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Original article

Diagnostic Value of Human Trophoblastic Transmembrane Glycoprotein (TROP-2) Expression in Diagnosing Papillary Thyroid Carcinoma Immunohistochemical Study

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Abstract:

Background: Characteristic histopathological characteristics are what determine the diagnosis of papillary thyroid carcinoma (PTC). In some instances, immunohistochemical markers may be necessary due to the presence of inconsistent features. It has been reported that IHC stains, including HBME-1, galectin-3, and CK19, are helpful in the diagnosis of PTC; however, the sensitivity and specificity of these stains vary. TROP-2 is a new and potential marker for PTC diagnosis, according to recent research. Aim: This study aimed to investigate the significance of TROP-2 expression in the diagnosis of PTC and its distinction from benign thyroid lesions and low-risk neoplasms (NIFTP). **Material and methods:** This retrospective study was carried out on fifty-one cases classified according to the fifth edition of the WHO classification 2022 as follows: thirteen benign thyroid lesion cases, twelve low-risk neoplasms (NIFTP) cases, and twenty-six papillary thyroid carcinoma cases. Six cases of breast carcinoma were taken as a control. Clinicohistopathological parameters were correlated with TROP-2 expression. **Results:** In the current study, there was a positive, significant statistical correlation($P<0.01$) between TROP-2 expression and the studied cases, as 7.7% of benign cases, 50% of low-risk neoplasms cases, and 92.3% of malignant cases were positive. **Conclusion:** With high sensitivity and specificity, TROP-2 may be a useful marker that can help diagnose PTC and distinguish it from its benign mimics and low-risk neoplasms (NIFTP).

Keywords: Human Trophoblastic Transmembrane Glycoprotein (TROP-2); Follicular variant-papillary thyroid carcinoma (FV-PTC); Papillary thyroid carcinoma (PTC).

Introduction

The eighth most prevalent tumor in 2020 was thyroid cancer, which is the most prevalent form of endocrine malignancy. Women have a global incidence rate of 10.1 per 100,000, which is three times higher than that of men. This disease accounts for one in every twenty cancers diagnosed in women. [1]

Currently, one in 55 U.S. women and one in 149 U.S. men are expected to be diagnosed with thyroid cancer during their lifetime. The incidence of thyroid cancer is high, but the mortality rate is low (approximately 0.5 fatalities per 100,000 per year). There is little evidence of a sex differential [2]

In Egypt 2020, thyroid cancer ranks 13th for incidence with an estimated 2661 new cases accounting for 2.0% of cancers and a five-year prevalence of estimated 7913 cases accounting for 7.73 per 100,000 of all cancers. It is the most common endocrine malignancy, contributing to about 80% of cases; however, the mortality rate is low (8%). [3]

The most recent fifth version of the WHO Classification of thyroid cancers includes innovative principles. [4] The phrase "thyroid follicular nodular disease" currently denotes both clonal and non-clonal proliferations that clinically present as multinodular goiter, comprising a varied assortment of benign neoplastic and non-neoplastic lesions [5] Thyroid neoplasms originating from fetal cells can be categorized as benign, low-risk, or malignant. The new classification scheme emphasizes that papillary thyroid cancer (PTC) must be subtyped according to histomorphological characteristics, regardless of tumor size, to avoid categorizing all sub-centimeter/small lesions as low-risk conditions. [6]

Papillary thyroid carcinoma, which makes up 80–85% of all thyroid cancer cases, is the most common type of well-differentiated thyroid cancer. A study utilizing the Surveillance, Epidemiology, and End Results (SEER) database indicated that the prevalence of PTC increased from 4.8 to 14.9 per 100,000 from 1975 to 2012. [7]

The diagnosis of PTC is contingent upon the presence of classic nuclear features and characteristic histopathological characteristics, which are occasionally observed in certain benign and non-neoplastic lesions. [8] When there are inconsistent features, the use of numerous immunohistochemical markers, either separately or in combination, helps distinguish PTC from mimickers. [9]

A range of immunohistochemical and biochemical markers, such as HBME-1, galectin-3, and cytokeratin nineteen, have been examined to clarify the inconsistency and establish a definitive diagnosis. Recent investigations have discovered TROP-2 as a unique and potential biomarker for the diagnosis of PTC. [10]

Trophoblast cell surface antigen 2 (*TROP2*), also known as tumor-associated calcium signal transducer 2 (*TACSTD2*), is a cell surface glycoprotein that acts as a transmembrane transducer of intracellular (IC) calcium signals. TROP2 is overexpressed in different tumor tissues and plays roles in cell proliferation, invasion, migration, and apoptosis. [11]**.** Among the intracellular axis in which Trop-2 is involved are the MAPK/PI3K/AKT pathways, which are implicated in the invasion, migration, and proliferation of cancer cells. [12]

Our goal was to assess Trop-2 expression's potential diagnostic utility in identifying and distinguishing PTC from low-risk neoplasms and their benign counterparts.

Materials and methods

Study group: This is a retrospective study performed upon formalin-fixed paraffin-embedded blocks from 51 different thyroid lesions classified according to the WHO classification, 5th edition 2022 [5] as follows: 6 cases of thyroid goiter designated now as (TFND), 7 cases provisionally diagnosed as FTA, 12 cases of low-risk neoplasms diagnosed as

(NIFTP), 26 cases of PTC, including (13 cases of conventional PTC)and (13 cases of FV-PTC, including ٧ cases of widely infiltrative FV-PTC and ٦ cases of invasive encapsulated FV-PTC). In addition, six cases of breast carcinoma were used as controls.

-The material included archived formalin-fixed, paraffin-embedded blocks processed during the years from 2017 to 2023, blocks werecollected from the Department of Pathology, Ben ha faculty of medicine, and clinicopathological data were collectedfrom the files of patients.

The Ethics Committee of the Faculty of Medicine, Benha University, Egypt, approved this study code (MS 4-7-2023)

Histopathological studies:

Revision of the diagnosis and other histopathological parameters was performed by two pathologists blinded to the original diagnosis.

From each selected formalin-fixed paraffin-embedded block, two sections, four microns each, were cut. Histopathological classification was reviewed according to the fifth edition of the WHO classification 2022 [(5)], and TNM staging was made depending on the AJCC, eighth edition [(13)]

TROP-2 immunohistochemical study:

Immunohistochemical staining was conducted on 3–4 μm sections derived from paraffin-embedded tissue blocks, employing a primary mouse polyclonal antibody against human TROP-2 prediluted (1:50) TO (1:200) *(TROP2/TACD1 prediluted, MC0386RTU7, 7ML, America).* The Avidin-Biotin Complex (ABC) method was utilized to apply anti-TROP-2 antibodies to each slide, following the manufacturer's guidelines. A ten mmol/L citrate buffer (pH 6.0) was employed to accomplish antigen retrieval for both. The tissue sections were incubated with primary antibodies at room temperature for a total of two hours. The immunoreaction was observed by incorporating DAB as a chromogen. The slides of positive and negative controls were incorporated into each iteration.

Marker : *TROP-2*
Clone: *TACSTD2l2153*
Host\isotope : *Mouse/IgG1K*
state: *Diluted*
dilution: *50:200*
incubation: *30-60 min at 95-99*
+ve control: *Breast Carcinoma*

Interpretation of TROP-2 expression:

Positivity was considered as brownish homogenous membranous staining of tumor cells. The staining intensity was multiplied by the percentage area of positive immunostaining within the visual field to derive the immunohistochemical combined scores using light microscopy. The positive immunostaining percentage area was scored on a scale of 0 to 4 as follows: 0 (0% to <5%), 1 (5-25%), 2 (25-50%), 3 (50-75%), and 4 (≥75%).Score 1 and 2 considered as focal positive, score 3, 4 considered as diffuse positive**.** On a scale of 0 to 3, the intensity of TROP-2 protein expression was assessed as follows: three high staining, two moderate staining, one mild staining, no staining or zero denoted. Staining intensity score was multiplied by the percentage score of positive tumor cells to determine the final score, which ranged from 0 to 12. The median marker score was employed as the defining threshold to stratify patients into high- and low-expression groups [(12)]

Statistical analysis:

Version 26 of the SPSS program (SPSS Inc., PASW Statistics for Windows) was used to analyze the data. SPSS Inc., Chicago. Numbers and percentages were employed to characterize qualitative data. The significance of the results was assessed at the 0.05 level.

When necessary, Monte Carlo, Fisher's exact, and chi-squared tests were employed to compare qualitative data between groups.

The validity (sensitivity and specificity) of continuous variables was determined by calculating the optimal cut-off point using the receiver operating characteristics curve

(ROC curve). The accuracy and predictive values are evaluated through cross-tabulation.

Descriptive statistics consist of the meaning, standard deviation (± SD), median, and standard error (±SE). Numerical data were described using range, while non-numerical data were described using frequency and percentage. A P value is regarded significant if it is less than 0.05 within a 95% confidence interval.

Results:

Clinicopathological results:

The Age distribution of the studied cases ranged from 18 to 83 years, with 52.55_+15.89 as the mean average age. The mean average age is 39.38±12.81 in PTC. Eighty percent of cases were females and 20% of cases were males. Regarding tumor size of the studied malignant cases, 18 cases (69.2%) were <2cm, 4 cases (15.4%) were 2-4cm, and 4 cases (15.4%) were >4 cm. Out of the studied PTC cases (9 cases (34.6%) were negative for nodal metastasis (N0) & 17 cases (65.4%) were positive (N1)), which was statistically non-significant (P >0.05). Histopathological data are illustrated in **Table 1.**

Immunohistochemical results:

The expression of TROP-2 showed the following: all TFND cases were negative 0%. One case of FTA was focally positive (14.3%) with weak staining intensity. Six cases of NIFTP were focally positive (50%) with moderate and strong staining intensity. Twenty-four cases of malignant PTC cases were positive (92%) (100% positivity in classic PTC, 79% positivity in FV-PTC) with moderate and strong staining intensity in all cases, with twenty-three cases showing a diffuse staining pattern. Immunohistochemical results were illustrated in **(Tables 2,3,4) (Graph 1) (Figure 1)**

Table (1): Histopathological parameters of the studied malignant cases by PTC:

Histopathologic feature		FV-PTC		classic PTC		Total	
		No.	%	No.	%		PV
Papillae	Absent	4	15.38	0	0.0	4(15.4)	**0.03***
	Present	9	34.62	13	50.0	22(84.6)	<0.05
Tumor size (T)	T1	8	30.77	10	38.46	18(69.2)	**0.685**
	T2	2	7.7	1	3.85	3(11.5)	**>0.05**
	T3	3	11.54	2	7.7	5(19.2)	
Lymph node	N0	5	19.23	4	15.38	9(34.6)	**0.685**
metastasis (N)	N1	8	30.77	9	34.62	17(65.4)	**>0.05**
Distant	M0	13	50.0	13	50.0	26(100)	
metastasis (M)	M1	0	0.0	0	0.0	0	**>0.05**
	I	11	42.31	13	50.0	24(92.3)	**0.141**
TNM stage	II	2	7.7	0	0	2(7.7)	**>0.05**
	Absent	8	30.77	10	38.46	18(69.2)	**0.395**
Extra thyroid extension	Present	5	19.23	3	11.54	8(30.8)	**(>0.05)**
Focality	Unifocal	8	30.77	6	23.07	14(53.8)	0.502
	Bifocal	5	19.23	6	23.07	11(42.3)	>0.05
	Multifocal	0	0.0	1	3.85	1(3.8)	
Lymphocytic	Absent	8	30.77	5	19.23	13(50)	0.239
infiltration	Present	5	19.23	8	30.77	13(50)	>0.05
Total		**13**	**50%**	**13**	**50%**	**26 (100%)**	

- **N.B**.: from the table, papillae formation was present in all cases (100%) of classic PTC in relation

to only 69.2% of FV-PTC, respectively, which was statisticallysignificant (P<0.05).

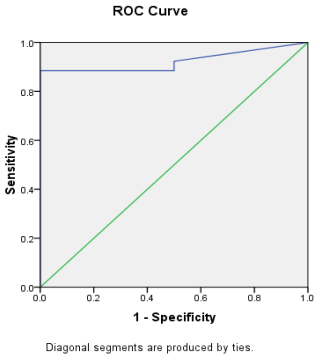
- Extra thyroid extension was higher among FV-PTC than classic type**,** and this was statistically non-significant (38.5% versus 23.1%) (P>0.05)
- All cases in the Classic PTC group were TNM stage I versus 84.6% of FV-PTC, and this was statistically non-significant (P>0.05)
- Unifocal and bifocal lesions were more frequent among FV-PTC than classic PTC, and this was statistically non-significant (P>0.05)

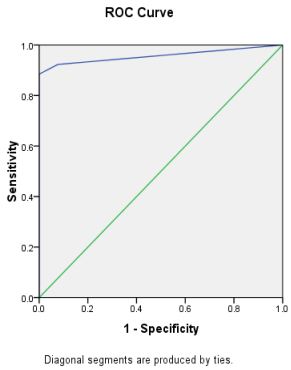
Table *(2)*. Comparison between different studied groups regarding TROP-2 expression (distribution and intensity of stain).

Pathological type	**Total**	**Distribution of TROP-2 Expression**						**PV**	**Intensity of TROP-2 Expression**								**PV**
		Negative		**Focal (+, ++)**		**Diffuse (+++, ++++)**			**Negative**		**Weak**		**Moderate**		**Strong**		
		NO.	**%**	**NO.**	**%**	**NO.**	**%**		NO	%	NO	%	NO	%	NO	%	
TFND	**6**	**6**	**100**	**0**	**0.0**	**0**	**0.0**		**6**	**100**	**0**	**0.0**	**0**	**0.0**	**0**	**0.0**	
FTA	**7**	**6**	**85.7**	**1**	**14.3**	**0**	**0.0**		**6**	**85.7**	**1**	**14.3**	**0**	**0.0**	**0**	**0.0**	**0.001****
NIFTP	**12**	**6**	**50**	**6**	**50.0**	**0**	**0.0**		**6**	**50.0**	**0**	**0.0**	**6**	**50.0**	**0**	**0.**	
FV-PTC	**13**	**2**	**15.4**	**1**	**7.7**	**10**	**76.9**		**2**	**15.4**	**1**	**7.7**	**4**	**30.8**	6	46.2	
Classical PTC	**13**	**0**	**0.0**	**0**	**0.0**	**13**	**100.0**		**0**	**0.0**	**0**	**0.0**	**3**	**23.1**	**10**	**76.9**	
Total	**51**	**20**	**39.2**	**8**	**15.7**	**23**	**45.1**	**0.001****	**20**	**39.2**	**2**	**3.9**	**13**	**25.5**	16	31.4	

-N.B.: From the table, it was found that there was a highly significant correlation between expression of TROP-2 and pathologic type of studied cases (p<0.01). Malignant cases showed the highest expression for TROP-2. The highest expression was in classical Papillary thyroid carcinoma, with 100% showing diffuse positivity.

-SE. Standard error, Min.: Minimum, Max.: Maximum, H: Kruskal Wallis, x^2: Chi-Square,
FE: Fisher-Exact, MC: Monte-Carlo, P: Comparing between the different studied groups.
*: Significant when p value < 0.05.





Graph (1):

(a): ROC curve of TROP-2 in differentiating between Benign lesions *vs*. malignant tumors.

(b): ROC curve of TROP-2 in differentiating between low-risk neoplasms *vs*. malignant tumors.

Table (3): Summary of markers with studied groups

		Benign N=13	low risk neoplasms (NIFTP)N=12	Malignant N=26	P Value
TROP-2 distribution -ve		12(92.3)	6(50)	2(7.7)	<0.001*
positive	Focal	1(7.7)			
	Diffuse	0	6(50)	1(3.8)	
			0	23(88.5)	
TROP-2 staining intensity. -ve		12(92.3)	6(50)	2(7.7)	<0.001*
positive	Weak	1(7.7)	0	1(3.8)	
	Moderate	0	6(50)	7(6.9)	
	Strong	0	0	16(61.5)	
Combined score Mean ±SD.		0.077±0.277	2.33±2.67	9.35±3.77	<0.001*
Median (IQR)		0(0-0)	1(0-5.5)	12(8-12)	

Table (4): Statistical analysis of TROP-2 as a marker for malignancy in thyroid lesions

Trop-2 expression	**Sensitivity %**	**Specificity %**	**PPV %**	**NPV %**	**AUC (95%CI)**	**Accuracy %**	**Cut-off point**
malignant tumors *vs*.	92.3	92.3	85.7	96.0	0.957 (0.892-1.02)	92.3	≥0.5
Benign lesions malignant tumors vs low-risk neoplasms (NIFTP)	88.5	100.0	100.0	80.0	0.923 (0.834-1.01)	92.1	≥7
PTC VS FV-PTC	53.8	76.9	70	62.5	0.692 (0.486-0.899)	65.4	≥8.5
NIFTP vs Benign lesions	50.0	100.0	100	68.4	0.731 (0.523-0.939)	76.0	≥1.5

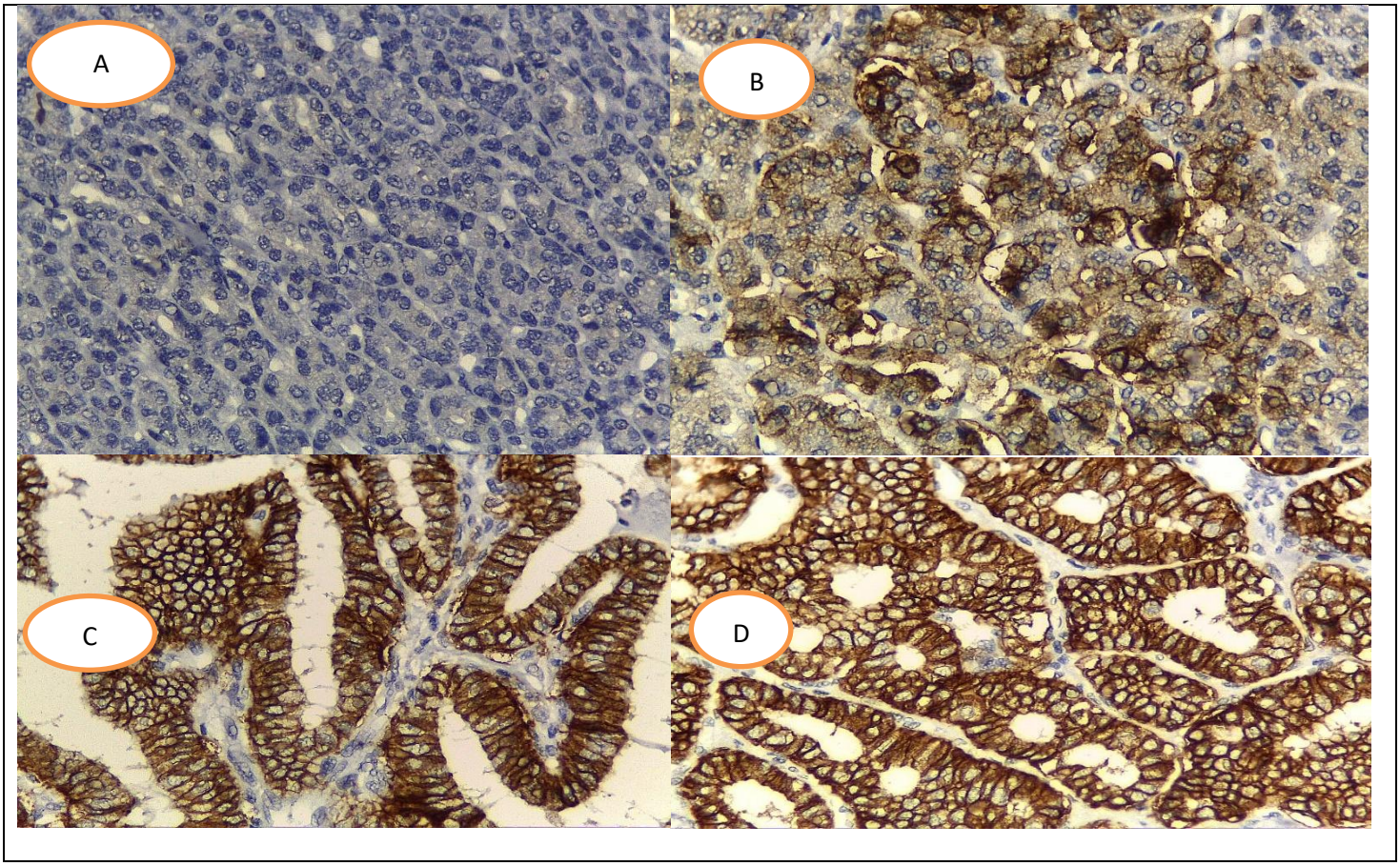


Figure 1:
Fig. A: Follicular Thyroid adenoma negative membranous stain for TROP2, score=0 (ABC, X400)
Fig. B: NIFTP showing focal moderate membrane& focal weak cytoplasmic stain for TROP2 *involving25-50% of cells*, score=4(ABC, X400)
Fig. C: Papillary thyroid carcinoma showing diffuse strong membranous & strong diffuse cytoplasmic stain for TROP2 *involving>75% of cells*, score=12 (ABC, X400)
Fig. D: Follicular variant-papillary thyroid carcinoma, showing diffuse strong membranous& strong diffuse cytoplasmic stain for TROP2 *involving>75% of cells*, score=12 (ABC, X400)

Discussion:

Thyroid cancers are the most common endocrine system malignancy, accounting for about 95 percent of tumors occurring in the endocrine system and around 2.5 percent of all cancers [14]. PTC is the most generic form of well-differentiated thyroid cancer, accounting for 80 to 85% of all cases of thyroid cancer. [15]
In Egypt, 1.96% of malignant tumors and 74.7% of malignant endocrine neoplasms are primary thyroid tumors. Primary malignant thyroid tumors are the most common type, accounting for 70.94% of all thyroid malignant tumors. [16]
In our study, the calculated mean average age was 44.92±12.48 in the benign lesions group, 40.17±14.91in the low-risk neoplasms group, and 39.38±12.81 in the malignant papillary thyroid carcinoma group, which means that the younger the patient, the higher the risk of being malignant.
TROP-2 positivity showed membranous expression. In certain instances, in our investigation, a mixed cytoplasmic and membranous pattern of localization was

noted. This outcome is consistent with the research of Eid and Abo Safia [9] & Shvartsur and Bonavida [17], He claimed that TROP-2 might be expressed in the cytoplasm during malignancy, recurrence, and metastasis. TROP-2 demonstrates cytoplasmic positivity due to its cross-reactivity with EpCAM/TROP-1, an epithelial cell adhesion molecule encoded by a separate gene within the same family (TACSTD1), and its highly similar sequence [18].

Regarding the thirteen benign cases studied that included seven cases of FTA, of which two cases of them are FTA with papillary architecture, and six cases of TFND with papillary hyperplasia present in three cases of them.

Most benign cases (all cases of TFND (85.7%) and six cases of FTA (85.7%)) were negative for TROP-2. Only one case of FTA (14.3%) showed focal weak membranous staining for TROP-2 (1/13).

Our results agreed with the results of the literature of Khalil et al [19]. The remaining cases were negative (15/16), while one case of benign thyroid lesions exhibited mild focal TROP-2 positivity (1/16).

The positivity that was found in benign lesions can be attributed to an unintentional technical error [20]. However, in the study done by Abdou et al [8], TROP-2 positive in benign lesions was linked to the existence of PTC-like nuclear characteristics in their investigation. This could indicate that an early malignant change is possible.

This result was against the results of Al-Sayed et al [21], who found that none of the benign thyroid lesion cases showed TROP-2 positivity; that discrepancy could be partially explained by the different clones of antibody employed for IHC.

In our study, the twelve cases studied were low-risk neoplasms (NIFTP) distributed as follows: six cases (50%) were negative, and six cases (50%) had moderate and strong staining intensity.

Our results agreed with the results Khalil et al [19], who found that whereas four (44.4%) of the nine cases of low-risk neoplasms were negative (4/9) and mostly consisted of localized staining with moderate and strong intensity, TROP-2 expression was found in five (55.6%) of the cases (5/9).

TROP-2 expression in low-risk neoplasms has been evaluated in a limited number of studies. One of the tasks was completed by Liu et al [22], In contrast to the previous study using the general term "adenomatoid nodule with focal nuclear atypia," they identified TROP-2 negativity in the subjects they analyzed. Zargari and Mokhtari (10) showed TROP-2 positive in the patients that were borderline (2/2).

In the present study, we identified positive TROP-2 expressions in twenty-four cases (92.3%) of the twenty-six malignant cases that were examined. The staining intensity was moderate to strong in all cases, with a diffuse staining pattern in twenty-three cases. Two cases (7.7%) were negative. This data illustrated that a TROP-2 membranous staining pattern was unique to thyroid PTC, including both classic and follicular variants, among the thyroid lesions.

Our results agreed with the results of Khalil et al [19], Out of the 30 PTC instances, twenty-six had positive TROP-2 expressions, making up 86.7% of the total. Four (13.3%) of the remaining instances were negative.

In our study, total PTC cases included thirteen cases of conventional PTC and thirteen cases of FV-PTC. Out of the studied 13 cases of FV-PTC, 2 cases (15.4%) were negative, one case (7.7%) showed focal expression, and 10 cases (76.9%) showed diffuse membranous staining, with strong intensity in 6 cases, moderate staining in 4 cases, and weak staining in only one case.

Out of the thirteen cases studied with conventional PTC, thirteen cases (100%) were positive with diffuse membranous staining pattern, strong intensity in ten cases, and moderate intensity in three cases.

Our study was in line with the results of Liu et al [22] that revealed that 97% (30/31) of CPTCs and 76% (13/17) of FVPTCs expressed TROP-2.

This was like the results of Al-Sayed et al [21], who discovered that a strong membranous staining with TROP-2 was observed in eleven cases of PTC 11/19 (60%), with the preponderance being diffuse. Bychkov et al [20] The classic variant of PTC is more likely to be diagnosed when a thyroid lesion exhibits diffused TROP-2 staining. The classic variant of PTC is ruled out by negative staining; however, follicular thyroid carcinoma and FV-PTC cannot be ruled out.

In our investigation, we discovered that the classic variant of PTC is characterized by diffuse and robust TROP-2 expressions, which are adorned with tiny, microscopic foci of PTC and lack background stains. These foci are readily visible in low-power views. The negative stain in TFND and FTA that was associated with papillary hyperplasia is convincing evidence against PTC.

This aberrant upregulation of *TROP-2* expression in malignant cases, rather than benign neoplastic and borderline cases, implicates a potential oncogenic role in thyroid carcinogenesis and makes it a promising biomarker for the diagnosis of papillary thyroid carcinoma.

A study done by Attia et al [16] demonstrated that activating MMP2 via the ERK and JNK pathways may promote thyroid cancer invasion, suggesting a potential role for TROP-2 in PTC carcinogenesis.

Based on a study done by Kong et al [23] Researchers found that TROP2 immunohistochemistry may be used to diagnose papillary thyroid cancer or predict BRAF mutations, and that TROP2 expression was linked with BRAF mutations. The mitogen-activated protein kinase (MAPK) pathway is known to be triggered by BRAF mutations, and this, in turn, causes PTC carcinogenesis [24]. In addition to promoting carcinogenesis, TROP2 expression also triggers the MAPK/ERK pathway, which has significant implications for several cellular functions, including migration, invasion, survival, and proliferation of cancer cells. Through its interactions with other chemicals and signaling pathways, the MAPK/ERK pathway's activation encourages tumor development and invasion. [25]

It is claimed that lowered TROP-2 expression in FVPTC is related to their genetic profile because RAS mutation is a common event in FVPTC, resembling FTA and follicular carcinoma, which is a rare event in CVPTC. It is reported that tumors driven by RAS mutation usually respond to ERK feedback, resulting in lower MAPK signaling, the pathway involved in TROP-2 signaling. [8]

We studied the diagnostic performance of TROP-2 in thyroid lesions by comparing its expression between different studied groups and assessing its sensitivity and specificity.

In the current study, we found a statistically highly significant increase in TROP-2 expression through progression from normal thyroid tissue towards malignant lesions ($P<0.01$), as we found 7.7% positivity in benign lesions, 50% positivity in low-risk neoplasms, and 92.3% positivity in malignant lesions.

In our study, in comparing TROP-2 expression between benign lesions (TFND and FTA) and low risk neoplasms (NIFTP), we found a statistically highly significant difference ($P<0.01$), in TROP-2 expression between benign lesions and low risk neoplasms cases (7.7% and 50% positivity, respectively), with 50% sensitivity and 100% specificity for borderline lesions with diagnostic accuracy 76%. The obtained cutoff points of TROP-2 combined score using the ROC curve are equal to or greater than 1.5.

Our results were like those of Khalil et al [19], They found that, in comparison to the benign group, the sensitivity was lower

(55.5%) in the low-risk neoplasms group, but the specificity and diagnostic accuracy were 93.75% and 80%, respectively.

In this work, while comparing TROP-2 expressions between low-risk neoplasms (NIFTP) and malignant lesions, we found a highly significant statistical difference (P<0.01), in TROP-2 expressions between low-risk neoplasms and malignant cases (50% and 92.3% positivity, respectively), with 88.5% sensitivity and 100% specificity for malignant lesions. Results of the ROC curve for the TROP-2 combined score cutoffs are seven or above, and the diagnostic accuracy is 92.1%.

Our results were against the results of Khalil et al [19], By comparing the groups with PTC and low-risk neoplasms, the researchers discovered a decline in specificity (44.44%) and diagnostic accuracy (74.92%). One explanation is that the two studies used different numbers of malignant patients.

In comparing TROP-2 expression between benign lesions (TFND and FTA) and malignant tumors, we found a statistically highly]y significant difference (P<0.01), in TROP-2 expression between benign lesions and malignant cases (7.7% and 92.3% positivity, respectively), with 92.3% sensitivity and 92.3% specificity for malignant tumors with diagnostic accuracy 92.3%. Using the ROC curve, the cutoff thresholds for the TROP-2 combined score are equal to or higher than 0.5.

Our results agreed with the results of Khalil et al [19], The calculated diagnostic indices of TROP-2 positivity in all PTC cases exhibited an accuracy rate of 89.13%, a specificity rate of 93.75%, and a sensitivity rate of 86.67% when compared to groups with benign thyroid lesions.

Our study was also in line with the results of Al-Sayed et al [21] TROP-2 had an accuracy of 95.2%, a specificity of 100%, a positive predictive value of 100%, and a sensitivity of 90.5% in discriminating PTC. This result is consistent with Simms et al [18], who had a high PPV of 97.7%, 90% TROP-2 sensitivity, and 95.2% specificity. Additionally, our outcome is near that of Addati et al [24], who showed TROP-2 sensitivity of 87% and specificity of 89%.

The results show that TROP-2 is highly accurate in distinguishing between benign and malignant papillary thyroid tumors, and it is also highly sensitive to PTC. Its PPV is high.

In our present work, comparing TROP-2 expressions between malignant lesions (FV-PTC and Classic PTC cases), we found there was no statistically significant difference (P>0.05) in TROP-2 expressions between FV-PTC and classic PTC cases (84.6% and 100% positivity, respectively), with 53.8% sensitivity and 76.9% specificity with a diagnostic accuracy of 65.4%. The ROC curve yielded cutoff criteria for the TROP-2 combined score that are at least 8.5.

Our study was the same as the results of Liu et al [22], of which TROP-2's overall sensitivity was shown to be 81% for proven FVPTC and 94% for traditional PTC.

In our study regarding age, sex, lymphatic/vascular invasion, capsular infiltration, tumor size, lymph node status, and TNM stage, no clear-cut correlation between these parameters and TROP-2 positivity could be established, and our results were statistically non-significant (P>0.05).

Our results were like those of Attia et al [16], who showed there was no significant correlation between clinicopathological parameters and TROP-2 IHC expression.

Conclusion:

To help diagnose PTC and differentiate it from low-risk neoplasms (NIFTP) and its benign counterparts, TROP-2 may prove to be an extremely sensitive and specific marker. The malignant precursor nature of these lesions is suggested by the immunohistochemical profile of NIFTP for TROP-2.

Conflicts of interest:

No conflicts of interest.

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