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TROP2 IMMUNOEXPRESSION IN THYROID NEOPLASMS: DIAGNOSTIC UTILITY AND HISTOPATHOLOGICAL CORRELATION

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ABSTRACT:
Background: Thyroid neoplasms, particularly follicular-patterned lesions, show considerable morphological overlap, creating diagnostic challenges. Trophoblast cell surface antigen 2 (TROP2), a transmembrane glycoprotein, has demonstrated potential diagnostic utility in papillary thyroid carcinoma (PTC). This study evaluated TROP2 immunoexpression across malignant and borderline thyroid neoplasms and its association with histopathological subtypes in an Indian cohort.
Materials and Methods: A cross-sectional study was conducted on 70 malignant and borderline thyroid neoplasms. Representative tissue sections were subjected to TROP2 immunohistochemistry. Membranous staining in ≥5% of tumor cells was considered positive. Diagnostic performance was evaluated using PTC as the target category.
Results: Of the 70 cases, 58 (82.9%) were PTC, 3 (4.3%) noninvasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP), 5 (7.1%) follicular thyroid carcinoma, 3 (4.3%) medullary thyroid carcinoma, and 1 (1.4%) anaplastic thyroid carcinoma. TROP2 positivity was observed in 55/58 (94.8%) PTCs, including 21/23 (91.3%) follicular variant PTCs. All NIFTP and non-papillary thyroid carcinomas were negative. TROP2 expression was significantly associated with histopathological diagnosis ($P < 0.0001$). Sensitivity, specificity, positive predictive value, negative predictive value, and diagnostic accuracy for identifying PTC were 94.8%, 100%, 100%, 80.0%, and 95.7%, respectively.
Conclusion: TROP2 demonstrates predominantly positive membranous expression in PTC and may serve as a useful adjunctive immunohistochemical marker in the evaluation of diagnostically challenging thyroid lesions, particularly follicular-patterned neoplasms.

KEYWORDS: Papillary thyroid carcinoma; Thyroid neoplasms; NIFTP; Follicular variant papillary thyroid carcinoma; Immunohistochemistry; Thyroid pathology; Diagnostic marker

INTRODUCTION

There has been a rapid increase in the incidence rate of thyroid cancer in India from 2.4 to 3.9 in women and from 0.9 to 1.3 in men [1]. Although papillary thyroid carcinoma generally has an excellent prognosis, diagnostic difficulty may arise in follicular-patterned lesions, particularly when nuclear features of papillary thyroid carcinoma are subtle or incompletely represented in cytological specimens. Such diagnostic uncertainty may influence the extent of surgery and subsequent clinical management.[2]. In addition, three borderline thyroid lesions have been newly grouped under other encapsulated follicular patterned thyroid tumours by WHO. It is in these types of cases that ancillary studies, like immunohistochemistry (IHC), become useful in making accurate diagnosis. Among all the IHC markers that are available for thyroid lesions, galectin- 3, HBME-1 and CK19 are usually used. Human trophoblast cell surface antigen (TROP-2) is a novel immunomarker which has gained focus in recent times. It was initially identified in human trophoblast and choriocarcinoma cell lines and was thereafter reported to be overexpressed in a wide range of human carcinomas but seldom in normal tissues[3-5].

In recent times, TROP-2 is being studied as a prognostic marker and as an immunotherapeutic target in human cancer treatment. It is also said that TROP-2 is linked to tumor aggressiveness and poor prognosis. However, its diagnostic significance is understudied.

This study aims to evaluate the frequency and pattern of TROP2 immunoexpression in malignant and borderline thyroid neoplasms and assess its association with histopathological subtypes.

Objectives

1. To determine the frequency of TROP2 immunohistochemical expression in malignant and borderline thyroid neoplasms.
2. To assess the distribution of TROP2 expression among different histopathological subtypes of papillary thyroid carcinoma and other thyroid neoplasms.

3. To evaluate the diagnostic performance of TROP2 for identifying papillary thyroid carcinoma within the studied cohort.

Methodology: Our study was conducted on the selected cases of malignant and borderline thyroid neoplasms received in the histopathological section in the Department of Pathology, Based on the study of Rana M Khalil et al, the expected sensitivity of 86.7% was adopted, and with 95% confidence and 8% absolute precision, the calculated sample size was 69.22, rounded to 70 [6].

Inclusion Criteria:

1. Patients willing to give informed consent.
2. Malignant and other encapsulated follicular patterned thyroid tumours as per WHO classification of tumours of endocrine organs.

Exclusion Criteria:

1. Patients not willing to give informed consent.
2. All thyroid lesions other than malignant and encapsulated follicular patterned thyroid tumours.

Workflow: Sample collection began after obtaining clearance from the ethical committee. Brief clinical history of the patient including name, age, sex and complaints were noted. The specimens were received in a labelled container containing 10% formalin. The biopsies were processed in 10% formalin and paraffin embedded. 4-5-micron thick sections were cut from the paraffin blocks and then taken onto labelled slides for routine Hematoxylin and Eosin staining. Microscopic features were noted and histological typing was done according to the fifth edition of WHO classification of endocrine organs. One representative block of each lesion was subjected to IHC with TROP-2 marker. Only membranous staining with TROP-2 in atleast 5% of the cells was considered positive.

Categorical variables were summarized using frequencies and percentages. The association between TROP2 expression and histopathological diagnosis was assessed using Fisher's exact test because several diagnostic subgroups contained small numbers of cases.

For diagnostic-performance analysis, papillary thyroid carcinoma was considered the target diagnostic category and all other included neoplasms were considered the comparator group. Sensitivity, specificity, positive predictive value, negative predictive value, and diagnostic accuracy were calculated from the resulting 2 × 2 contingency table. A two-sided P value <0.05 was considered statistically significant.

RESULTS

Demographic and Clinical Features: The cohort comprised 61 females (87.1%) and 9 males (12.9%). The largest proportion of cases occurred in the 20–49-year age range.

Papillary thyroid carcinoma constituted the majority of the study population, accounting for 58 of 70 cases (82.9%). The PTC group comprised 29 classic PTCs, 23 follicular variant PTCs, 3 micropapillary PTCs, 1 hobnail variant, 1 trabecular variant, and 1 mixed variant. The remaining 12 cases comprised 3 NIFTP, 5 follicular thyroid carcinomas, 3 medullary thyroid carcinomas, and 1 anaplastic thyroid carcinoma.

Trop2 Expression In The Cases Studied (Table 1):

Overall, TROP2 expression was observed in 55 of 70 cases (78.6%).

Among the 58 PTC cases, 55 demonstrated TROP2 expression, corresponding to a positivity rate of 94.8%.

All cases of classic PTC (29/29), micropapillary PTC (3/3), hobnail PTC (1/1), and mixed-variant PTC (1/1) demonstrated TROP2 positivity.

TROP2 expression was observed in 21 of 23 FVPTC cases (91.3%). Two FVPTC cases were negative.

The single case of trabecular variant PTC was TROP2-negative.

All three NIFTP cases were TROP2-negative. Similarly, all five FTC cases, three MTC cases, and the single ATC case were TROP2-negative.

Table 1: Trop2 expression in the cases studied

HISTOPATHOLOGICAL DIAGNOSIS	TOTAL NUMBER OF CASES	CASES POSITIVE FOR TROP2 (%) (Fig. 1-8)
NIFTP	03	00 (0)
MiPTC	03	03 (100)
cPTC	29	29 (100)
FVPTC	23	21 (91.3)
PTC-HOBNAIL	01	01 (100)
PTC-TRABECULAR VARIANT	01	00 (0)
PTC-MIXED VARIANT	01	01 (100)

FTC	05	00 (0)
MTC	03	00 (0)
ATC	01	00 (0)
TOTAL	70	55 (78.6)

Association With Histopathological Diagnosis:
The observed distribution was characterized by predominantly positive TROP2 expression in PTC and absence of membranous staining in the non-PTC neoplasms included in the cohort.
A statistically significant association was observed between PTC status and TROP2 expression (two-sided Fisher's exact test, $P < 0.0001$). TROP2 expression was observed in 55 of 58 PTCs (94.8%), whereas all 12 non-PTC neoplasms were negative.

Diagnostic Performance Of Trop2 For Papillary Thyroid Carcinoma:
For diagnostic-performance analysis, 58 PTCs were classified as the target disease group and the remaining 12 cases (NIFTP, FTC, MTC, and ATC) were classified as the comparator group.
The diagnostic performance was:

- Sensitivity: 55/58 = 94.8%
- Specificity: 12/12 = 100.0%
- Positive predictive value: 55/55 = 100.0%
- Negative predictive value: 12/15 = 80.0%
- Diagnostic accuracy: 67/70 = 95.7% within the studied cohort

DISCUSSION:
The present study evaluated TROP2 immunohistochemical expression across a spectrum of malignant and borderline thyroid neoplasms. TROP2 was expressed in 78.6% of all cases and in 94.8% of PTCs. The highest proportion of positivity was observed in classic PTC, micropapillary PTC, hobnail PTC, and mixed-variant PTC, whereas 91.3% of FVPTCs were positive. All NIFTP, FTC, MTC, and ATC cases included in the study were negative.
The findings support the previously described association between membranous TROP2 expression and PTC. Simms et al. demonstrated TROP2 positivity in 61 of 64 classic PTC cytology cell blocks and 7 of 10 FVPTC cell blocks, while other thyroid lesions in their cytology cohort were negative. Their study used membranous staining involving more than 5% of tumor cells as the positivity threshold, similar to the criterion used in the present study.
Bychkov et al. evaluated a substantially larger cohort comprising 226 thyroid tumors and 207 controls [7]. TROP2 was expressed in 94 of 114 PTCs (82.5%), and classic PTC, micropapillary PTC, and tall-cell PTC showed particularly high expression. FVPTC demonstrated considerably lower positivity. Importantly, their study found that TROP2 expression varied according to PTC subtype, supporting the concept that the biological and diagnostic utility of TROP2 may not be uniform across all PTC variants.
The overall PTC positivity rate in the present study was higher than that reported by Bychkov et al [7]. This difference may partly reflect differences in case composition, particularly the predominance of classic PTC and the relatively small number of less commonly encountered variants in the present cohort. Differences in antibody clone, staining methodology, positivity threshold, and scoring method may also contribute to variation between studies.
The study by Simms et al. similarly demonstrated high TROP2 sensitivity for classic PTC and reported that membranous TROP2 staining could help distinguish PTC from benign thyroid nodules [8]. However, unlike that study, the present cohort did not include a benign thyroid control group. Therefore, the current findings cannot establish the ability of TROP2 to distinguish PTC from benign thyroid lesions.
A larger study by Turan and Erkılıç involving 308 thyroid cases further demonstrated substantial heterogeneity of TROP2 expression among PTC variants [9]. Classic PTC showed 100% positivity, while follicular, solid, hobnail, Warthin-like, columnar, and oncocytic variants showed variable rates of expression. Most non-PTC neoplasms and benign/non-neoplastic lesions were negative. These findings are broadly consistent with the present observation of high expression in classic PTC and variable expression in PTC variants.
The FVPTC findings in the present study are of particular interest. TROP2 was positive in 21 of 23 FVPTCs (91.3%), while all three NIFTP cases were negative. FVPTC and NIFTP may present diagnostic challenges because both belong to the spectrum of follicular-patterned thyroid tumors and may show overlapping nuclear features. However, the number of NIFTP cases in the present study is very small. Therefore, the observed difference should be regarded as a preliminary finding rather than evidence that TROP2 can reliably distinguish FVPTC from NIFTP.
The 2016 study by Bychkov et al. found considerably lower TROP2 positivity among FVPTCs and demonstrated that the staining pattern differed between PTC variants[7]. They also reported an association between TROP2 H-score and capsular invasion in encapsulated FVPTC. This difference from the present study emphasizes the need for larger cohorts and standardized scoring methods before TROP2 can be recommended as a definitive marker for follicular-patterned thyroid tumors.
More recent evidence continues to support TROP2 as a potential diagnostic adjunct. A 2022 study of 308 thyroid neoplasms reported predominantly negative staining in benign lesions and most non-PTC neoplasms, with variable but often high expression across several PTC variants. In 2026, Elmetwally et al. evaluated 144 thyroid lesions and reported

TROP2 positivity in 82.3% of PTCs compared with 7.7% of other thyroid lesions[10]. These findings further support the association between TROP2 and PTC but also demonstrate that TROP2 is not uniformly expressed across all thyroid carcinomas.

The absence of TROP2 expression in the five FTCs, three MTCs, and one ATC in the present study is consistent with previous reports showing predominantly negative TROP2 expression in several non-PTC thyroid neoplasms. However, the small sample sizes of these subgroups preclude reliable estimation of sensitivity or specificity for individual tumor types.

The single hobnail PTC in the present study showed TROP2 positivity. Although the hobnail variant is recognized as a morphologically and clinically distinctive PTC subtype, a single case is insufficient to establish an association between TROP2 expression and aggressive behavior. Similarly, the single trabecular and mixed PTC cases should be interpreted descriptively.

Although TROP2 has been associated with tumor progression and aggressive behavior in several epithelial malignancies, the present study did not evaluate tumor recurrence, metastasis, survival, or treatment response. Consequently, the present findings cannot establish a prognostic role for TROP2 in thyroid carcinoma. Likewise, the potential therapeutic implications of TROP2 expression require independent investigation and should not be inferred from immunohistochemical expression alone.

The diagnostic-performance analysis in the present study demonstrated a sensitivity of 94.8%, specificity of 100%, positive predictive value of 100%, negative predictive value of 80%, and accuracy of 95.7% when PTC was considered the target diagnostic category and the other included neoplasms were considered the comparator group. These figures should be interpreted cautiously because the comparator group was composed of selected neoplastic and borderline lesions rather than a representative spectrum of thyroid disease. In particular, benign thyroid lesions were not included.

Therefore, the principal implication of the present study is not that TROP2 can independently diagnose thyroid malignancy. Rather, the findings suggest that TROP2 may provide useful adjunctive information when evaluating selected morphologically challenging thyroid neoplasms, particularly within the spectrum of PTC and follicular-patterned lesions.

CONCLUSION

TROP2 immunohistochemical expression was predominantly observed in papillary thyroid carcinoma in the present cohort. TROP2 was positive in 55 of 58 PTCs (94.8%), including all classic PTC, micropapillary PTC, hobnail PTC, and mixed-variant cases, and 21 of 23 FVPTCs (91.3%). In contrast, all NIFTP, FTC, MTC, and ATC cases included in the study were negative.

These findings support the potential role of membranous TROP2 expression as an adjunctive immunohistochemical marker in the evaluation of selected thyroid neoplasms. The observed difference between FVPTC and NIFTP is potentially relevant but requires confirmation because of the small number of NIFTP cases. TROP2 should not currently be regarded as an independent diagnostic or prognostic marker on the basis of this study alone.

Larger multicentric studies incorporating benign thyroid lesions, a greater number of borderline and uncommon PTC variants, standardized immunohistochemical scoring, and clinical follow-up are required to establish the diagnostic and potential prognostic significance of TROP2 in thyroid neoplasia.

LIMITATIONS:

First, the sample size was relatively small, and several histological subtypes were represented by only one to three cases. Therefore, the apparent 100% positivity or negativity in these rare subtypes should not be interpreted as definitive evidence of subtype-specific TROP2 expression.

Second, the study was cross-sectional and did not include longitudinal follow-up. Therefore, no conclusions regarding the prognostic significance of TROP2 expression, recurrence, metastasis, survival, or treatment response can be drawn.

Third, TROP2 expression was assessed using a binary membranous-staining threshold of 5%. Differences in antibody clones, staining platforms, scoring systems, and positivity thresholds across published studies may contribute to differences in reported expression rates.

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Author approval: All authors have read and approved the final manuscript and agree to its submission for publication. All authors meet the authorship criteria and believe that the manuscript represents honest and accurate work.

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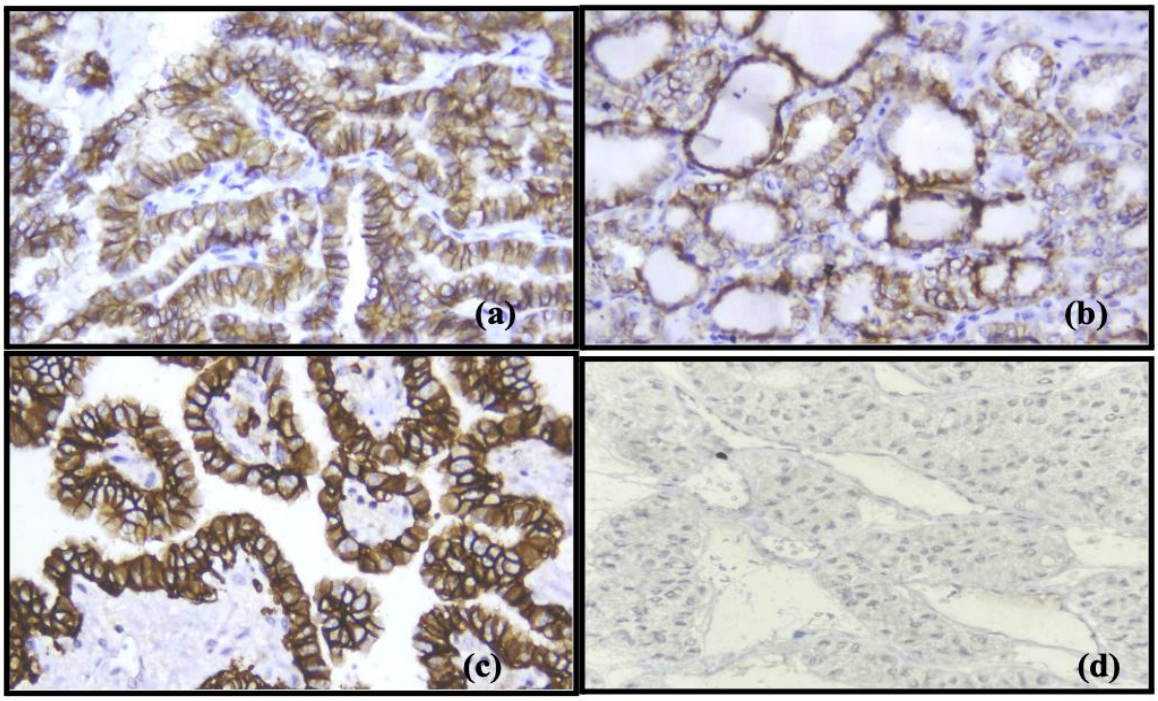

Fig. 1: (a) Representative IHC staining of TROP2 in cPTC showing diffuse positive membranous expression in tumor cells (IHC, ×400). (b) Representative IHC staining of TROP2 in FVPTC showing diffuse positive membranous expression in tumor cells (IHC, ×400). (c) Representative immunohistochemical staining of TROP2 in the hobnail variant of papillary thyroid carcinoma (PTC) showing strong, diffuse membranous positivity in tumor cells at high magnification (IHC, ×400). (d) Representative IHC staining of TROP2 in the trabecular variant of PTC showing negative expression, with an absence of membranous staining in tumor cells (IHC, ×400).

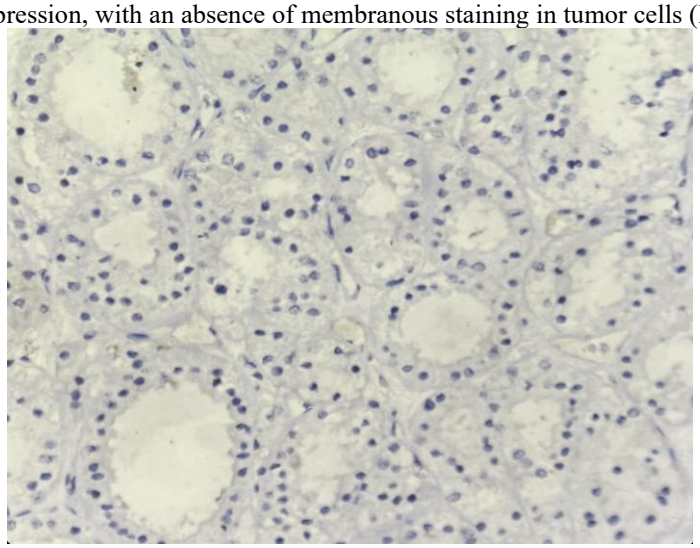

Fig. 2: Representative immunohistochemical staining of TROP2 in follicular thyroid carcinoma showing negative expression (IHC, ×400).

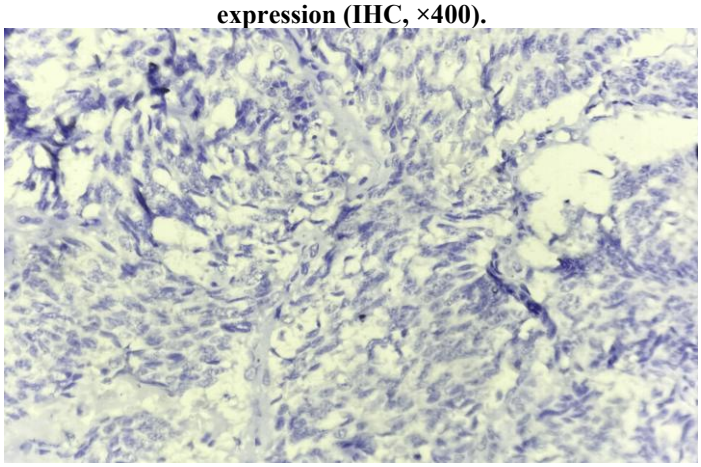

Fig. 3: Representative immunohistochemical staining of TROP2 in medullary thyroid carcinoma showing negative expression (IHC, ×400).

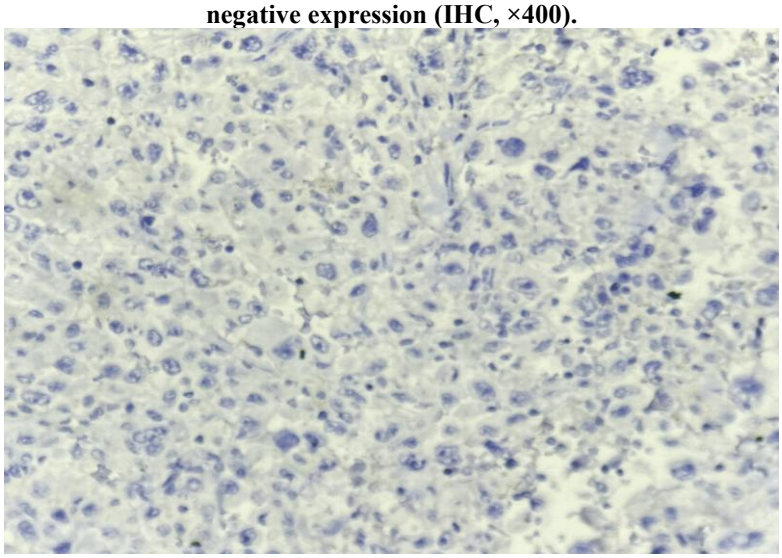

Fig. 4: Representative immunohistochemical staining of TROP2 in anaplastic thyroid carcinoma showing negative expression (IHC, ×400).