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BRAF V600E Immunohistochemical Expression in Non-invasive Follicular Thyroid Neoplasm with Papillary-like Nuclear Features

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ABSTRACT

Background: Non-invasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP) was introduced to avoid overtreatment of indolent tumours, although risks of misclassification and rare metastasis remain. According to the 2022 WHO (World Health Organization) classification, BRAF V600E-mutated cases should be reclassified as classical papillary thyroid carcinoma (PTC) with predominant follicular architecture. VE1 immunohistochemistry is a reliable surrogate for detecting the BRAF V600E mutation.

Objectives: To determine the frequency of BRAF V600E mutation among NIFTP using VE1 immunohistochemistry, and to assess its correlation with clinicopathological characteristics.

Materials and methods: Forty-six tumours originally diagnosed as NIFTP during the period from 2020 to 2024 were retrospectively identified. All haematoxylin-eosin slides were re-evaluated according to the WHO 2022 criteria. VE1 immunohistochemistry was performed on all cases (rabbit monoclonal anti-BRAF V600E, BIO-SB, USA). VE1 status was then correlated with clinicopathological features.

Results: VE1 staining reclassified 13% of suspected NIFTPs. 2.2% showed capsular invasion highlighted by VE1 and were reclassified as invasive encapsulated follicular variant of PTC (IEFVPTC), while 11% demonstrated diffuse cytoplasmic VE1 positivity indicative of BRAF V600E mutation. No significant association was observed between VE1 positivity and clinicopathological parameters (P-value > 0.05); however, VE1-positive cases tended to be larger and more frequent in males.

Conclusion: VE1 immunohistochemistry identified a small but clinically important subset of tumours originally labelled as NIFTP that belong to the PTC category. Routine VE1 staining reduces the risk of undertreating aggressive BRAF-driven disease and provides a rapid, economical quality control step to ensure adherence to the WHO 2022 criteria.

Keywords: Non-invasive follicular thyroid neoplasm with papillary-like nuclear features; BRAF V600E; VE1 immunohistochemistry; Thyroid neoplasms.

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INTRODUCTION

The non-invasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP) was first proposed by Nikiforov et al. in 2016 [1]. This revised nomenclature replaced the term "non-invasive encapsulated follicular variant of papillary thyroid carcinoma (FVPTC)" to better reflect the indolent biological behaviour of these tumours and to reduce overtreatment, as NIFTP patients can avoid aggressive interventions such as radioactive iodine therapy or total thyroidectomy [2].

Accurate diagnosis of NIFTP depends on strict histological criteria, which include tumour encapsulation or well-defined boundaries, lack of vascular or capsular invasion, infrequent papillary structures (<1%), and the presence of nuclear characteristics of PTC [1, 2]. Even with these well-defined criteria, it remains difficult to distinguish NIFTP from its morphological mimics in routine practice, especially invasive encapsulated FVPTC and CPTCPFA (papillae ≥1%). To rule out microscopic capsular or vascular invasion and true papillary structures, which are features that preclude a diagnosis of NIFTP, a thorough sampling and assessment of the whole

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tumour capsule and parenchyma is necessary [3]. However, current pathology practice lacks standardized procedures for the optimal sampling of the tumour capsule and parenchyma. The standard procedure usually involves submitting the entire capsule and representative pieces from the tumour center. This method has a risk of over diagnosing NIFTP or underdiagnosing PTC, particularly in larger tumours where papillary formations may be missed due to incomplete sampling [4].

Additionally, precise histological evaluation of the entire tumour–capsule interface is important to detect subtle infiltrative growth, capsular penetration, or vascular invasion [5]. Identification of any microscopic invasive focus excludes the diagnosis of NIFTP, and the tumour is diagnosed as minimally invasive FVPTC even when a lesion appears grossly well circumscribed and has intratumoral features consistent with NIFTP. Stojanov et al. [6] highlighted limitations in routine diagnostic practice, noting that differentiation between NIFTP and minimally invasive FVPTC relies on capsular integrity, yet routine pathology protocols examine only a limited fraction (1%) of the tumour capsule microscopically, thereby increasing the risk of undetected invasion.

Although NIFTP was introduced as an indolent tumour, several studies have reported lymph node and distant metastases [7–11]. Furthermore, a few studies have reported the presence of the high-risk BRAFV600E mutation in lesions classified as NIFTP [10–14]. This mutation is associated with more aggressive clinical behaviour, extrathyroidal extension, advanced tumour stage at presentation, and lymph node or distant metastases [15]. Misclassifying a BRAF V600E–mutated tumour as NIFTP may result in undertreatment of a potentially aggressive malignancy. Accordingly, the 2022 WHO classification excludes tumours harbouring a BRAF V600E–like alteration from the NIFTP category [16].

The BRAF gene, located on chromosome 7q34, encodes a serine/threonine-protein kinase that is activated by rat sarcoma (RAS) protein and plays a key role in the MAPK/ERK signalling pathway, which regulates cell growth, differentiation, and survival [15]. Oncogenic mutation in the kinase region of the BRAF gene most commonly involves a thymine-to-adenine transversion at nucleotide 1799 (T1799A), resulting in the substitution of valine with glutamic acid at codon 600 (V600E). This point mutation causes continuous activation of the BRAF serine kinase, leading to persistent stimulation of the MAPK signalling pathway and promoting uncontrolled cellular proliferation [17]. The BRAF mutation is the most common genetic alteration in thyroid carcinoma, with most studies reporting a prevalence of approximately 40-45% in PTC. It is detected in about 24% of anaplastic thyroid carcinomas and occurs at a lower frequency in the follicular variant of PTC, at around 10% [18].

Molecular sequencing is still the gold standard for identifying BRAFV600E, although it is multi-step, requires high-quality deoxyribonucleic acid (DNA), and is expensive. BRAF V600E (clone VE1) immunohistochemistry (IHC), on the other hand, is rapid, inexpensive, and widely accessible in diagnostic laboratories. Multiple studies have demonstrated excellent concordance between VE1 IHC and molecular genotyping, with a specificity of 99-100% and a sensitivity of 84-100% [19]. Accordingly, BRAF V600E IHC is widely regarded as a reliable and practical alternative to routine BRAF sequencing.

Given that PTC frequently harbours the BRAFV600E mutation [5, 20]. In contrast to the RAS-like profile expected in NIFTP [5], BRAF V600E IHC (VE1) assists in excluding BRAF-mutated tumours from the NIFTP category and reduces the risk of diagnostic misclassification.

The reported prevalence of BRAF V600E in tumours meeting morphological NIFTP criteria ranging from 0% to 28%. Most data on BRAF mutation prevalence in NIFTP derive from Western and East Asian populations, whereas studies from the Middle East remain limited. Determining the frequency of BRAF V600E in our population is therefore important to identify cases that require reclassification and appropriate clinical management. Therefore, the present study aimed to evaluate the frequency of VE1 positivity in NIFTP and to examine whether VE1 status is associated with clinicopathological features.

MATERIALS AND METHODS

A retrospective cross-sectional study was performed using formalin-fixed, paraffin-embedded (FFPE) tissue blocks diagnosed as NIFTP. Samples have been collected from the National Centre for Educational Laboratories and the Histopathology Laboratory at Baghdad Teaching Hospital (Medical City Campus), Baghdad, Iraq. The departmental database was searched for thyroid resections performed between January 2020 and August 2024 with a diagnosis of NIFTP. This work received ethical approval from the Research Ethics Committee of the Department of Pathology and Forensic Medicine, College of Medicine, University of Baghdad (Reference number 124, dated September 29, 2024). Informed consent from the participants was waived owing to the retrospective nature of the study. The study was conducted in accordance with the Declaration of Helsinki (October 2024 revision).

The inclusion criteria comprised all cases with a final diagnosis of NIFTP, regardless of patient age or sex. Exclusion criteria included insufficient tissue for IHC and cases that did not meet the NIFTP diagnostic criteria on serial sections. The required sample size was calculated using the finite population correction formula for proportion estimation. The calculations used a 95% confidence level, an expected BRAF V600E positive rate of 10% derived from previous literature [10], and margin of error of ±5%. Given a total of 70 NIFTP cases available during the study period, the formula yielded a required sample size of 47

$$n' = e^2 + Nz^2 \times p(1-p)z^2 \times p(1-p)$$

$$n' = \frac{(1.96)^2 \times 0.10(1-0.10)}{0.05^2 + \frac{(1.96)^2 \times 0.10(1-0.10)}{70}}$$

$$n' = 46.5 \approx 47 \; cases$$

Data collected for each case included demographic variables (age and sex), tumour size (maximum diameter), tumour multifocality, encapsulation status, background pathology, and the presence of coexisting thyroid neoplasms. All haematoxylin and eosin (H&E)-stained sections were re-examined by an expert pathologist in accordance with the WHO 2022 classification criteria for NIFTP, which include complete encapsulation or clear demarcation of the tumour, an exclusively follicular growth pattern with less than 1% true papillary structures, PTC-type nuclear features in at least 30% of tumour cells, absence of capsular or vascular invasion, no psammoma bodies, no solid, trabecular, or insular growth pattern exceeding 30% of the tumour, no tumour necrosis,

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and no increased mitotic activity (≥3 mitoses per 10 high-power fields).

For IHC staining, 4 μm sections were cut from FFPE blocks, deparaffinised and subjected to heat-induced antigen retrieval in a water bath at 90-95°C for 20 minutes. Endogenous peroxidase activity was blocked with a peroxidase-blocking reagent. Sections were then incubated for 24 hours in a humid chamber with the primary antibody (rabbit monoclonal anti-BRAF V600E, BIO-SB, USA; RTU, IVD). After rinsing in Tris-buffered saline between steps, Horseradish peroxidase (HRP) was added to the sections for 30 minutes. Then, one drop of 3,3-diaminobenzidine tetrahydrochloride (DAB) was added to one ml of substrate buffer and mixed; 100 μl of the mixture was added to the sections. Subsequently, sections were counterstained with haematoxylin for 2 minutes to visualize the nuclei. A PTC with a known BRAF V600E mutation was used as a positive control. The intensity of staining was graded from 0 to 3+, and the proportion of tumour cells that were stained was recorded. Positivity was defined as diffuse cytoplasmic staining of any intensity. [19]. After excluding one case in which BRAF immunostaining revealed capsular invasion (Figure 1), the final study sample included 45 tumours that met the 2022 WHO histological criteria for NIFTP.

Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) version 29 (IBM Corp., Armonk, NY, USA). Categorical variables were presented as frequencies and percentages, whereas continuous variables were expressed as mean ± standard deviation or median with interquartile range (IQR), as appropriate. Normality of continuous variables was assessed using the Shapiro–Wilk test. Comparisons between BRAF-positive and BRAF-negative groups were performed using the Mann-Whitney U test for continuous variables and Fisher's exact test for categorical variables, given the small number of BRAF-positive cases (n=5). A P-value of less than 0.05 was considered statistically significant.

RESULTS

Clinicopathological findings

The cohort showed a female predominance (female-to-male ratio: 3.5:1). Tumour size varied considerably, ranging from < 1 cm in 10 cases (22.2%) to ≥ 4 cm in 14 cases (31.1%). The clinicopathological characteristics of the 45 NIFTP cases are summarised in Table 1.

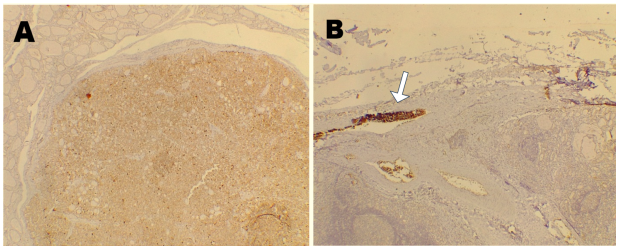

Figure 1. Diagnostic utility of BRAF V600E immunohistochemistry in NIFTP. A: BRAF V600E immunostaining delineates tumour boundaries, showing cytoplasmic positivity within the encapsulated follicular-patterned neoplasm and negative staining in surrounding normal thyroid tissue. B: Capsular Invasion highlighted by BRAF V600E immunohistochemistry (White arrow).

Table 1. Demographic, clinical, and pathological characteristics of NIFTP cases (n=45)*.

Variables	Value
Demographics	
Age per years, mean (range)	38.6 (20–66)
Sex, n (%)	
Female	35 (77.8)
Male	10 (22.2)
Tumour size, cm	
Mean (median; range)	2.63 (2.0; 0.1–9.0)
Focality, n (%)	
Unifocal	43 (95.6)
Multifocal	2 (4.4) *
Capsule status, n (%)	
Encapsulated	37 (82.2)
Well-demarcated	6 (13.3)
Partially encapsulated	2 (4.4)
Background thyroid pathology, n (%)	
Nodular goitre	24 (53.3)
Lymphocytic thyroiditis	6 (13.3)
Hashimoto's thyroiditis	2 (4.4)
None	13 (28.9)
Coexisting contralateral tumours, n (%)	5 (11.1)
Micro-PTC	3 (6.7)
Follicular adenoma	1 (2.2)
FT-UMP	1 (2.2)

* One unilateral, one bilateral. Abbreviations: PTC: Papillary thyroid carcinoma; FT-UMP: Follicular tumour of uncertain malignant potential.

VE1 immunohistochemical staining

VE1 immunostaining was absent in the adjacent normal follicular epithelium but present within the colloid material. BRAF V600E IHC was effective in outlining tumour boundaries and identifying capsular invasion (Figure 1).

Diffuse VE1 staining was identified in 5 of 45 cases (11.1%). The intensity of BRAF V600E immunostaining is shown in Table 2 and Figure 2.

VE1 positivity was more frequent among male patients compared with females; however, this difference did not reach statistical significance (P-value > 0.05). VE1-positive tumours tended to be larger than VE1-negative ones, although this association was also not statistically significant (P-value > 0.05). The associations between clinicopathological variables and BRAF V600E status are summarised in Table 3.

The coexisting PTCs were also subjected to VE1 immunostaining. The three micro-PTCs mirrored their matched NIFTPs: two pairs were VE1-negative, whereas the third pair displayed only focal, faint (1+) cytoplasmic staining.

Table 2. VE1 staining intensity in positive cases.

VE1 staining intensity	Number	Percent
+1	1	20
+2	2	40
+3	2	40

Table 3. Association between clinicopathological variables and BRAF mutation status.*

Characteristic	BRAF Negative (n=40)	BRAF Positive (n=5)	P-value
Mean age per years	38.3 ± 10.3	40.8 ± 12.5	0.894[a]
Age groups per years n(%)			
< 40	21 (52.5)	2 (40)	0.665[b]
≥ 40	19 (47.5)	3 (60)	
Sex n(%)			
Female	33 (82.5)	2 (40)	0.065[b]
Male	7 (17.5)	3 (60)	
Mean tumour size per cm	2.6 ± 2.1	3.7 ± 2.9	0.426[a]
Tumor size per cm n(%)			
< 4 cm	29 (72.5)	2 (40)	0.166[b]
≥ 4 cm	11 (27.5)	3 (60)	
Multiplicity n(%)			
Unifocal	39 (97.5)	4 (80)	0.212[b]
Multifocal/Bilateral	1 (2.5)	1 (20)	
Tumor Encapsulation n(%)			
Encapsulated	33 (82.5)	4 (80)	
Well-demarcated	5 (12.5)	1 (20)	0.529[b]
Partially encapsulated	2 (5)	0 (0)	
Background pathology n(%)			
None	10 (25)	3 (60)	
Nodular goiter	22 (55)	2 (40)	0.116[b]
Lymphocytic thyroiditis and Hashimoto thyroiditis	8 (20)	0 (0.0)	

* a: Mann-Whitney U test, b: Fisher's exact test.

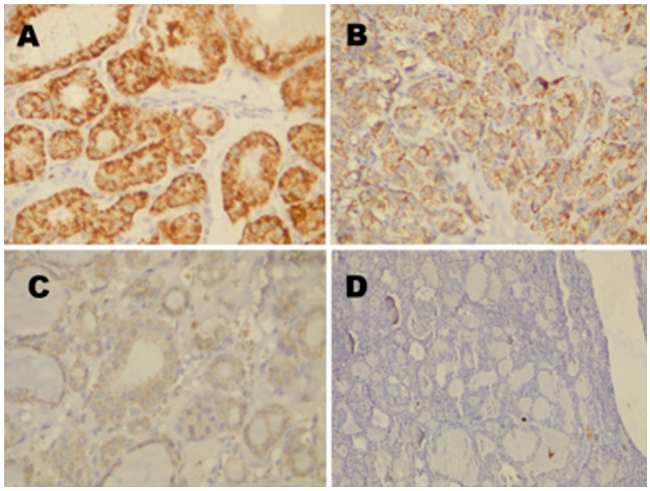

Figure 2. The intensity of BRAF V600E IHC in NIFTP. A: The intensity of staining +3 X400, B: The intensity of staining +2 X400, C: The intensity of staining +1 X400, D: Negative BRAF V600E IHC staining X100.

DISCUSSION

BRAF V600E is a gain-of-function mutation that constitutively activates the MAPK signalling pathway, promoting tumour proliferation and progression in thyroid carcinoma. This mutation is characteristically absent in NIFTP, consistent with its indolent biological behaviour, and its detection therefore has important implications for both diagnosis and patient management. This study highlights the diagnostic utility of BRAF V600E IHC in refining the diagnosis of NIFTP.

The VE1 positivity rate observed in this study lies between the 0% mutation rate reported in several studies [1, 20, 21] and the notably higher prevalence of 28.6% reported in the multi-institutional Korean series by Lee et al [12]. These variations may reflect regional differences, variability in the permitted proportion of papillary structures, differences in sample size, and differences in sampling methodology.

Our results are comparable to those of Cubero-Rego et al., who identified diffuse VE1 staining in 4 of 29 morphologically defined NIFTPs (14%); all four lesions were subsequently excluded from their final NIFTP set [13].

Genetic testing has also revealed comparable positivity rates in some series: Kim TH et al., using reverse transcription real-time PCR with Sanger sequencing confirmation and < 1% papillary structures as diagnostic criteria, found the mutation in 5 of 41 lesions (12.2%) [11]. Notably, the application of strict diagnostic criteria significantly impacts these rates. Cho et al., using PCR amplification followed by Sanger sequencing, found BRAF V600E in 10 of 105 (10%) NIFTP tumours when ≤ 1% papillae were permitted, but 0% when strict absence of papillae was applied [10]. Similarly, Kuchareczko et al., using next-generation sequencing, reported 5 of 23 cases (22%) positive for BRAF V600E when applying NIFTP criteria that permitted < 1% papillae, but 0% when a complete absence of papillae was required [22].

Johnson and Sadow [20], were among the first to systematically assess VE1 IHC as a diagnostic tool to differentiate NIFTP from its morphological mimics, particularly invasive EFVPTC and CPTCPFA, Their study found that VE1 labelled none of the 92 NIFTPs diagnosed using the < 1% papillae criterion, whereas VE1 positivity was observed in 18 of 33 CPTCPFA cases (54.5%) and in 12 of 81 IEFVPTC

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cases (14.8%). The absence of BRAF V600E in their NIFTP may be explained by their extensive sampling protocol, which averaged 2.86 blocks per cm of tumour tissue with complete capsular examination in 99.2% of cases. This extensive sampling strategy likely enabled better detection of subtle invasive features or papillary structures. They proposed that VE1 IHC could reduce the need for extensive sampling of tumour centres, particularly in large follicular-patterned lesions.

The wide variation in reported BRAF V600E prevalence across NIFTP studies reflects several factors. Geographic variation appears to play a role, with several studies from East Asian populations reporting relatively higher prevalence rates, as observed in the study by Lee et al. [12]. The extent of histological sampling also plays a role, as more comprehensive sampling protocols are more likely to detect features that exclude a tumour from NIFTP, thereby lowering BRAF positivity in the final cohort. In addition, the threshold of permitted papillary structures is important, as strict absence of papillae is associated with lower rates of reported BRAF mutation. Finally, variations in sample size across studies may affect the precision of reported prevalence.

The association between male sex and higher BRAF mutation rates in thyroid carcinoma has been reported in larger datasets, including a meta-analysis by Wei et al. (2022) [23] and the recent study by Nechifor-Boilă et al [24]., Both of which demonstrated a higher prevalence of BRAF mutations among male patients with thyroid carcinoma. The biological basis for this sex disparity remains unclear but may relate to hormonal influences on thyroid carcinogenesis.

Regarding tumour size, although Xu et al. demonstrated that large NIFTPs behave similarly to smaller ones when properly classified [25], isolated case reports raise concerns about diagnostic accuracy in large tumours. Parente et al. reported an NIFTP with lung metastasis measuring > 4 cm [9], and Glomski et al. described a follicular adenoma with distant metastasis lacking capsular or vascular invasion that also exceeded 4 cm [26]. These cases suggest that large tumour size may predispose to misclassification due to suboptimal sampling or evaluation of the capsule and intratumoral parenchyma. Furthermore, in routine practice, only a limited proportion of the tumour capsule is examined microscopically, thereby increasing the risk of missing subtle invasion or papillae [6].

Two independent reassessment studies have demonstrated that most reported cases of "aggressive NIFTP" in the earlier literature represent diagnostic errors rather than true biological aggressiveness [27, 28]. Therefore, the detection of a BRAF V600E mutation in a tumour initially classified as NIFTP should raise concerns about diagnostic accuracy and lead the pathologist to re-examine the case meticulously for overlooked capsular or vascular invasion and missed papillary structures.

According to the WHO 2022 classification, the presence of BRAF V600E-like alterations excludes a diagnosis of NIFTP [16]. Therefore, the VE1-positive cases identified in our study would be reclassified as CPTCPFA. While NIFTP does not require structured surveillance [29], reclassified cases require risk stratification according to the 2025 American Thyroid Association guidelines, integrating American Joint Committee on Cancer staging with clinicopathologic features and postoperative assessment of serum Tg and TgAb levels and imaging findings to guide consideration of radioiodine therapy and surveillance intensity [29].

The findings of this study have important clinical implications for the diagnosis and management. VE1 IHC can serve as a valuable tool when morphological assessment of capsular integrity is equivocal, as it can highlight the distribution of BRAF-mutant cells, thereby facilitating the identification of subtle invasion that might otherwise be overlooked on routine H&E sections [30]. Furthermore, VE1 testing is especially recommended in large tumours, where under sampling and misdiagnosis risk is higher, and in male patients, given the higher rate of VE1 positivity observed in males.

Several authors have proposed adding BRAF V600E IHC to morphological criteria to better identify NIFTP with benign outcomes [5, 13, 20] Our findings support this recommendation, as the combination of morphological assessment and VE1 immunostaining identified cases requiring reclassification that might have been missed on histological examination alone.

Limitations of this study include its retrospective, single-centre design, limited cohort size, particularly among males, and the absence of confirmatory DNA sequencing or long-term outcome data. Future multi-centre studies with integrated molecular profiling are needed to validate these observations and further refine the role of VE1 in NIFTP diagnostics.

CONCLUSION

VE1 IHC served a critical quality assurance role, unmasking occult invasion and identifying cases with diffuse BRAF expression that warranted reconsideration of the diagnosis. In NIFTP cases, VE1 positivity should warrant meticulous reevaluation for subtle invasive foci or papillary architectural features that may have been overlooked on initial examination, ensuring accurate classification and appropriate patient management.

ETHICAL DECLARATIONS

Acknowledgments

None.

Ethics Approval and Consent to Participate

This study was approved by the Research Ethics Committee of the Department of Pathology and Forensic Medicine, College of Medicine, University of Baghdad (Reference number 124, dated September 29, 2024). All procedures involving human tissue and data were conducted in accordance with the institutional ethical standards. Informed consent was not required due to the retrospective nature of the study. The study followed the ethical guidelines of the Declaration of Helsinki (October 2024 version).

Consent for Publication

Not applicable, as no personal information or data are included in the manuscript.

Availability of Data and Material

The data generated and analyzed during this study are available from the corresponding author upon reasonable request.

Competing Interests

The authors declare that there is no conflict of interest.

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Use of Artificial Intelligence

Artificial intelligence has been used to correct spelling and grammar.

Authors' Contributions

Ismael AH collected and analyzed the data, listed the references, and wrote the first draft of the manuscript. Hameedi AH planned the study, reviewed the immunohistochemistry results, supervised the work, and edited the manuscript. Both authors read and approved the final version of the manuscript.

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