RESEARCH ARTICLE

Editorial Process: Submission:12/26/2022 Acceptance:07/11/2023

Immunohistochemical Expression of *HBME-1* and *TROP-2* in Some Follicular-Derived Thyroid Lesions

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Abstract

Background and objectives: Detecting thyroid tumors depends on histologic characteristics. However, distinguishing malignant from benign thyroid abnormalities may be challenging and contentious, particularly in tumors with a follicular appearance. Therefore, immunohistochemistry might be useful and essential. Immunohistochemical biomarkers, such as human trophoblast cell surface antigen (TROP) and Hector Battifora Mesothelial-1 (HBME-1), have helped diagnose thyroid cancers. In addition, mesothelial cells have an antigen called *HBME-1* on their membranes, but its role is unclear. Thyroid epithelial neoplasms have lately been studied, and *TROP-2* is a helpful marker of these tumors. Recently, researchers have explored *HBME-1* upregulation in benign and malignant thyroid tumors. This research aimed to show that the immunohistochemical biomarkers *TROP-2* and *HBME-1* might be employed to distinguish malignant from benign follicular-derived thyroid lesions. **Materials and methods:** The research consisted of 50 specimens of various follicular thyroid lesions. From October 2018 to March 2021, blocks of follicular thyroid lesions and clinical information were collected from the Pathology Departments of Al-Azhar University Hospitals. Additionally, the *HBME-1* and *TROP-2* antigens were stained immunohistochemically. **Results:** Expression of *TROP-2* along with *HBME-1* distinguished benign from malignant follicular-derived thyroid lesions with respective sensitivities of 74.2 and 87.1% and specificities of 84.2 and 78.9%. Furthermore, positive *HBME-1* expression was significantly less prevalent in benign lesions (15.8%) than in malignant lesions (74.2%) (P-value <0.001). Moreover, positive *TROP-2* expression was significantly lower in benign lesions (21.1%) than in malignant lesions (87.1%) (P-value <0.001). The P value of <0.001 indicated an extremely strong positive correlation between *HBME-1* and *TROP-2* expression across all instances investigated. **Conclusion:** With high sensitivity and specificity, both *HBME-1* and *TROP-2* are beneficial in identifying thyroid cancer, particularly papillary carcinoma, and separating malignant follicular-derived thyroid lesions from benign ones.

Keywords: Follicular thyroid lesions- Immunohistochemistry- HBME-1-*TROP-2*

Asian Pac J Cancer Prev, **24 (7)**, 2305-2311

Introduction

Thyroid cancers are prevalent, accounting for around 2.5 percent of all cancers and about ninety-five percent of tumors occurred in the endocrine system (Vojuhi et al., 2021). Thyroid nodules are one of the most prevalent health issues. The identification and treatment of thyroid nodules give the clinician a formidable task. The capacity to effectively identify and manage affects individuals' prognosis and quality of life (Vella et al., 2022).

The new WHO categorization divides thyroid tumors into numerous new groups, resulting in a more thorough knowledge of molecular categorization, pathological characteristics (histopathology and cytopathology), the cell of origin, and biological activity. Most thyroid tumors are now classified as malignant, low-risk, or benign follicular cell-derived tumors (Baloch et al., 2022).

There are two categories of thyroid follicular tumors, malignant and benign, and each comprises several subgroups. Included under benign thyroid follicular tumors is follicular adenoma. Papillary thyroid carcinoma (PTC), Follicular thyroid carcinoma (FTC), anaplastic thyroid carcinoma (ATC), and poorly differentiated thyroid carcinoma (PDTC) are all malignant thyroid follicular neoplasms. Sixty percent to seventy percent of all malignant thyroid cancers are PTC (Vojuhi et al., 2021).

To better identify cancer, the quest for an optimal biomarker with high specificity and sensitivity continues (Turan and Erkilic, 2022). Developing from thyroid follicular cells, PTC is a well-differentiated cancer with

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distinctive nuclear characteristics (Schlumberger and Leboulleux, 2021). Even though papillary carcinoma instances with specific nuclear characteristics are often straightforward to identify, the pathologist may have diagnosing challenges. Consequently, studies on numerous immunohistochemical and molecular markers have been performed to minimize discrepancies among pathologists and assure accurate identification (Ma et al., 2014; Nechifor-Boila et al., 2014).

The reason behind the increasing prevalence of thyroid cancer throughout the years is still not properly known. Unquestionably, the rise in microcarcinoma and occult disease is a contributor (Chen et al., 2009). Follicular adenoma, papillary carcinoma, follicular carcinoma, and papillary budding multinodular goiter all share morphological characteristics, making a diagnosis difficult. Thus, several immunohistochemical biomarkers have been investigated to aid the diagnosis of overlapped thyroid lesions (Vella et al., 2022).

Hector Battifora Mesothelial-1 (HBME-1) is an unknown function membrane antigen discovered in the microvilli of mesothelial cells. It has grown in prominence during the last decade, and researchers have examined its production in both cancerous and benign thyroid tissues. *HBME-1* is not produced in typical thyroid tissue but is highly produced in malignant tumors, particularly papillary thyroid cancer (Vella et al., 2022). The tumor marker *HBME-1* has been proposed for the identification and prognosis of several forms of differentiated thyroid cancer (Qiao et al., 2017). Lipinski et al. originally characterized trophoblast cell surface antigen 2 (*TROP-2*) as a type I transmembrane glycoprotein in trophoblastic tissue from a human placenta in 1981 (Lipinski et al., 1981). *TROP-2* is sometimes called tumor-associated calcium signal transducer 2 (TAC-STD2) (Zargari and Mokhtari, 2019).

There have been reports of *TROP-2* upregulation in several human malignant cancers. Increased production of *TROP-2* is related to aggressive tumor behavior and poor prognosis (Liu et al., 2017; Simms et al., 2016). It has been intensively explored as a prognostic indicator and enticing treatment option in the therapy of human malignancies (Wang et al., 2008; Trerotola et al., 2013). Differential diagnosis of thyroid lesions arising from follicular epithelial cells has recently been reported as a potential role for *TROP-2* (Murtezaoglu and Gucer, 2017).

In this study, our objective was to assess the expression of *HBME-1* and *TROP-2* in the commonly encountered benign and malignant follicular-derived thyroid lesions. Furthermore, to study the effectiveness of these markers for the distinction between malignant and benign challenging cases of follicular thyroid lesions.

Materials and Methods

Tissue samples

Fifty paraffin-embedded, formalin-fixed specimens of follicular thyroid lesions were obtained from the Al-Azhar University Hospitals' Pathology Departments and prepared for this retrospective study, between October 2018 and March 2021, after obtaining approval from the local ethics committee.

Clinicopathological data were extracted from medical charts. Each patient had completed a surgical procedure (thyroidectomy for various reasons). The WHO categorization of thyroid tumors, 5th edition, was used to classify and assess thyroid tumors (Baloch et al., 2022).

The paraffin blocks were sectioned into three sections having a thickness of 5 microns; one was colored with eosin and hematoxylin to reevaluate the diagnosis; the other two were placed on positively charged slides and immunostained with *HBME-1* and *TROP-2*.

Immunohistochemistry

Using a mouse monoclonal antibody against *HBME-1* and a mouse monoclonal antibody against *TROP-2* (acquired from Santa Cruz Biotechnology, California, and diluted 1:50), positive slides (Biogenix) were made from each paraffin block for immunohistochemical analysis.

Immunohistochemical reactions were performed using LSAB2 System-HRP (Labeled Streptavidin-Biotin2 System-Horseradish Peroxidase), based on LAB (Avidin-Biotin) a modified labelling technique whereby a secondary biotinylated antibody establishes a compound with peroxidase-conjugated streptavidin molecules. The entire antibody complex is rendered noticeable with the addition of an effective substrate chromogen reagent, which is transformed by the peroxidase label into a brownish precipitate at the place of antigen in the tissue. Diaminobenzidine (DAB), developed by Dako (USA), was the chromogen used.

Positive and negative control

A tissue was processed with PBS instead of the primary antibody and was used as a control negative. In the case of *TROP-2* and HBME-1, the placenta and mesothelioma tissues served as external control positive, respectively.

Evaluation of immunostaining

Positive findings were determined for *HBME-1* and *TROP-2* if more than 10% of the cells were positively identified by staining. The outcome was considered negative otherwise. Membrane staining was deemed positive for both indicators (Vojuhi et al., 2021).

Statistical analysis

Using version 23.0 of the statistical program for social sciences, data were examined (SPSS Inc., Chicago, Illinois, USA). Mean ±SD and ranges were used to describe the quantitative data. Likewise, qualitative characteristics were reported in numerical and percentage format. One-way ANOVA was implemented. Whenever three or more means need to be compared, the Post Hoc test is performed. Multiple comparisons between distinct variables were performed using Tukey's test. Accuracy was measured in terms of negative predictive value (NPV), specificity, positive predictive value (PPV), sensitivity, and total accuracy during the diagnostic performance evaluation. Sensitivity = [(true +ve)/ (true +ve) + (false –ve)]. Specificity = [(true –ve)/ (true –ve) + (false +ve)]. NPV = [(true –ve)/ (true –ve) + (false –ve)]. Accuracy = [(TP+TN)/ (TP+FP+TN+FN)]. PPV = [(true +ve)/ (true

+ve) + (false +ve)]. An acceptable error margin of 5% was set, and a 95% confidence interval was established. Consequently, the P-value was deemed as follows: P-values < 0.05, < 0.001, and > 0.05 were deemed significant, highly significant, and non-significant, respectively.

Results

In this research, 50 samples of follicular-derived thyroid lesions were included. All patients were categorized and assessed following the WHO categorization of thyroid tumors, 5th edition (Baloch et al., 2022). Consequently, patients were categorized as 19 benign lesions (38%) and 31 malignant tumors (62%). There were nine cases of follicular adenoma (47.4%) and ten instances of multinodular goiter (52.6%) among the benign patients. Seven cases of follicular carcinoma (22.6%) and 24 instances of papillary carcinoma (77.4%) constituted the malignant cases (Table 1).

The average age of the participants varied from 23 to 71 years (48.50). With P-value of less than 0.001, there was a significant statistical association between age and different cases. Regarding sex, the number of female patients (38 cases; 76%) was nearly three times that of male patients (12 cases; 24%). P = 0.866 indicates that there was no statistically significant association between sex and the various instances (Table 1).

HBME-1 expression in different studied cases

Membranous staining was considered a positive result in different cases (Figure 1). Twenty-six cases showed positive *HBME-1* expression (52%), and the remaining 24 cases showed negative expression (48%). The ratio of positive *HBME-1* expression in papillary carcinoma (79.2%) and follicular carcinoma (57.1%) was higher than that in follicular adenoma (22.2%) and multinodular goiter (10%) with a highly statistically significant P-value of <0.001 (Table 2).

Table 1. Different Cases Regarding Demographic Data

Demographic Data	Benign Lesions (n=19) -38%		Malignant Lesions (n=31) -62%		Total (n=50) -100%	P-value
	MNG (n=10) -52.60%	FA (n=9) -47.40%	FC (n=7) -22.60%	PC (n=24) -77.40%		
Age (years)						
Mean±SD	36.50±9.05C	42.00±7.07B	53.14±7.49A	54.58±8.84A	48.50±11.19A	<0.001**
Range	23-51	30-51	41-63	42-71	23-71	
Sex						
Female	8 (80.0%)	6 (66.7%)	5 (71.4%)	19 (79.2%)	38 (76.0%)	0.866
Male	2 (20.0%)	3 (33.3%)	2 (28.6%)	5 (20.8%)	12 (24.0%)	

Values in each row with different letters are significantly different at (P<0.05) through the Post Hoc test: Tukey's test; P-value >0.05 is insignificant; **p-value <0.001 is highly significant

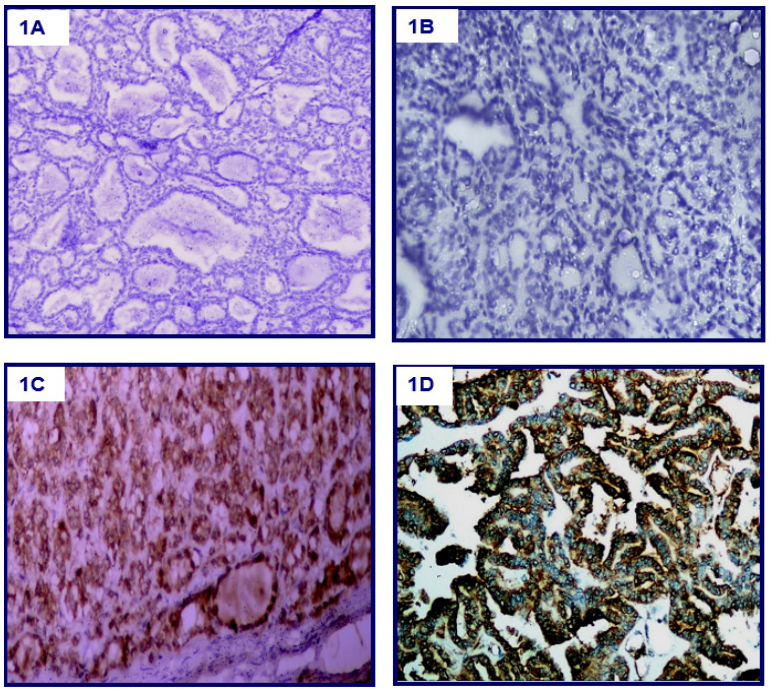

Figure 1. Immunohistochemical Expression of HBME-1 in Different Studied Thyroid Cases. (A) Negative HBME-1 expression in multinodular goiter (× 200). (B) Negative HBME-1 expression in follicular adenoma (× 200).(C) Positive membranous HBME-1 expression in follicular carcinoma (× 200). (D) Positive membranous HBME-1 expression in papillary carcinoma (× 200).

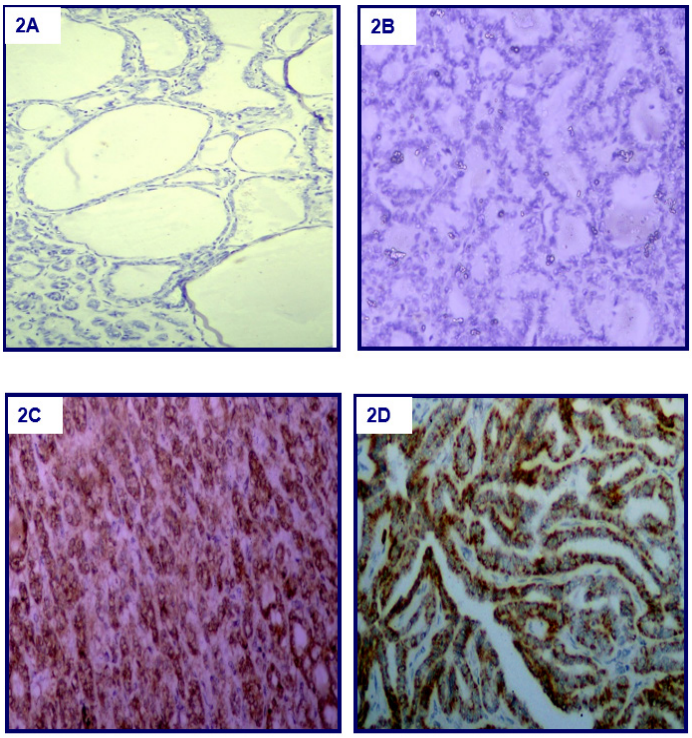

Figure 2. Immunohistochemical expression of TROP-2 in different studied thyroid cases. (A) Negative TROP-2 expression in multinodular goiter (× 200). (B) Negative TROP-2 expression in follicular adenoma (× 200). (C) Positive membranous TROP-2 expression in follicular carcinoma (× 200). (D) Positive membranous TROP-2 expression in papillary carcinoma (× 200).

Table 2. HBME-1 Expression in Different Cases

HBME-1		Different Cases				Total	P-value
		MNG	FA	FC	PC		
Negative	No.	9	7	3	5	24	<0.001**
	%	90.00%	77.80%	42.90%	20.80%	48.00%	
Positive	No.	1	2	4	19	26	
	%	10.00%	22.20%	57.10%	79.20%	52.00%	
Total	No.	10	9	7	24	50	
	%	100.00%	100.00%	100.00%	100.00%	100.00%	

**P-value <0.001 is highly significant

TROP-2 expression in different studied cases

Membranous staining was considered a positive result in different cases (Figure 2). Thirty-one cases showed positive *TROP-2* expression (62%), while 19 cases showed negative expression (38%). The ratio of positive *TROP-2* expression in papillary carcinoma (91.7%) and follicular carcinoma (71.4%) was higher than that in follicular adenoma (22.2%) and multinodular goiter (20%) with a highly statistically significant P-value of <0.001 (Table 3).

HBME-1 expression in benign versus malignant lesions

The ratio of positive *HBME-1* expression in malignant thyroid lesions (74.2%) was significantly higher than that in benign lesions (15.8%), with a highly statistically

Table 3. TROP-2 Expression in Different Cases

TROP-2		Different Cases				Total	P-value
		MNG	FA	FC	PC		
Negative	No.	8	7	2	2	19	<0.001**
	%	80.00%	77.80%	28.60%	8.30%	38.00%	
Positive	No.	2	2	5	22	31	
	%	20.00%	22.20%	71.40%	91.70%	62.00%	
Total	No.	10	9	7	24	50	
	%	100.00%	100.00%	100.00%	100.00%	100.00%	

**P-value <0.001 is highly significant

Table 4. HBME-1 Expression in benign versus Malignant Lesions

HBME-1	Benign Thyroid Lesions		Malignant Thyroid Lesions		Total		P-value
	No.	%	No.	%	No.	%	
Negative	16	84.20%	8	25.80%	24	48.00%	<0.001**
Positive	3	15.80%	23	74.20%	26	52.00%	
Total	19	100.00%	31	100.00%	50	100.00%	

**P-value <0.001 is highly significant

Table 5: TROP-2 Expression in benign versus Malignant Lesions

TROP-2	Benign Thyroid Lesions		Malignant Thyroid Lesions		Total		P-value
	No.	%	No.	%	No.	%	
Negative	15	78.90%	4	12.90%	19	38.00%	<0.001**
Positive	4	21.10%	27	87.10%	31	62.00%	
Total	19	100.00%	31	100.00%	50	100.00%	

**P-value <0.001 is highly significant

Table 6. Correlation between HBME-1 and TROP-2 among All Cases

		HBME-1				Total		P-value
		Negative		Positive				
		No.	%	No.	%	No.	%	
TROP-2	Negative	19	79.20%	0	0.00%	19	38.00%	<0.001**
	Positive	5	20.80%	26	100.00%	31	62.00%	
Total		24	100.00%	26	100.00%	50	100.00%	

**P-value <0.001 is highly significant

significant P-value of <0.001 (Table 4).

TROP-2 expression in benign versus malignant lesions

The ratio of positive *TROP-2* expression in malignant thyroid lesions (87.1%) was significantly higher than that in benign lesions (21.1%), with a highly statistically significant P-value of <0.001 (Table 5).

Correlation between HBME-1 and TROP-2 expression

According to the relation between *HBME-1* and *TROP-2* expression in all studied cases, there was a statistically highly significant direct positive relation between *HBME-1* and *TROP-2* expression in different studied cases with a P-value <0.001. All 26 cases with positive *HBME-1* expression showed positive expression with *TROP-2* (Table 6).

Diagnostic performance of both markers in discrimination between benign and malignant lesions

Sensitivity, positive predictive value (PPV), specificity, negative predictive value (NPV), and accuracy of *HBME-1* and *TROP-2* for differentiating malignant (papillary carcinoma and follicular carcinoma) from benign thyroid lesions (multinodular goiter and follicular adenoma) are shown in (Table 7). Both markers demonstrated extremely high sensitivity (74.2% for *HBME-1* and 87.1% for *TROP-2*) and specificity (84.2% for *HBME-1* and 78.9% for TRPO-2) for distinguishing benign from malignant follicular thyroid lesions.

Table 7. Diagnostic Performance of Both Markers

	HBME-1	TROP-2
Sensitivity	74.20 %	87.10 %
Specificity	84.20 %	78.90 %
PPV	88.50 %	87.10 %
NPV	66.70 %	78.90 %
Accuracy	78.00 %	84.00 %

Discussion

In our study, the average age of the participants varied from 23 to 71 years (48.50 as the mean average age). The association between age and various instances (P-value < 0.001) was extremely statistically significant. Regarding sex, the number of female patients (38 cases; 76%) was nearly three times that of male patients (12 cases; 24%). With a P-value = 0.866, there was no significant statistical association between sex and various instances. According to Addati et al., (2015), the age of thyroid neoplasm patients ranged between 18 and 73 years, but the mean age was 53. This study is in line with Asmaa et al., (2018) findings that the thyroid neoplasms women/men ratio is 2:1; hence they are more prevalent than in men.

While histology remains the gold standard for identification, several diagnostic hazards and morphological characteristics may create predictive problems and disagreements even among professional pathologists (Turan and Erkilic, 2022). The first objective is to arrive at an appropriate evaluation of patients between malignant and benign thyroid nodules, specifically in

identifying follicular patterned abnormalities, especially those encapsulated (Baloch et al., 2017).

It is possible to differentiate between thyroid tumors types (malignant or benign) using ancillary investigations, like IHC markers. Because fifty percent of the adenomas had positivity with HBME-1, it was not an effective IHC marker for distinguishing adenomas from carcinomas (Saleh et al., 2010). No single marker is specific or sensitive enough to serve this role independently (Zargari and Mokhtari, 2019). Consequently, an IHC panel including two or more markers might be necessary. Immunohistochemistry markers such as HBME-1, gal-3, CK19, and TPO have been suggested to enhance cancer detection, and their diagnostic efficacies for thyroid malignancy have been assessed (Arcolia et al., 2017).

Several investigations have examined the function of *TROP-2* and *HBME-1* markers in detecting thyroid tumors. *TROP-2* identified papillary cancer with a specificity of 89.0% and a sensitivity of 95.5%, as per Simms et al. (Simms et al., 2016). The average specificity and sensitivity of *HBME-1* were 85.4% and 78.3%, respectively, according to several research findings, despite contradictory findings (Lacoste-Collin et al., 2014; Murtezaoglu and Gucer, 2017).

In this study, we elucidate the usage of *HBME-1* and *TROP-2* in identifying thyroid follicular lesions. The production of *HBME-1* between malignant and benign thyroid cases was statistically highly significant. Increased *HBME-1* production was found in 74.2% of malignant tumors, compared to 15.8% of benign lesions (P <0.001). At the same time, the production of *TROP-2* between malignant and benign thyroid cases was statistically highly significant. The percentage of malignant tumors with elevated *TROP-2* production was 87.1%, substantially greater than that of benign lesions, 21.9% (P <0.001). When comparing both markers' expression in studied cases, a significant positive association was found between *HBME-1* and *TROP-2* production in different studied cases with a P-value <0.001. All 26 cases with positive *HBME-1* expression showed positive expression with *TROP-2*. Both markers demonstrated extremely high sensitivity (74.2% for *HBME-1* and 87.1% for *TROP-2*) and specificity (84.2% for *HBME-1* and 78.9% for TRPO-2) in distinguishing benign from malignant follicular thyroid lesions.

Near to this study, Abd-El Raouf and Ibrahim, 2014, investigated the role of IHC activation of galectin-3 and *HBME-1* in the differential identification of thyroid nodules produced from follicular cells. Both markers were shown to exhibit localized staining in benign neoplastic (FA) and benign non-neoplastic (MNG) tumors while displaying widespread responsiveness in malignant tumors (PTC, FC, and FVPTC). The sensitivity of *HBME-1* staining in malignant tumors was 89.3%, whereas its specificity was 66.7%.

In agreement with our results, Zargari and Mokhtari, (2019) stated that the vast majority of malignant PTCs (27/29, 93%) and FVPTCs (17/21, 81%), as well as 50% of malignant FCs (3/6, 50%), had robust and widespread reactivity towards HBME-1. In addition, Vella et al., (2022) discovered that *HBME-1* was mostly present in malignant tissue and either missing or poorly stained in benign lesions.

Palo and Biligi (2017), demonstrated that *HBME-1* is the most specific and sensitive biomarker for differentiating malignant from benign thyroid tumors. Findings from our investigation confirmed that PTC had a greater positivity rate than FC. According to a study by Turan and Erkilic, 2022, *TROP-2* had a 63.5% sensitivity, 100% positive predictive value, 100% specificity, and 44.6% negative predictive value across all PTC patients. The control group consisted of 50 instances of Hürthle cell adenoma (n=10), follicular adenoma (n=10), MNG (n=20), and hyperfunctioning thyroid disease (n=10), and no response was detected within any of them.

Overexpression of *TROP-2* in PTC cases was linked to an increased TNM stage and lymph node metastasis, as well as the induction of MMP2 (matrix metalloproteinase 2) via the JNK (the c-Jun N-terminal kinases) pathways and ERK (extracellular signal-regulated kinases), according to an investigation by Guan et al., (2017).

The expression of *TROP-2* in thyroid tumors was assessed by Liu et al., (2017). They found that typical thyroid tissue had faint cytoplasmic (but no membranous) staining. Most PTCs stained membranous (3+ or 4+), whereas the vast majority of FCs and benign neoplasms stained negative. Using immunohistochemistry (IHC), Bychkov et al., (2016) investigated *TROP-2* as a reliable marker for PTC differential diagnosis. They suggested that *TROP-2* would be effective for identifying PTC from complicated non-neoplastic abnormalities such as papillary hyperplasia in thyroid nodules and separating PTC and its variants with solid components from FC. Hashimoto's thyroiditis, Nodular goiter, and Grave's disease were shown to lack *TROP-2* staining, demonstrating that they are not neoplastic tumors. In contrast to the 12 oncocytic variations of FAs, all FCs tested negative for *TROP-2*. Detection of PTCs was reported to be highly sensitive (98.1%) and specific (97.5%) using *TROP-2*.

Furthermore, our investigation found that 20% of MNGs had *TROP-2* immunoreactivity, consistent with a previous report (Liu et al., 2017). *TROP-2* reactivity was shown in Hurthle cells and Hashimoto's thyroiditis regions (Zargari and Mokhtari, 2019), suggesting that *TROP-2* is not a reliable diagnostic for malignancy in thyroid tumors with oncocytic transformation. As a result, when trying to distinguish benign from malignant thyroid tumors with Hurthle cell morphology, it is best to employ another IHC biomarker (such as HBME-1) or molecular investigation in addition to *TROP-2*. The differences among our current study and some other studies may be due to immunostaining technique, staining scoring methods and sample size differences.

In conclusion, overall, the current study and related studies proved that using *HBME-1* and *TROP-2* in combination may accurately identify cancer with ambiguous morphology with high specificity and sensitivity. Furthermore, compared to FCs, these two markers exhibit greater immunoreactivity in PTCs and their variations. Because Hurthle cell neoplasms were so significantly positive for *TROP-2*, this biomarker might not be useful in the differential identification of malignant

and benign tumors with oncocytic appearance. Therefore, combining both markers is helpful, especially in these cases. Consequently, using a panel of two markers with a modest immunohistochemical cost minimizes the need for unneeded surgical removal of benign nodules while also improving patient quality of life and the financial load on healthcare services.

Author Contribution Statement

All authors contributed equally in this study.

Acknowledgements

None.

Ethical Approval

The research has approval from Al-Azhar Faculty of Medicine under the registration no: Pat._22Med. Research-Immunohistochemical expression of *HBME-1* and *TROP-2* in some follicular-derived thyroid lesions. _0000022.

Availability of data (if apply to your research)

Available on request.

Conflict of interes

No Conflict of interest to declare.

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