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Synergistic Upregulation of BRAF^V600E and MET as Diagnostic and Prognostic Biomarkers in Papillary Thyroid Carcinoma

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Abstract

Background: Among endocrine cancers, papillary thyroid carcinoma (PTC) is the most common and is predominantly driven by the oncogenic *BRAF^V600E* mutation. Although *MET* is well studied in other cancers, its role in thyroid cancer progression and diagnosis remains underexplored. This study investigates the combined expression of *BRAF^V600E* and *MET* and evaluates their potential as molecular biomarkers.

Methods: A case-control study was conducted with 44 patients, including 22 with malignant thyroid cancer (PTC) and 22 with non-malignant thyroid disorders. Gene expression of BRAF^V600E and MET was quantified via quantitative real-time PCR (qRT-PCR). Correlation analyses assessed relationships between gene expression and clinical variables, including tumor grade, inflammatory markers.

Results: Expression of *BRAF^V600E* and *MET* was significantly elevated in malignant thyroid tissues, with fold changes of 330% and 286%, respectively. A moderate direct correlation between *BRAF^V600E* and *MET* expression was observed ($r=0.67$, $p=0.0007$). In malignant patients, BRAF^V600E correlated with NPR; MET showed weak associations. In non-malignant patients, MET was negatively correlated with NLR and NPR

Conclusion: *BRAF^V600E* and *MET* are synergistically upregulated in malignant thyroid cancer and correlate with tumor grade. These findings highlight their potential utility as diagnostic and prognostic biomarkers and support further research into targeted therapies.

Keyword: Papillary Thyroid Carcinoma (PTC), *BRAF V600E*, *MET*, Thyroid Cancer Biomarkers, Tumor Progression.

1. INTRODUCTION

Thyroid cancer represents the most prevalent endocrine malignancy, with GLOBOCAN 2024 estimating approximately 586,000 new cases annually worldwide (Alanazi, 2025) (Shank et al., 2022). It exhibits a marked female predominance and a steadily increasing global incidence. Characterized by the unregulated proliferation of thyroid epithelial cells, thyroid cancer constitutes a significant and growing public health concern (Pizzato et al., 2022, Kruger et al., 2022). The female-to-male incidence ratio is about 3:1, indicating that women are roughly three times more likely to develop thyroid cancer than men (Li et al., 2021). This notable gender disparity is consistently observed worldwide and is linked to hormonal, genetic, and environmental factors. Thyroid cancer also ranks among the most prevalent endocrine malignancies, with its incidence has been gradually increasing over recent decades (Suteau et al., 2021). Thyroid cancer comprises multiple histological subtypes, with papillary thyroid carcinoma (PTC) being the most frequently

diagnosed (Ulisse et al., 2021). Its pathogenesis is driven by a range of genetic alterations that facilitate tumor initiation, progression, and metastasis (Hu et al., 2021).

BRAF^V600E stands out as the most commonly occurring mutation associated with thyroid cancer pathogenesis (Alhejaily et al., 2023, Troshin, 2024). The *BRAF* gene product is a kinase essential for transmitting signals through the MAPK/ cERK pathway, thereby regulating cellular proliferation (Xu et al., 2025, Bahar et al., 2023). The V600E point mutation, substituting valine with glutamic acid at codon 600, causes continuous activation of *BRAF* kinase, promoting oncogenic signaling (Roa et al., 2024). Consequently, the MAPK pathway remains persistently activated, promoting uncontrolled cell proliferation, resistance to apoptosis, and tumor progression (Yang et al., 2022). In 40–60% of PTC cases globally, the *BRAF V600E* mutation is present and corresponds with aggressive clinical manifestations such as extrathyroidal spread, lymph node metastases, and poorer patient outcomes (Attia et al., 2022). It is also linked to resistance to radioiodine therapy due to suppression of iodine-handling genes (Mechahougui et al., 2025). Alongside *BRAF*, the *MET* proto-oncogene is recognized as a key driver of oncogenesis across diverse cancer types. *The MET* gene codes for a receptor tyrosine kinase that interacts with hepatocyte growth factor *(HGF)*, activating critical signaling pathways such as PI3K/AKT and RAS/MAPK, which regulate essential cellular functions including proliferation, survival, migration, and invasion. Aberrant *MET* expression and activation have been implicated in promoting tumor invasiveness, angiogenesis, and metastasis in multiple malignancies. Despite this well-established role, investigations into *MET*'s contribution to thyroid cancer pathogenesis remain limited (Johansson et al., 2021, Viana et al., 2021). Nevertheless, integrative analyses of transcriptomic and proteomic datasets from the Gene Expression Omnibus (GEO) database, a comprehensive public repository, reveal significant upregulation of *MET* mRNA and protein in thyroid cancer tissues (Liu et al., 2018) . These findings underscore a potentially underappreciated role for *MET* signaling in thyroid tumor biology. This study aims to investigate the expression patterns of *BRAF V600E* and *MET* in thyroid cancer patients, examine their associations with clinicopathological features, and evaluate their potential as targets for personalized therapies.

2. Materials and methods

2.1. Patient Recruitment and Thyroid Tissue Sampling.

In the present case-control study, a total of 44 thyroid tissue samples were collected from patients aged 16 to 70 years between August 2024 and June 2025. The study cohort comprised 22 thyroid cancer tissue samples and 22 non-malignant thyroid tissue samples, serving as controls. All specimens were freshly resected and subsequently confirmed by histopathological examination (Table 1). Tissue collection was performed at several medical centers across the Kurdistan Region of Iraq, including Erbil (Par Hospital, Zheen International Hospital, Rezgary Teaching Hospital) and Sulaymaniyah (Anwar Medical City and Smart Hospital). Following surgical excision, each sample was sectioned into smaller portions, immersed in 10× phosphate-buffered saline (PBS), rapidly frozen, and the samples were preserved at minus 80 °C until RNA extraction. The study received ethical approval from the Institutional Medical Ethics Committee (approval number: 25/0060 HRE; date: 21 April 2025). Informed consent was secured from each participant before inclusion in the study, and participant confidentiality was maintained in accordance with established ethical standards.

Table 1: Demographic and Histopathological Features of Patients with Thyroid Disorders.

Characteristic	Category	Percentage (%)
Gender	Male	(15) 34%
	Female	(29) 66%
Age (years)	< 50	72%
	51-60	16%
	61-70	12%
Histopathology Result	Papillary Thyroid Carcinoma	50%
	Multinodular	45%
	Adenoma	5%

2.2. RNA Extraction.

Total RNA was obtained from the thyroid tissues of patients by following the manufacturer's protocol with a total RNA mini kit. (Geneaid, Korea). For RNA extraction, tissue samples were first cut into smaller pieces using a mortar and pestle to ensure thorough homogenization. The tissue was then processed for cell lysis by adding an appropriate lysis buffer, which facilitates the breaking down of cell membranes and releases RNA into the solution. After lysing, the samples were subjected to a washing step to remove contaminants and impurities. Following these initial steps, the RNA was further purified using a combination of organic solvents and centrifugation to isolate high-quality RNA, which was subsequently quantified and stored for further analysis. The total RNA concentration and purity were measured using a NanoDrop instrument (Thermo Scientific, USA). Electrophoresis on a 2% agarose gel, stained with ethidium bromide, was performed to evaluate RNA integrity, visualized under UV light using a Wix electrophoresis system (Fisher Scientific, USA)

2.3. Complementary DNA (cDNA) Synthesis.

Complementary DNA was synthesized using the UltraScript® Reverse Transcriptase Kit (PCR BIOSYSTEMS) following the manufacturer's instructions (Andongma et al., 2020). A 20 µL PCR mixture was prepared, consisting of 4 µL of 5× cDNA synthesis mix, 1 µL of enzyme mix, 10 µL of PCR-grade water, and 5 µL of purified RNA. cDNA synthesis was performed in a SimpliAmp™ Thermal Cycler (Applied Biosystems, USA) under the following conditions: Reverse transcription was performed at 42°C for 30 minutes, followed by inactivation at 85°C for 10 minutes. The resulting cDNA was stored at −20°C for further analysis.

2.4. Quantification of Gene Expression via qRT-PCR

Relative expression of *BRAF V600E* and *MET* was assessed through real-time PCR analysis. Primer sequences were designed and validated via Primer-BLAST and synthesized by LGC Biosearch Technologies. Primer sequences used for amplification were as follows: *BRAF V600E* forward 5′-TTGGATCTGGATCATTTGGAACA-3′ and reverse 5′-CTCAATAGAGGCGAGAATTT-3′; *MET* forward 5′-TGCTCAGACTTTTCACACAAGA-3′ and reverse 5′-GCAGTGCTCATGATTGGGTC-3′. The housekeeping gene *β-actin* served as an internal control, with forward primer 5′-GTGGAGCATTCAGACTTGTCTTT-3′ and reverse primer 5′-TGCTTACATGTCTCGATCCCAC-3′. qRT-PCR was conducted using BIO-RAD® MJ Mini Cycler on CFD-3120 MINI OPTICON qRT-PCR™ system. For each 20 µL reaction, 10 µL of 2× SyGreen Blue Mix was used, 1.25 µL of each primer (forward and reverse), 3 µL of synthesized cDNA, along with 4.5 µL of nuclease-free water. The qRT-PCR protocol

involved an initial denaturation at 95°C for 2 minutes, followed by 40 amplification cycles consisting of 95°C for 5 seconds and 60°C for 30 seconds. Confirmation of amplification specificity was achieved by assessing product size and melt curve profiles via melt curve analysis, ranging from 65°C to 95°C. All samples were analyzed in triplicate alongside no-template controls to exclude contamination. Gene expression levels were determined using the comparative 2^−ΔΔCt method, with β-actin serving as the reference gene for normalization.

2.5. Statistical analysis.

Statistical comparisons among groups were conducted using GraphPad Prism version 10 (GraphPad Software, USA). The strength and direction of the linear Pearson's correlation coefficient was used to evaluate the relationships between continuous variables. Biomarker diagnostic efficacy was evaluated via ROC curve analysis, and corresponding AUC values were calculated to quantify performance and determine sensitivity and specificity. A p-value < 0.05 (two-tailed) was used to define statistical significance.

3. Results

3.1 Gene Expression Analysis

Quantitative PCR analysis demonstrated significant upregulation of both *BRAF V600E* and *MET* gene expression in malignant thyroid cancer tissues compared to non-malignant controls. *BRAF V600E* expression showed a marked increase, with a 3.3-fold (330%) elevation in the malignant group, consistent with its established role as a key driver of aggressive thyroid cancer, particularly in papillary thyroid carcinoma. *MET* expression was significantly upregulated in malignant thyroid tissues, showing a 2.86-fold increase compared to non-malignant samples. Both *BRAF V600E* and *MET* were concurrently overexpressed in the malignant group (Figure 1)

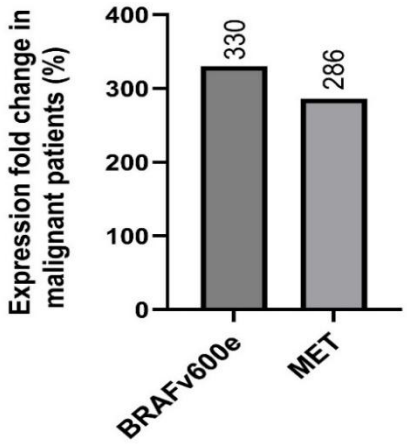

Figure 1. Expression fold changes of *BRAF V600E* and *MET* genes in malignant thyroid cancer patients. Both genes were significantly upregulated compared to non-malignant controls, with *BRAF V600E* showing a 330% increase and *MET* showing a 286% increase.

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3.2. Correlation analysis

3.2.1 Correlation between BRAF V600E Mutation and MET Gene Expression in Thyroid Cancer

To evaluate the relationship between *BRAF V600E* and *MET* expression in thyroid cancer tissues, we conducted a Pearson correlation analysis using the ΔCt values of both genes. The analysis demonstrated a moderate positive correlation, with a Pearson's r of 0.67 and a p-value of 0.0007, indicating a highly significant association. This suggests that increased expression of *BRAF V600E* is accompanied by a corresponding rise in MET expression (Figure 2).

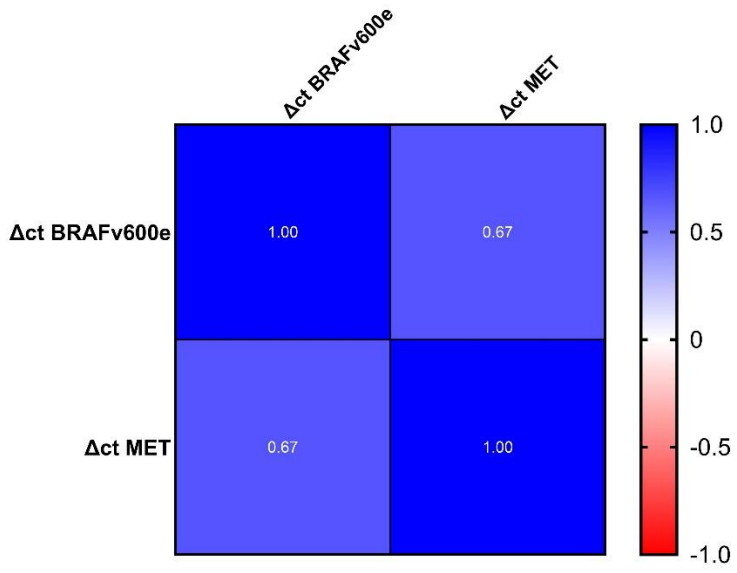

Figure 2. Correlation heatmap showing associations between ΔCt values of BRAF V600E and MET. The Pearson correlation coefficient of 0.67 (p = 0.0007) indicates a significant moderate positive correlation between the expressions of these genes in malignant thyroid cancer samples.

3.2.2. Associations between Gene Expression and Blood Cell Ratios

In the malignant cohort, *BRAF^V600E* expression (measured by ΔCt) demonstrated a weak positive correlation with the neutrophil-to-lymphocyte ratio (NLR) (r = 0.27), and a negligible positive correlation with the platelet-to-lymphocyte ratio (PLR) (r = 0.03). Notably, a moderate positive correlation was identified between *BRAF^V600E* expression and the neutrophil-to-platelet ratio (NPR) (r = 0.32). Regarding *MET* gene expression in malignant patients, ΔCt values exhibited a weak positive correlation with NLR (r = 0.09), a very weak negative correlation with PLR (r = -0.11), and a weak positive correlation with NPR (r = 0.24). In the non-malignant group, *BRAF^V600E* expression showed very weak positive correlations with both NLR (r = 0.08) and PLR (r = 0.12), and a weak positive correlation with NPR (r = 0.11). Conversely, *MET* expression in non-malignant patients was moderately negatively correlated with NLR (r = -0.18) and NPR (r = -0.23), while exhibiting a weak positive correlation with PLR (r = 0.14) (Figure 3).

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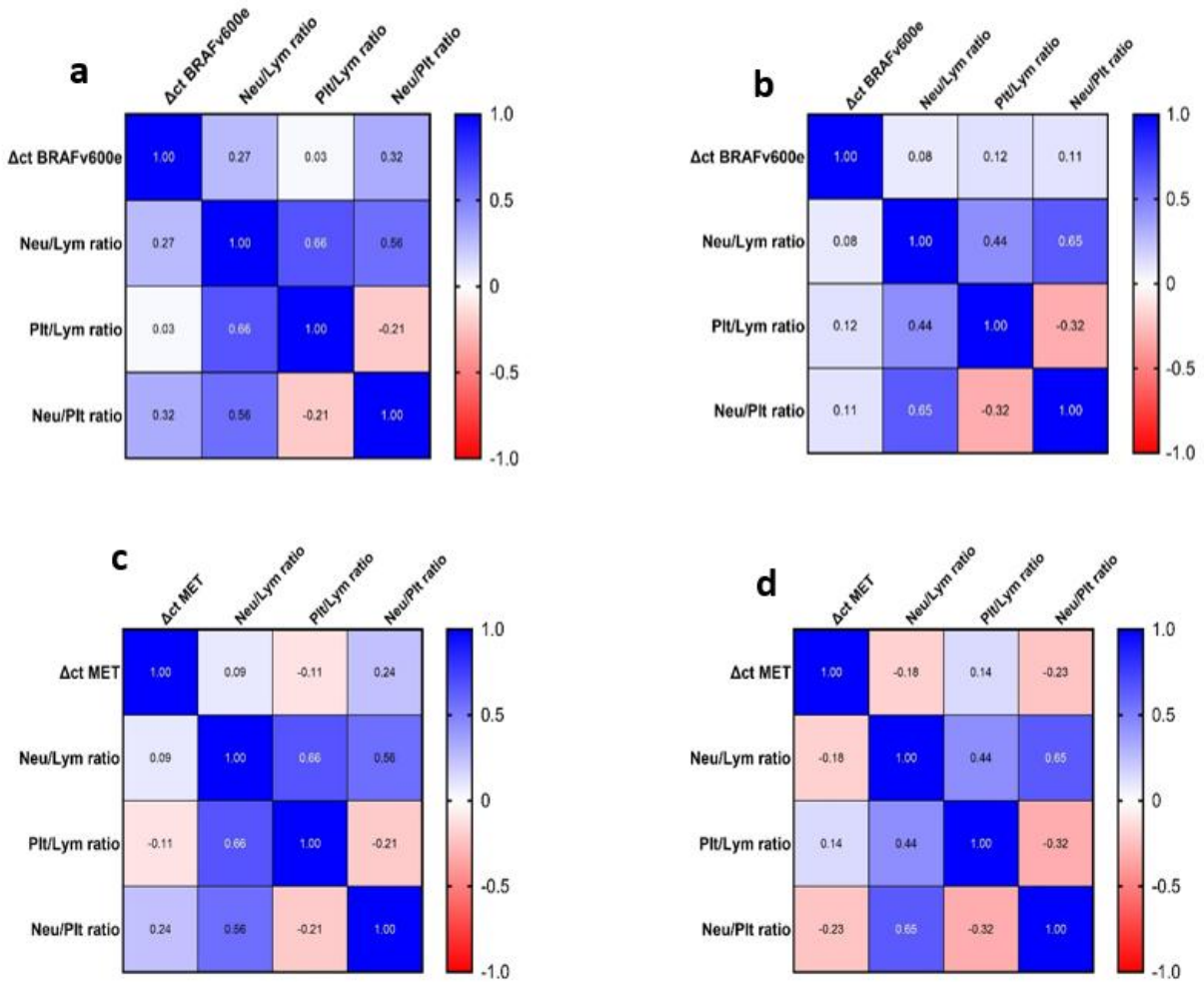

Figure 3. Correlation of ΔCt values for BRAF^V600E and MET with inflammatory ratios (NLR, PLR, NPR) in malignant and non-malignant patients. Heatmaps (a–d) display Pearson correlation coefficients, ranging from -1 (red, strong negative) to +1 (blue, strong positive), with values near zero indicating weak or no correlation.

3.3. Expression Levels of BRAF^V600E and MET Across Tumor Grades

Expression levels of *BRAF^V600E* and *MET* were compared between Grade I and Grade II malignant thyroid cancer samples using a two-tailed t-test (Figure 4). Both markers showed significantly higher expression in Grade II compared to Grade I tumors. *BRAF^V600E* expression was increased in Grade II samples ($p = 0.0140$), and *MET* expression was also elevated in Grade II samples relative to Grade I ($p = 0.0442$).

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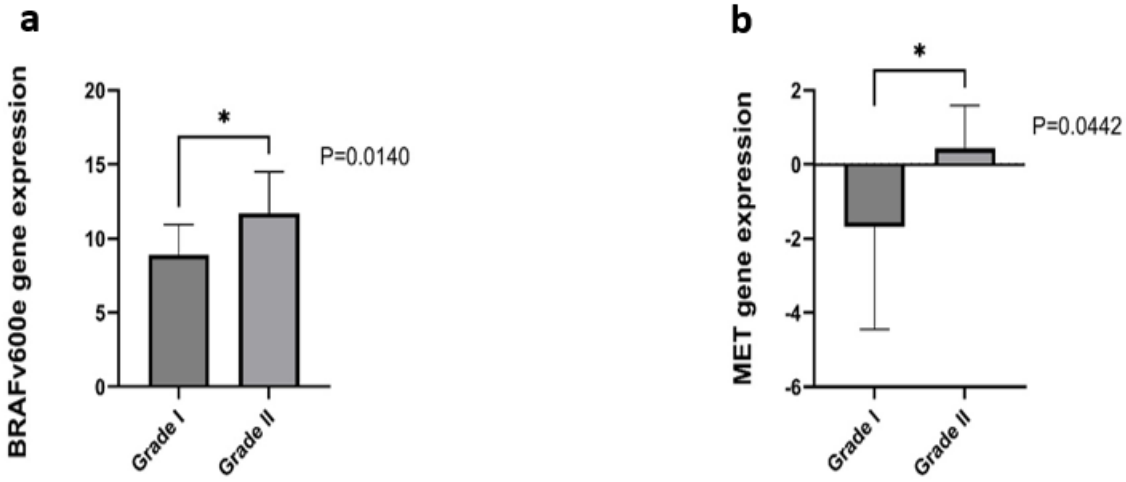

Figure 4. Expression levels of *BRAF^V600E* and *MET* in Grade I and Grade II malignant thyroid cancer samples. (a) *BRAF^V600E* expression was significantly higher in Grade II samples compared to Grade I ($p = 0.0140$). (b) *MET* expression was also significantly increased in Grade II samples relative to Grade I ($p = 0.0442$).

Discussion

This study provides a comprehensive analysis of MET and BRAF^V600E expression in thyroid cancer tissues, underscoring MET's confirmed role as a key molecular driver through its correlation with clinical features. Our findings provide strong evidence supporting the critical role of MET, alongside BRAF^V600E, in thyroid cancer development and progression, underscoring its potential as a valuable biomarker and therapeutic target. *BRAF^V600E* and *MET* expression levels were significantly higher in malignant thyroid tissues compared to non-malignant controls, consistent with previous studies highlighting *BRAF^V600E* as a major driver mutation in PTC (Menicali et al., 2021, Agarwal et al., 2021). The pronounced upregulation of *BRAF^V600E* aligns with its association characterized by aggressive tumor behavior, including extrathyroidal extension and lymph node metastasis, and radioiodine resistance (Huang et al., 2022). Similarly, increased *MET* expression supports its reported role in promoting tumor invasiveness and therapeutic resistance (Wood et al., 2021). The concurrent overexpression of these markers in malignant samples suggests a potential synergistic contribution to thyroid cancer progression (Luo et al., 2021). The clear positive association revealed between *BRAF^V600E* and *MET* expression supports the notion of potential co-regulation or functional crosstalk between these oncogenes, consistent with their established roles in the MAPK and PI3K/AKT signaling pathways, which are critical drivers of cell proliferation, survival, and metastasis in thyroid cancer (Kim et al., 2024). Previous studies have also highlighted interactions between these pathways that contribute to tumor aggressiveness and therapeutic resistance (Yang et al., 2022). Furthermore , the weak or absent correlations between gene expression and inflammatory markers such as NLR, PLR, and NPR align with mixed findings in the literature, where the prognostic value of these systemic inflammatory indices in thyroid malignancies remains uncertain and may vary depending on tumor microenvironment and disease stage (Russo et al., 2023). Moreover, the

elevated expression of *BRAF^V600E* and *MET* in higher-grade tumors corroborates existing evidence linking these molecular markers to increased tumor aggressiveness and invasiveness (Hu et al., 2021). Their differential expression between tumor grades highlights their potential utility in risk stratification and as targets for personalized therapeutic strategies, as suggested by prior research emphasizing their role in tumor progression and treatment resistance (Munkácsy et al., 2022). This study offers detailed molecular profiling and clinical integration in thyroid cancer, but its cross-sectional design and limited sample size restrict the ability to draw causal conclusions. Future research should clarify the functional roles of *BRAF^V600E* and *MET* in tumor biology, including their signaling mechanisms and impact on therapy resistance. Larger, longitudinal studies are needed to validate these biomarkers and support targeted treatment development.

Conclusion

Our findings reveal a significant synergistic upregulation of BRAF^V600E and MET in malignant thyroid cancer, with their expression levels closely associated with tumor grade. These results underscore the potential of BRAF^V600E and MET as complementary diagnostic and prognostic biomarkers. Integrating molecular markers with clinicopathological features may substantially improve the precision of thyroid cancer diagnosis and risk stratification. Further research is essential to elucidate the underlying molecular processes and to advance the development of targeted therapeutic strategies that exploit these pathways.

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Author Contributions

Payam Amanj conducted the experimental work, performed data analysis, and drafted the initial manuscript. Dr. Zjwan Housein conceptualized and designed the study, provided critical intellectual guidance, supervised the research, and reviewed and edited the manuscript. The final version of the manuscript has been read and approved by both authors.

Conflict of Interest Declaration

The authors declare no competing interests or conflicts of interest related to this study.

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