small case series (less than 5 enrolled patients) on the analyzed topic (as these articles are characterized by poor-quality evidence and are typically affected by publication bias) and original articles dealing with different fields of interest.

Study Selection

E.G. and C.C. independently read the titles and abstracts of the records generated by the search algorithm; discrepancies were resolved through discussion with a third reviewer (I.P.). They then determined which studies were eligible based on predefined criteria.

Reporting

The protocol of this systematic review is registered in the International prospective register of systematic reviews (PROSPERO) (CRD420251114432) and followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.[8] The quality assessment of the studies, including the risk of bias and applicability concerns, was carried out using Quality Assessment of Diagnostic Accuracy Studies version 2 (QUADAS-2) evaluation.[9] The corresponding Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram and QUADAS-2 summary figures are reported in Supplementary File 1.

Data Extraction

The reviewers collected data from all of the included studies, taking advantage of full-text, tables, and Supplementary Material concerning general study information (authors, publication year, country, study design, and clinical setting), patients' characteristics (sample size, age, sex, inclusion/exclusion criteria, and relevant clinical characteristics), BRAF V600E mutational status, markers of tumor aggressiveness (lymph node metastasis, recurrence, distant metastasis, and disease-specific mortality), and follow-up duration. The main findings of the articles included in this review are reported in the Results section.

Statistical Analysis

Data from the included studies were analyzed using a random-effects model, accounting for each study's relative weight. This approach was chosen due to either high heterogeneity or small sample sizes across studies. Pooled estimates were reported with 95% confidence intervals (CIs) and graphically displayed using forest plots. Statistical heterogeneity was assessed using the I^2 statistic (inconsistency index), with values > 50% considered indicative of substantial heterogeneity.

Potential publication bias was evaluated through both visual inspection of funnel plots and Egger's linear regression test for funnel plot asymmetry. The robustness of the pooled effect estimates was further assessed through a leave-one-out sensitivity

Table 1
Characteristics of the Human Studies Considered for the Review

First author	Ref. N.	Year	Country	Study design	N. Pts.	Age (y)	Sex M:F
Nikiforova	[10]	2003	United States	Retrospective study	104	40.2 ± 16.8	35/69
Kim	[11]	2005	Korea	Retrospective study	60	NA	4/56
Liu	[12]	2005	Taiwan	Prospective study	101	NA	30/71
Fugazzola	[13]	2006	Italy	Prospective study	260	NA	70/190
Durante	[14]	2007	Italy	Prospective study	93	49.7 ± 16.3	23/66
Frasca	[15]	2008	Italy	Prospective study	323	46.0 ± 14.6	56/267
Xing	[16]	2009	United States	Retrospective study	190	NA	53/137
Jung	[17]	2010	Korea	Retrospective study	357	NA	57/300
Sykorova	[18]	2010	Czech Republic	Retrospective study	242	47 (range: 6-81)	46/196
Ahn	[19]	2011	Korea	Prospective study	107	51.4 ± 12.0	21/86
Howell	[20]	2011	United States	Retrospective study	219	NA	56/163
Lee	[21]	2012	Korea	Retrospective study	166	43.5 ± 12.6	40/126
Park	[22]	2012	Korea	Retrospective study	187	45.9 ± 13.0	31/156
Pelttari	[23]	2012	Finland	Retrospective study	51	NA	11/40
Alzahrani	[24]	2013	United States	Prospective study	379	44 (range: 12-85)	102/277
Choi	[25]	2013	Korea	Retrospective study	101	NA	11/90
Gouveia	[26]	2013	United States	Retrospective study	370	46.8 ± 14.4	93/277
Lee	[27]	2013	Korea	Retrospective study	605	47	132/437
Li	[28]	2013	United States	Retrospective study	315	45.8 ± 14.3	70/245
Lim	[29]	2013	Korea	Retrospective study	2947	45 (range: 10-84)	588/2359
Chai	[30]	2014	Korea	Retrospective study	137	NA	25/112
Daliri	[31]	2014	Iran	Retrospective study	69	40.4 ± 13.3	14/55
He	[32]	2014	China	Prospective study	187	42.6 ± 12.9	28/159
Hong	[33]	2014	Korea	Retrospective study	2624	47.6 ± 12.3	451/2173
Pelizzo	[34]	2014	Italy	Retrospective study	226	44 (range: 8-78)	47/179
Russo	[35]	2014	Italy	Retrospective study	103	44.2 ± 14.9	17/86
Shao	[36]	2014	China	Retrospective study	200	NA	36/164
Xing	[37]	2014	United States	Retrospective study	507	45.9 ± 14.0	142/365
Yim	[38]	2014	Korea	Prospective study	164	43.9 ± 11.7	28/136
Kwak	[39]	2015	Korea	Retrospective study	1945	45.9 ± 12.0	346/1599
Wang	[40]	2015	Taiwan	Prospective study	115	NA	97/18
Nasirden	[41]	2016	Japan	Prospective study	144	56.4 ± 15.6	35/109
Zeng	[42]	2016	China	Retrospective study	619	45.7 ± 11.9	135/484
Kowalska	[43]	2017	Poland	Retrospective study	723	52 (range: 15-80)	88/635
Liu	[44]	2017	United States	Retrospective study	1051	46 (IQR: 36-57)	287/764
de Castro	[45]	2019	Brazil	Retrospective study	53	44 (range: 18-81)	10/43
Tabriz	[46]	2020	Germany	Retrospective study	186	46.9 ± 14.7	46/140
Barreno	[47]	2022	Brazil	Retrospective study	85	54 (range: 45-77)	12/73
Ye	[49]	2022	China	Retrospective study	1257	42 (IQR: 32-53)	348/909
Nechifor-Boilă	[50]	2023	Romania	Retrospective study	127	48.6 ± 1.3	17/110
Pérez-Fernández	[48]	2023	Spain	Retrospective study	685	48.3	145/540
Cao	[51]	2024	China	Retrospective study	322	43.7 ± 12.2	90/232
Lai	[52]	2024	Taiwan	Retrospective study	672	49.7 ± 13.2	173/499
Uno	[53]	2024	Japan	Retrospective study	80	57.2 ± 16.8	22/58
Brumfield	[54]	2025	United States	Retrospective study	301	48.1 (IQR: 33.7-60.6)	90/211
Hu	[55]	2025	China	Retrospective study	811	NA	239/572

Abbreviations: F = female; IQR = interquartile range; M = male; N. = number; NA = not available; Pts. = patients; Ref. = references.

analysis, whereby each study was sequentially excluded to determine its influence on the overall summary effect. In addition, a meta-regression analysis using a mixed-effects model (τ^2 estimator: residual maximum likelihood) was performed to explore whether the prognostic impact of the BRAF V600E mutation varied according to its prevalence across studies. The relationship between mutation prevalence and pooled effect size was visualized through a bubble plot, illustrating the fitted regression line and the weight of each study. All analyses were performed using RStudio (version 2025.05.1 + 513), calculating pooled odds ratios (ORs).

Results

Characteristics of Selected Studies

A total of 2239 articles were identified through the electronic literature search. After removing duplicates, by screening titles and abstracts, 775 articles were excluded as not relevant to the focus of this review. The remaining 137 articles were assessed in full text. 46 studies ultimately met the inclusion criteria and were included in the review[10-55] (Supplementary File 1), encompassing a total of 20,570 patients, 22% of whom were male. Most of the studies were conducted in Asia (23/46; 50%), followed by Europe (12/46; 26%), North America (9/46; 20%), and South America (2/46; 4%).

The main characteristics of the studies and their results are briefly presented in Tables 1 and 2.

The QUADAS-2 assessment showed an overall low risk of bias across the included studies, particularly regarding patient selection and flow/timing. Some concerns emerged in the index test and reference standard domains, where a small proportion of studies presented high or unclear risk of bias. Similarly, applicability concerns were generally low, although a few studies showed limitations related to the index test and reference standard (Supplementary File 1).

Table 2
Results and Main Findings of the Human Studies Considered for the Review

First author	Patients' characteristics	Method of BRAF analysis	Follow-up time (mo)	Outcomes evaluated
Ahn[19]	Patients who received surgical treatment and genetic testing for BRAF for PTC	PCR	NA	Lymph node metastasis
Alzahrani[24]	Patients who received surgical treatment with or without CND and genetic testing for BRAF for PTC	Colorimetric detection assay and PCR	35 (IQR: 15-81)	Lymph node metastasis, tumor recurrence
Barreno[47]	Patients aged ≥ 45 y who received surgical treatment and genetic testing for BRAF for PTC	PCR	NA	Lymph node metastasis, tumor recurrence
Brumfield[54]	Patients who received surgical treatment and genetic testing for BRAF for PTC	Immunohistochemistry	23.4 (IQR: 11.9-37.2)	Lymph node metastasis, tumor recurrence, distant metastasis, cancer-related mortality
Cao[51]	PTMC patients with known BRAF V600E status who received surgery treatment and RAI therapy	PCR	51 (range: 36-70)	Lymph node metastasis, tumor recurrence, distant metastasis
Chai[30]	Patients who received surgical treatment and genetic testing for BRAF for follicular variant of PTC	PCR	29	Lymph node metastasis, tumor recurrence
Choi[25]	Patients who received surgical treatment and genetic testing for BRAF for follicular variant of PTMC	PCR	NA	Lymph node metastasis, tumor recurrence, distant metastasis
Daliri[31]	Patients who received surgical treatment and genetic testing for BRAF for PTC	PCR-RFLP	40.6 ± 14.4	Lymph node metastasis, distant metastasis
de Castro[45]	Patients who received surgical treatment and genetic testing for BRAF for PTC	Immunohistochemistry	156 (range: 120-240)	Tumor recurrence
Durante[14]	Patients who received surgical treatment and genetic testing for PTC, negative for ret/PTC 1 and ret/PTC 3 rearrangements	PCR	NA	Lymph node metastasis, distant metastasis
Frasca[15]	Patients who received surgical treatment and genetic testing for BRAF for PTC	PCR	24 to 48	Lymph node metastasis, tumor recurrence
Fugazzola[13]	Patients who received surgical treatment and genetic testing for BRAF for PTC	PCR and SSCP	72	Lymph node metastasis, distant metastasis
Gouveia[26]	Patients who received surgical treatment and genetic testing for BRAF for PTC	PCR	NA	Lymph node metastasis, distant metastasis
He[32]	Patients who received surgical treatment and genetic testing for BRAF for PTC	PCR and DHPLC	24	Lymph node metastasis, distant metastasis
Hong[33]	Patients who received surgical treatment and genetic testing for BRAF for PTC	PCR and DHPLC	120	Lymph node metastasis, tumor recurrence
Howell[20]	Elderly patients (aged ≥ 65 y) who received surgical treatment and genetic testing for BRAF for PTC, compared to a youngest cohort	RT-PCR and fluorescence melting curve analysis	18 (range: 0-41)	Lymph node metastasis
Hu[55]	Patients who received surgical treatment and genetic testing for BRAF for PTC	NA	41.52 (IQR: 32.97-57.60)	Lymph node metastasis
Jung[17]	Patients who received surgical treatment including CND and genetic testing for BRAF for PTC	PCR	NA	Lymph node metastasis
Kim[11]	Patients who received surgical treatment and genetic testing for BRAF for PTMC	PCR	50.8 ± 20.1	Lymph node metastasis, tumor recurrence
Kowalska[43]	Patients who underwent surgical treatment, RAI therapy when indicated, and genetic testing for BRAF mutation in PTC	DNA sequencing, PCR, RT-PCR	78 (range: 9-186)	Lymph node metastasis, tumor recurrence, cancer-related mortality
Kwak[39]	Patients who received surgical treatment and genetic testing for BRAF for PTC	PCR	27.0 (range: 9-55)	Lymph node metastasis, tumor recurrence, cancer-related mortality
Lai[52]	Patients who received surgical treatment and genetic testing for BRAF for PTC	PCR and direct Sanger sequencing	70	Lymph node metastasis, distant metastasis
Lee[21]	Patients who received surgical treatment and genetic testing for BRAF for PTC	PCR	NA	Lymph node metastasis
Lee[27]	Patients who received surgical treatment for PTC and genetic testing for BRAF on FNAB sample	PCR and direct sequencing	23.6 ± 6.3	Lymph node metastasis, tumor recurrence
Li[28]	Patients who received surgical treatment including CND and genetic testing for BRAF for PTC	PCR	NA	Lymph node metastasis
Lim[29]	Patients who received surgical treatment and genetic testing for BRAF for PTC	PCR	NA	Lymph node metastasis
Liu[12]	Patients who received surgical treatment and genetic testing for BRAF, RET, RAS, and NTRK1 for PTC	PCR	NA	Lymph node metastasis, distant metastasis
Liu[44]	Patients who received surgical treatment and genetic testing for BRAF and TERT for PTC	PCR and direct Sanger sequencing	89 (IQR: 48-142)	Cancer-related mortality
Nasirden[41]	Patients who received surgical treatment and genetic testing for BRAF and TERT for PTC	PCR and direct sequencing	56.9	Lymph node metastasis, tumor recurrence, distant metastasis
Nechifor-Boilă[50]	Patients who received surgical treatment and genetic testing for BRAF for PTC	PCR	57 (CI: 9-130)	Lymph node metastasis, tumor recurrence, distant metastasis
Nikiforova[10]	Patients who received surgical treatment and genetic testing for BRAF for PTC	LightCycler PCR and FMCA; SSCP; Direct sequencing	NA	Lymph node metastasis, distant metastasis
Park[22]	Patients who received surgical treatment and genetic testing for BRAF and Notch1/Notch3 receptors for PTC	Denaturing HPLC and direct sequencing	NA	Lymph node metastasis, tumor recurrence
Pelizzo[34]		PCR		Tumor recurrence

Table 2 (*continued*)

First author	Patients' characteristics	Method of BRAF analysis	Follow-up time (mo)	Outcomes evaluated
	Patients who received surgical treatment and genetic testing for BRAF on FNAB sample for PTC		43 (range: 3-156)	
Pelttari[23]	PTMC patients with known BRAF V600E status who received surgery treatment and RAI therapy	PCR	192 (range: 120-288)	Lymph node metastasis, tumor recurrence
Pérez-	Fernández[48]	Patients who received surgical treatment, if necessary RAI, and genetic testing for BRAF for PTC	Direct Sanger	sequencing
45 (range: 23-77)	Lymph node metastasis, distant metastasis			
Russo[35]	Patients who received surgical treatment and genetic testing for BRAF for PTC	PCR	55.0 ± 13.3	Lymph node metastasis, tumor recurrence
Shao[36]	Patients who received surgical treatment and genetic testing for BRAF for PTC	PCR	NA	Lymph node metastasis
Sykorova[18]	Patients who received surgical treatment and genetic testing for BRAF for PTC	PCR and SSCP	NA	Lymph node metastasis, tumor recurrence, distant metastasis
Tabriz[46]	Patients who received surgical treatment and genetic testing for BRAF for PTC	PCR	60 ± 37	Lymph node metastasis, tumor recurrence, distant metastasis
Uno[53]	Patients who received surgical treatment and genetic testing for BRAF for PTC	Direct Sanger sequencing	NA	Lymph node metastasis, distant metastasis
Wang[40]	Patients who received surgical treatment and genetic testing for BRAF for PTC	Direct Sanger sequencing	NA	Lymph node metastasis, distant metastasis
Xing[16]	Patients who received surgical treatment for PTC and genetic testing for BRAF on FNAB sample	Colorimetric detection assay	36 (range: 7.2-120)	Lymph node metastasis, tumor recurrence
Xing[37]	Patients who received surgical treatment and genetic testing for BRAF and TERT for PTC	PCR and direct Sanger sequencing	24 (IQR: 8-78)	Lymph node metastasis, tumor recurrence, distant metastasis
Ye[49]	Patients who received surgical treatment and genetic testing for BRAF for PTC	PCR	21 (IQR: 15-29)	Lymph node metastasis, tumor recurrence, distant metastasis
Yim[38]	Patients who underwent surgical treatment, RAI therapy genetic testing for BRAF mutation and evaluation of the expression of XIAP for PTC	PCR and direct sequencing	132 (12-168)	Lymph node metastasis
Zeng[42]	Patients who received surgical treatment and genetic testing for BRAF for PTC	PCR	NA	Lymph node metastasis

Abbreviations: BRAF = B-type Raf kinase; CI = confidence interval; CND = central neck dissection; DHPLC = denaturing high-performance liquid chromatography; FMCA = fluorescence melting curve analysis; FNAB = fine-needle aspiration biopsy; HPLC = high-performance liquid chromatography; IQR = interquartile range; NA = not available; NTRK1 = neurotrophic tyrosine receptor kinase 1; PCR = polymerase chain reaction; PCR-RFLP = polymerase chain reaction with restriction fragment length polymorphism; PTC = papillary thyroid carcinoma; PTMC = papillary thyroid microcarcinoma; RAI = radioactive iodine; RAS = rat sarcoma; RET = rearranged during transfection; ; RT-PCR = real-time polymerase chain reaction; SSCP = single-strand conformational polymorphism; TERT = telomerase reverse transcriptase; XIAP = X-linked inhibitor of apoptosis protein.

Quantitative Analysis

Nodal Metastasis

Data from 42 studies[10-33,35-43,46-55] encompassing 19,045 patients, of whom 68% harbored the BRAF mutation, were pooled using a random-effects model to assess the association between BRAF mutation and lymph node metastasis. The meta-analysis demonstrated a significantly increased risk of nodal metastasis in patients with the BRAF mutation (OR = 1.38; 95% CI: 1.17-1.61), although substantial heterogeneity was observed across studies ($I^2 = 71.8\%$, $P < .0001$) (Fig. 1).

Leave-one-out sensitivity analysis confirmed the robustness of the pooled effect estimate comparing lymph node metastasis rates between BRAF-mutated and wild-type PTC. Sequential omission of individual studies did not materially alter the overall effect size (pooled OR range: 1.35-1.41), and the direction and magnitude of the association remained consistent across all iterations (Supplementary File 2, Supplementary Fig. A). This indicates that no single study exerted a disproportionate influence on the summary estimate, supporting the overall stability and reliability of the meta-analytic findings.

The meta-regression analysis, using BRAF mutation prevalence as the explanatory variable, revealed a significant inverse association with the pooled OR ($\beta = -1.31$, standard error [SE] = 0.42, $P = .0019$), indicating that the higher the prevalence of the mutation in a study population, the lower its discriminative prognostic power. The model explained approximately 29% of the between-study heterogeneity ($R^2 = 29.3\%$), with residual heterogeneity remaining substantial ($\tau^2 = 0.12$; $I^2 = 67.9\%$). The fitted regression line and study-specific weights are displayed in the bubble plot (Supplementary File 2, Supplementary Fig. B).

Funnel plot analysis revealed an approximately symmetrical distribution of studies around the pooled effect size, suggesting no strong indication of publication bias. Nonetheless, a slight asymmetry was noted, with fewer small studies reporting null or inverse associations on the left side of the plot. While this pattern does not conclusively indicate selective reporting or small-study effects, such biases cannot be entirely ruled out (Supplementary File 2, Supplementary Fig. C). Consistently, Egger's linear regression test did not reveal significant funnel plot asymmetry ($t = -0.62$, $df = 41$, $P = .54$), further supporting the absence of relevant publication bias.

Tumor Recurrence

To assess differences in recurrence risk between the 2 patient groups, data from 24 studies[11,15,16,18,22-25,27,30,33-35,37,39,41,43,45-47,49-51,54] including 7515 patients (64% with BRAF mutation) were pooled using a random-effects model. The analysis revealed a borderline increased risk of recurrence in patients harboring the BRAF mutation (OR = 1.56; 95% CI: 1.00-2.41), with substantial heterogeneity among studies ($I^2 = 69.3\%$, $P < .0001$) (Fig. 2).

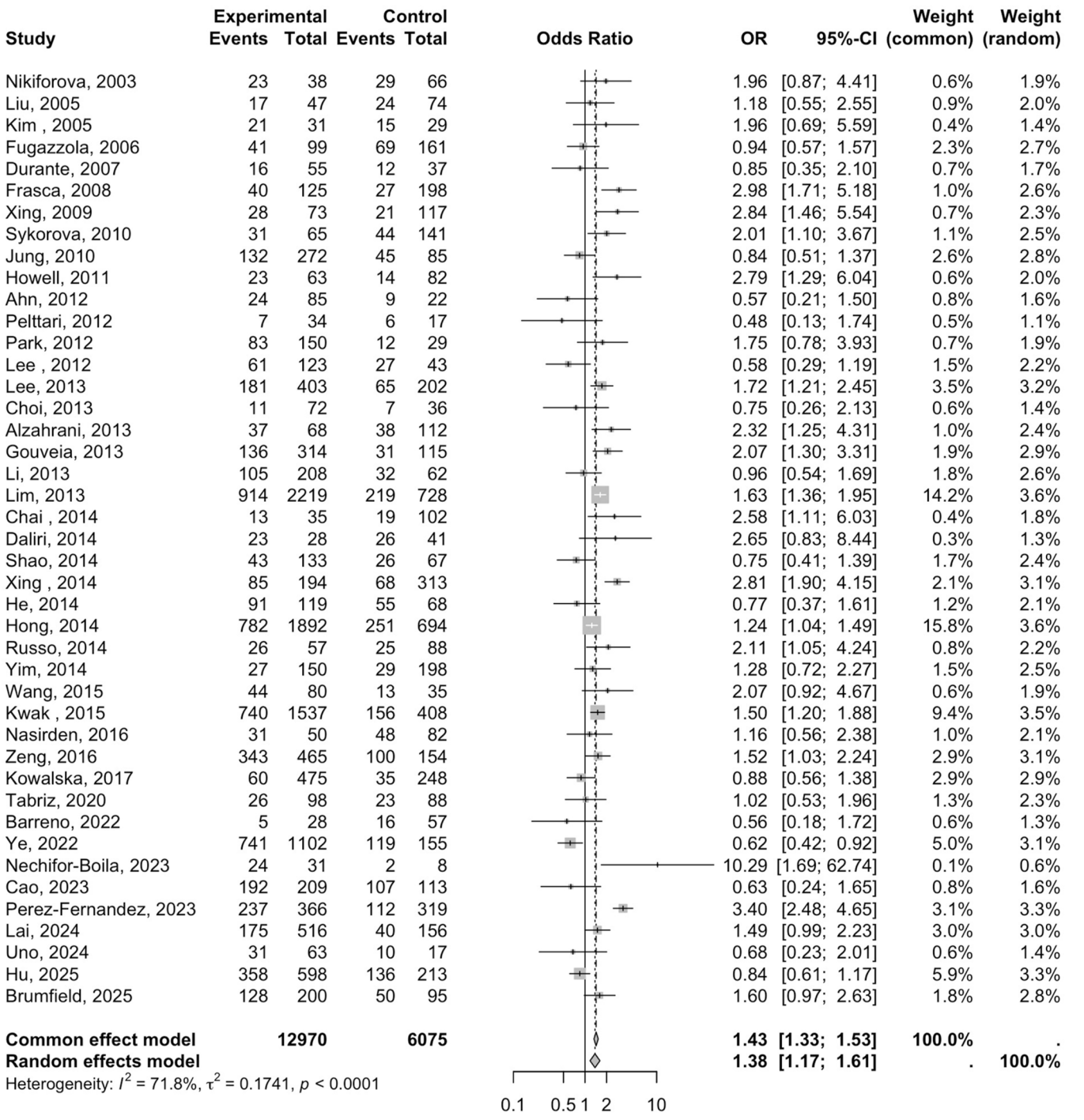

Fig. 1. Forest plots of the meta-analysis comparing lymph node metastasis rate between BRAF-mutated and wild-type papillary thyroid carcinoma. BRAF = B-type Raf kinase.

Leave-one-out sensitivity analysis confirmed the robustness of the association between BRAF mutation and lymph node recurrence. Sequential omission of individual studies did not materially affect the overall pooled effect size (pooled OR range: 1.52-1.60), with stable CIs across all iterations (Supplementary File 2, Supplementary Fig. D). This consistency indicates that no single study exerted an undue influence on the summary estimate, reinforcing the stability and reliability of the meta-analytic findings.

A mixed-effects meta-regression model evidenced a substantial residual heterogeneity ($\tau^2 = 0.614$; $I^2 = 66.1\%$; $P < .0001$), indicating variability not fully explained by sampling error. The meta-regression showed a statistically significant negative association between BRAF V600E prevalence and log(OR) values ($\beta = -2.17$, SE = 1.10, $P = .048$), suggesting that studies with a higher prevalence of the mutation tended to report a lower relative risk of tumor recurrence compared with wild-type cases. Overall, the moderator explained an approximately 17.6% of between-study heterogeneity ($R^2 = 17.61\%$). The fitted regression line and study-specific weights are represented in the bubble plot (Supplementary File 2, Supplementary Fig. E).

The funnel plot showed an overall symmetrical distribution of studies around the pooled effect size, with most estimates

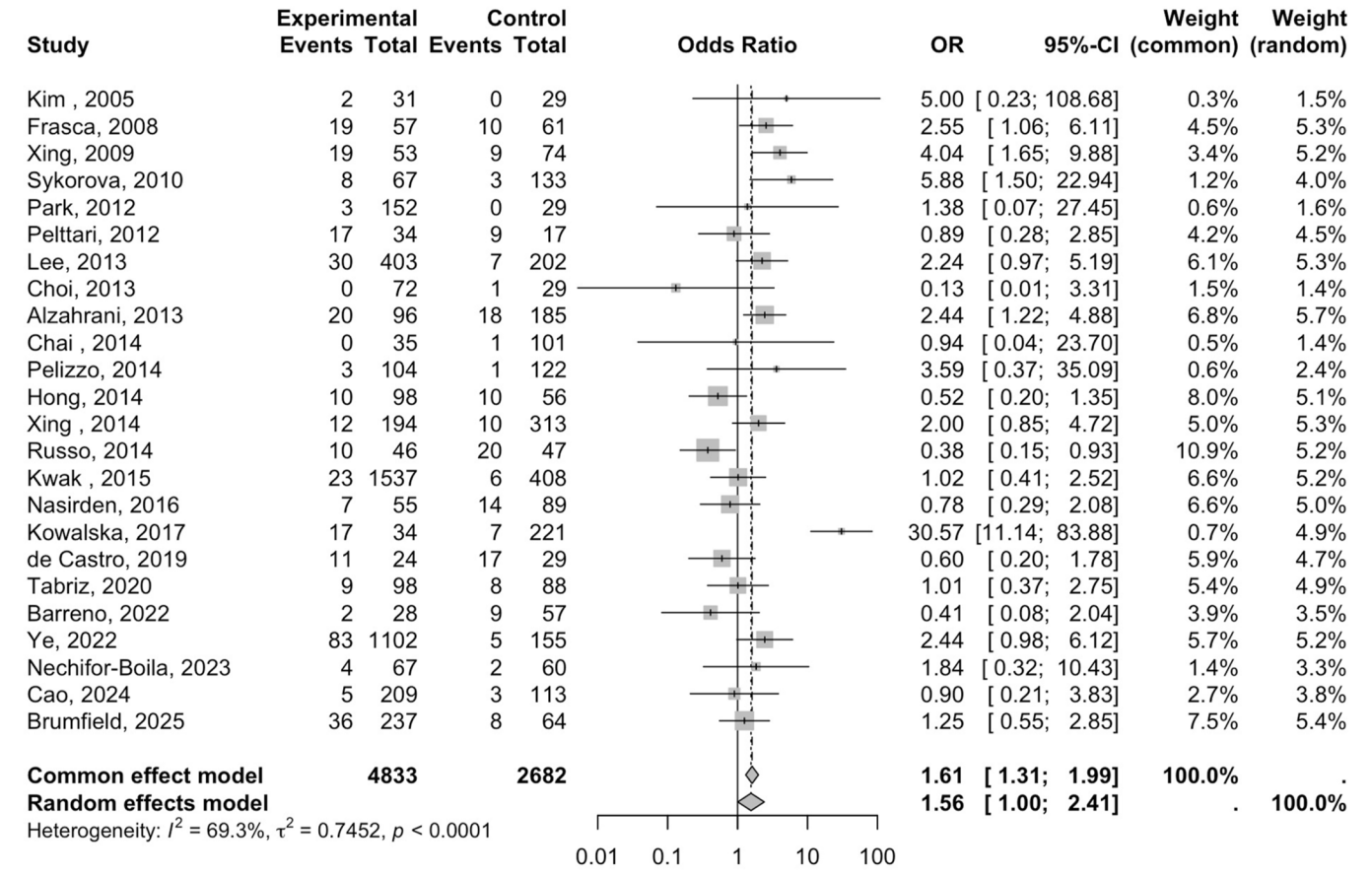

Fig. 2. Forest plots of the meta-analysis comparing tumor recurrence rate between BRAF-mutated and wild-type papillary thyroid carcinoma. BRAF = B-type Raf kinase.

clustering near the summary OR. Although a few studies were scattered at lower precision levels, no marked asymmetry was observed. This distribution suggests a low likelihood of major publication bias; however, the potential influence of small-study effects cannot be entirely ruled out (Supplementary File 2, Supplementary Fig. F). Consistently, Egger's linear regression test did not reveal significant funnel plot asymmetry (t = −0.47, df = 22, P = .64), further supporting the absence of substantial publication bias.

Distant Metastases

A total of 20 studies[10,12-14,18,25,26,31,32,37,40,41,46,48-54] entailing 4398 patients (64% with BRAF mutation) were pooled using a random-effects model to evaluate the association between BRAF mutation and the development of distant metastasis. The meta-analysis showed no significant difference between the 2 groups (OR = 0.75; 95% CI: 0.48-1.17), with substantial heterogeneity across studies (I^2 = 55.1%, P = .4403) (Fig. 3).

Leave-one-out sensitivity analysis confirmed the robustness of the pooled estimate comparing extrathyroidal extension between BRAF-mutated and wild-type PTC. Sequential exclusion of each study did not materially alter the overall effect size, with pooled ORs ranging from 0.72 to 0.77 and overlapping CIs across all iterations (Supplementary File 2, Supplementary Fig. G). These results indicate that no individual study had a disproportionate influence on the overall summary estimate, supporting the stability and reliability of the meta-analytic findings.

The mixed-effects meta-regression showed that residual heterogeneity remained moderate (τ^2 = 0.474; I^2 = 57.8%; P = .0012), suggesting relevant between-study variability not fully explained by sampling error. The moderator variable (BRAF mutation prevalence) did not significantly explain this heterogeneity (QM = 0.655, P = .418). The regression coefficient for mutation prevalence was negative but not statistically significant (β = −1.14, SE = 1.41, P = .418), indicating no clear association between BRAF V600E prevalence and the risk of distant metastasis.

Overall, the model explained no additional heterogeneity (R^2 = 0.0%). The fitted regression line and study-specific weights are displayed in the bubble plot (Supplementary File 2, Supplementary Fig. H).

The funnel plot revealed a generally symmetrical distribution of studies around the pooled OR, with only a few estimates scattered at lower precision levels. While minor asymmetry cannot be entirely excluded, there was no clear indication of substantial publication bias (Supplementary File 2, Supplementary Fig. I). Consistently, Egger's linear regression test did not reveal significant funnel plot asymmetry (t = 0.63, df = 18, P = .54), further supporting the absence of major publication bias across the included studies.

Cancer-Related Mortality

Five studies[28,39,43,44,54] including 3833 patients (69% of whom with BRAF mutation) were pooled using a random-effects model to assess cancer-related mortality. The meta-analysis did not reveal a significant difference in mortality between patients with and without BRAF mutation (OR = 0.97; 95% CI: 0.64-1.49), with substantial heterogeneity observed across studies (I^2 = 32.8%, P = .0939) (Fig. 4).

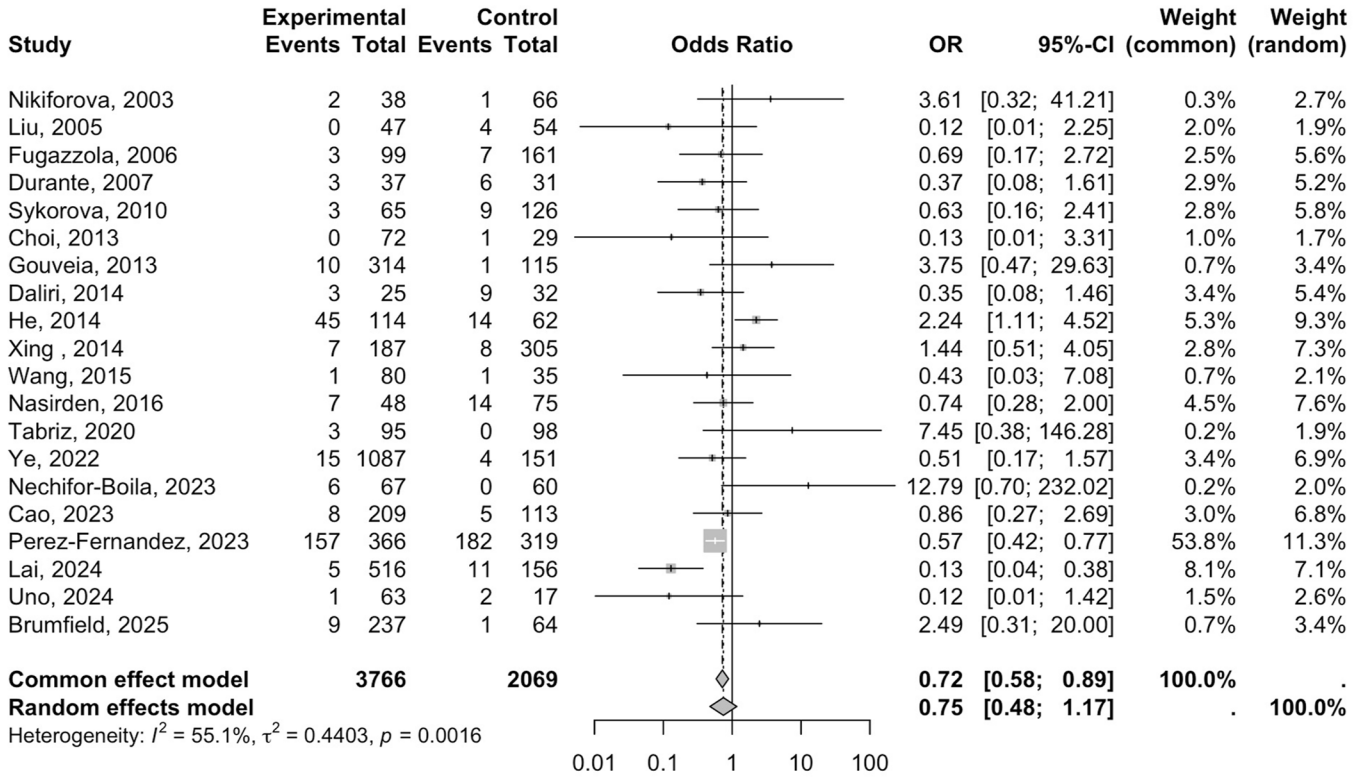

Fig. 3. Forest plots of the meta-analysis comparing distant metastasis rate between BRAF-mutated and wild-type papillary thyroid carcinoma. BRAF = B-type Raf kinase.

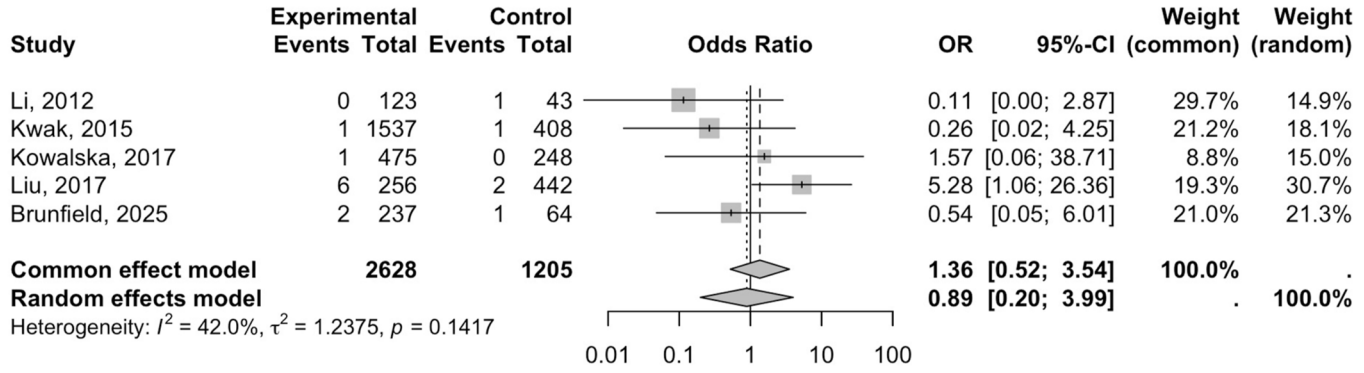

Fig. 4. Forest plots of the meta-analysis comparing cancer-related mortality between BRAF-mutated and wild-type papillary thyroid carcinoma. BRAF = B-type Raf kinase.

Leave-one-out sensitivity analysis confirmed the stability of the pooled estimate for mortality. Sequential omission of individual studies produced pooled ORs ranging from 0.84 to 0.92, with largely overlapping CIs (Supplementary File 2, Supplementary Fig. J). No single study exerted a disproportionate influence on the overall effect size, indicating that the observed lack of association between BRAF mutation and mortality risk was not driven by any individual dataset.

The mixed-effects meta-regression detected no residual heterogeneity ($\tau^2 = 0$; $I^2 = 0.0\%$; $P = .7835$), indicating high consistency across studies. The moderator variable (BRAF mutation prevalence) showed a statistically significant negative association with log(OR) values ($\beta = -6.73$, SE = 2.79, $P = .016$), suggesting that higher prevalence of BRAF mutation was associated with a markedly lower relative risk of cancer-related mortality compared with wild-type cases. The model explained all between-study heterogeneity ($R^2 = 100\%$). The fitted regression line and study-specific weights are displayed in the bubble plot (Supplementary File 2, Supplementary Fig. K).

The funnel plot for mortality includes only a few studies, with a scattered distribution around the pooled OR. Given the small number of studies, the assessment of asymmetry and potential publication bias is unreliable, and no firm conclusions can be drawn (Supplementary File 2, Supplementary Fig. L). Consistently, Egger's linear regression test did not show statistically significant funnel plot asymmetry ($t = -2.66$, df = 3, $P = .08$), although the small number of studies limits the interpretability of this result.

Discussion

This meta-analysis, encompassing more than 20,000 patients, confirms that the BRAF V600E mutation in PTC is significantly associated with lymph node metastasis and, to a lesser extent,

with tumor recurrence, whereas its impact on distant metastasis and cancer-specific mortality remains negligible.

Over recent decades, the global incidence of well-differentiated thyroid carcinoma, particularly PTC, has markedly increased. This trend is largely attributed to the widespread implementation of imaging modalities and the routine use of thyroid ultrasound combined with fine-needle aspiration cytology, facilitating the detection of subclinical microcarcinomas.[56-58] Despite this rising incidence, mortality rates from well-differentiated thyroid carcinoma have remained stable, underscoring its generally favorable prognosis.[59,60]

Among the most relevant prognostic indicators for progression and mortality, the presence of distant metastases—either at diagnosis or during follow-up—plays a pivotal role. Additional clinical predictors include age at diagnosis, tumor size, aggressive histologic features such as extrathyroidal extension, histologic subtype, and the presence of lymph node metastases.[61,62]

Beyond conventional histopathologic features, molecular profiling has been increasingly recognized as a valuable prognostic tool. Genetic alterations such as BRAF V600E and telomerase reverse transcriptase promoter mutations have been linked to more aggressive tumor behavior, including extrathyroidal invasion, lymph node involvement, and distant dissemination.[7,63-68] The oncogenic role of the BRAF V600E mutation in thyroid cancer was first identified by Davies et al in 2002, establishing its transforming capacity and laying the groundwork for subsequent molecular investigations into thyroid tumorigenesis.[69] The reported frequency of the mutation ranges from 27% to 83% in adult PTC cohorts.[70] However, its prognostic significance remains controversial. For example, Gouveia et al reported a significantly higher prevalence of lymph node involvement in PTC patients harboring the BRAF V600E mutation ($P = .002$),[26] whereas Cao et al found no significant difference between mutated and wild-type cases.[51] Our meta-analysis, including 39 studies encompassing 17,362 patients, demonstrated a significantly increased risk of nodal metastasis in patients with the BRAF V600E mutation (OR: 1.34) (Fig. 1). However, the substantial heterogeneity and slight funnel plot asymmetry indicate that this result should be interpreted with caution. Comparable findings were observed for tumor recurrence, with data from more than 7000 patients suggesting a 1.56-fold increased risk, although the association was of borderline statistical significance (Fig. 2). It is important to underline that the leave-one-out analyses consistently demonstrated that no single study exerted a disproportionate influence on pooled results, confirming the stability of both nodal and recurrence associations (Supplementary File 2, Supplementary Figs. A and D). In addition, the inverse relationship between BRAF mutation prevalence and its prognostic effect indicates that, in populations where the mutation is highly prevalent, its discriminative value as a prognostic biomarker tends to decrease (Supplementary File 2, Supplementary Figs. B and D).

Seventeen studies evaluated the association between BRAF V600E mutation and the occurrence of distant metastases[10,12-14,18,25,26,31,32,37,40,41,46,49-51,54]; the majority (11 studies) reported no significant difference between mutated and wild-type patients. This finding was corroborated by our meta-analysis (Fig. 3). Going on, given that the development of distant metastases is a well-established predictor of cancer-related mortality in PTC patients,[71] no association between BRAF V600E and mortality would be expected. Accordingly, our meta-analysis showed no significant difference in mortality rates between the 2 groups (Fig. 4).

Regarding the clinical impact of the BRAF V600E mutation in PTC, Brumfield et al[54] recently concluded that its presence 'is not a risk factor for recurrence and that consideration should be given to minimizing its importance in clinical decision-making'. In fact, we demonstrated that BRAF mutation status is a risk factor for the development of nodal metastases and disease recurrence, but not for distant metastases and, more importantly, cancer-related mortality.

Several limitations of this study must be acknowledged. First, the follow-up duration was highly heterogeneous across the included studies, and in many cases, it was not reported at all, thereby limiting the reliability of outcome comparisons over time. Second, substantial variability existed in the therapeutic approaches adopted. For instance, in some cohorts a prophylactic central neck dissection was systematically performed, while in others this procedure was omitted. Similarly, not all studies clearly specified whether patients had undergone postoperative radioiodine treatment. In addition, many studies did not provide details on the histological variants of PTC. This omission is particularly relevant, since aggressive variants (eg, tall-cell, columnar-cell, or hobnail variants) are known to have a worse prognosis and could partly explain the heterogeneity observed in the pooled results. Finally, the vast majority of studies focused exclusively on the presence of the BRAF V600E mutation, without systematically evaluating other molecular alterations, which has been increasingly recognized as important determinants of tumor aggressiveness and may act synergistically with BRAF V600E in shaping the biological behavior of PTC, such as telomerase reverse transcriptase mutation.[1]

Nevertheless, the large number of studies and patients included in this meta-analysis strengthens the robustness of our findings. Moreover, the most recent American Thyroid Association guidelines emphasize that the BRAF V600E mutation, when considered in isolation, is not clearly associated with more aggressive disease or adverse outcomes,[1] thereby reinforcing the conclusions of our study.

Conclusion

The BRAF V600E mutation is associated with an increased risk of lymph node metastasis and shows a borderline association with disease recurrence in patients with PTC. In contrast, its influence on distant metastasis and disease-specific mortality appears minimal, thereby reducing its clinical utility as an independent prognostic biomarker for risk stratification and therapeutic decision-making.

Disclosure

The author is an Editorial Board Member/Editor-in-Chief/Associate Editor/Guest Editor for this journal and was not involved in the editorial review or the decision to publish this article.

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