

# *TROP-2* Immunohistochemistry as a Diagnostic Adjunct in Follicular-Patterned Thyroid Neoplasms: A Comparative Study of 100 Cases

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## Abstract

**Introduction:** In routine histopathological practice, thyroid neoplasms showing a follicular growth pattern often present diagnostic difficulty due to the overlapping morphological features of follicular adenoma, follicular carcinoma, and the follicular variant of papillary thyroid carcinoma. Trophoblast Cell Surface Antigen-2 (*TROP-2*), a transmembrane glycoprotein implicated in tumor proliferation and progression, has emerged as a potential adjunct immunohistochemical marker. This study aimed to evaluate and compare *TROP-2* expression in benign and malignant thyroid neoplasms. **Methods:** A cross-sectional analytical study was performed on 100 formalin-fixed, paraffin-embedded thyroid neoplasms specimens, consisting of 25 cases each of follicular adenoma (FA), follicular thyroid carcinoma (FTC), follicular variant papillary thyroid carcinoma (FVPTC), and papillary thyroid carcinoma (PTC). Immunohistochemical staining was performed using a rabbit monoclonal anti-*TROP-2* antibody (clone MSVA-733R, GeneTex, GTX04443; dilution 1:200), and expression was evaluated semi-quantitatively using the H-score method (range 0–300), which incorporates both staining intensity and percentage of positive tumor cells. Statistical analysis was performed using the Kruskal–Wallis test followed by the Mann–Whitney test where appropriate, with  $p \leq 0.05$  considered statistically significant. **Results:** *TROP-2* expression differed significantly among the four groups ( $p = 0.001$ ). Mean H-scores were lowest in FA ( $57.40 \pm 29.97$ ) and progressively increased in FTC ( $142.16 \pm 26.76$ ), FVPTC ( $182.80 \pm 38.41$ ), and PTC ( $258.00 \pm 20.92$ ). A significant stepwise increase in H-scores was observed across the groups (FA < FTC < FVPTC < PTC), with the highest expression observed in classic PTC. **Conclusion:** *TROP-2* expression is significantly elevated in malignant thyroid neoplasms and may serve as a useful adjunct immunohistochemical marker in the evaluation of follicular-patterned thyroid lesions.

**Keywords:** *TROP-2*, thyroid neoplasms, follicular adenoma, papillary thyroid carcinoma, immunohistochemistry

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## Introduction

Thyroid cancer is among the most common endocrine malignancies encountered in clinical practice, and its incidence has shown a consistent increase over recent decades in many parts of the world. Recent global epidemiological data indicate that thyroid cancer ranks among the most prevalent malignancies worldwide, with the number of newly diagnosed cases continuing

to increase annually [1]. A similar upward trend has also been observed in Indonesia, where thyroid cancer has emerged as a growing public health concern, contributing substantially to the national cancer burden [2].

The majority of thyroid malignancies arise from follicular epithelial cells, with papillary thyroid carcinoma (PTC) accounting for approximately 80–90% of all

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cases [3,4]. Classic *PTC* is generally straightforward to diagnose due to its distinctive papillary architecture and characteristic nuclear features. However, the follicular variant of papillary thyroid carcinoma (*FVPTC*) remains diagnostically challenging. *FVPTC* exhibits a predominantly follicular growth pattern that closely resembles follicular adenoma (*FA*) and follicular thyroid carcinoma (*FTC*), leading to potential overlap in histomorphological appearance [5,6]. In the absence of well-formed papillary structures and when nuclear features are subtle or borderline, establishing a definitive diagnosis can be particularly challenging. It is precisely in these equivocal scenarios that adjunct immunohistochemical markers may provide valuable supportive information to assist morphologic interpretation [7,8].

In recent years, advances in molecular and immunohistochemical biomarkers have aimed to improve diagnostic precision in thyroid neoplasms, particularly in lesions with a follicular growth pattern [9,10]. One biomarker that has recently attracted considerable interest in thyroid pathology is trophoblast cell surface antigen 2 (*TROP-2*), a transmembrane glycoprotein that plays a role in epithelial cell proliferation, migration, and invasive behavior [11–13]. Initially identified in trophoblastic tissue, *TROP-2* has since been recognized as being overexpressed in various epithelial malignancies, while its expression in normal tissues remains limited [14,15].

Several studies have reported that increased *TROP-2* expression is associated with more aggressive tumor characteristics, including higher proliferative activity, enhanced invasiveness, and less favorable clinical outcomes in a variety of epithelial malignancies [15,16]. In thyroid neoplasms, previous studies have reported higher *TROP-2* expression in papillary thyroid carcinoma compared to benign follicular lesions and other follicular-derived tumors, indicating its potential role as an adjunct immunohistochemical marker, particularly in cases with overlapping or equivocal morphological features [17–19].

Despite the growing body of literature on *TROP-2* in thyroid pathology, several aspects remain inadequately explored. Most previous studies have primarily focused on distinguishing papillary thyroid carcinoma from benign lesions, with limited evaluation across the full spectrum of follicular-patterned thyroid neoplasms. In particular, comparative analyses involving balanced representation of follicular adenoma, follicular carcinoma, and follicular variant papillary thyroid carcinoma remain relatively scarce. Furthermore, data from Southeast Asian populations remain limited. Differences in genetic background, including reported geographic variation in driver mutations such as *BRAF* and *RAS*, as well as environmental and healthcare-related factors, may influence tumor biology and downstream biomarker expression patterns. Therefore, additional studies are warranted to better clarify the expression profile of *TROP-2* across different follicular-derived thyroid neoplasms within diverse populations.

In light of these considerations, the present study aims to evaluate and compare the immunohistochemical expression of *TROP-2* in benign and malignant thyroid

neoplasms, specifically follicular adenoma, follicular thyroid carcinoma, follicular variant papillary thyroid carcinoma, and classic papillary thyroid carcinoma. By analyzing the expression pattern across these entities, this study seeks to further elucidate the potential role of *TROP-2* as an adjunct marker in the evaluation of follicular-patterned thyroid lesions encountered in routine histopathological practice.

## Materials and Methods

This study was designed as an observational analytical study using a cross-sectional approach to evaluate *TROP-2* expression in thyroid neoplasms. The research was conducted from November 2025 to January 2026 at Sentra Diagnostik Patologi Makassar, in collaboration with the Department of Anatomical Pathology, Hasanuddin University Hospital and Dr. Wahidin Sudirohusodo Hospital, Makassar, Indonesia. The study population consisted of archived formalin-fixed, paraffin-embedded (FFPE) thyroid tissue specimens diagnosed histopathologically between January 2024 and December 2025 as follicular adenoma (*FA*), follicular thyroid carcinoma (*FTC*), follicular variant papillary thyroid carcinoma (*FVPTC*), and papillary thyroid carcinoma (*PTC*).

A total of 100 cases were included using a consecutive sampling method, comprising 25 cases in each diagnostic category. Inclusion criteria were: (1) Histopathologically confirmed diagnosis of *FA*, *FTC*, *FVPTC*, or *PTC* based on hematoxylin–eosin (H&E) examination. (2) Availability of adequate FFPE tissue blocks for immunohistochemical analysis. Exclusion criteria included incomplete clinical or pathological data and damaged or insufficient paraffin blocks unsuitable for further processing. Archived H&E slides were reviewed to confirm the diagnosis prior to immunohistochemical staining. Tissue sections of 3–4  $\mu\text{m}$  thickness were prepared from selected paraffin blocks.

### Immunohistochemical Staining

Immunohistochemical staining was performed on 3–4  $\mu\text{m}$  sections obtained from formalin-fixed, paraffin-embedded thyroid tissue blocks. A rabbit monoclonal anti-*TROP-2* primary antibody (clone MSVA-733R, GeneTex, GTX04443) was applied at a dilution of 1:200 in accordance with the manufacturer's instructions. Sections were first deparaffinized in xylene and rehydrated through graded ethanol solutions. Antigen retrieval was carried out using heat-induced epitope retrieval as recommended by the detection system protocol. Endogenous peroxidase activity was blocked prior to incubation with the primary antibody to reduce non-specific staining. The slides were subsequently incubated with the primary antibody, followed by application of a secondary antibody and chromogenic detection using diaminobenzidine (DAB), which produced a brown reaction product at sites of antigen expression. The sections were counterstained with hematoxylin and mounted for evaluation. A previously confirmed *TROP-2*-positive triple-negative breast carcinoma of no special type (NST) specimen was used

as a positive control. For negative control, the primary antibody was omitted and replaced with non-immune serum.

*TROP-2* expression was considered positive when distinct membranous and/or cytoplasmic brown staining was observed in tumor cells. All slides were examined independently under light microscopy at 400× magnification using an Olympus CX-43 microscope.

#### Evaluation of *TROP-2* Expression

*TROP-2* expression was assessed semi-quantitatively using the Histochemical Score (H-score) system, with a total score ranging from 0 to 300. The H-score was calculated by multiplying the percentage of positively stained tumor cells by the corresponding staining intensity. Staining intensity was categorized as follows: 0 (no staining), 1+ (weak), 2+ (moderate), and 3+ (strong). The proportion of positive tumor cells was estimated as a percentage of the total tumor cell population observed in representative high-power fields. Membranous and/or cytoplasmic staining was considered in the assessment. All slides were independently evaluated by two observers, including a board-certified anatomical pathologist, who were blinded to the original histopathological diagnosis at the time of scoring. The level of agreement between observers was high, and discrepancies were infrequent and resolved through joint review to achieve consensus.

#### Statistical Analysis

Data were analyzed using SPSS version 30. Descriptive statistics were presented as mean ± standard deviation (SD), median, minimum, and maximum values. Comparisons among the four groups were performed using the Kruskal–Wallis test. Pairwise comparisons were conducted using the Mann–Whitney U test when indicated. A  $p$ -value  $\leq 0.05$  was considered statistically significant.

## Results

#### Clinicopathological Distribution

A total of 100 thyroid neoplasms cases were included in this study, with balanced representation across the four diagnostic categories. Each group consisted of 25 cases: follicular adenoma (*FA*), follicular thyroid carcinoma (*FTC*), follicular variant papillary thyroid carcinoma (*FVPTC*), and papillary thyroid carcinoma (*PTC*). All cases were confirmed through histopathological review prior to immunohistochemical analysis. Figure 1 displays representative staining patterns by intensity in thyroid neoplasms.

#### *TROP-2* Expression Across Thyroid Neoplasms

Overall comparison using the Kruskal–Wallis test demonstrated a statistically significant difference in *TROP-2* expression among the four diagnostic groups ( $p = 0.001$ ). Mean H-scores showed a progressive increase from benign to malignant lesions, with values of  $57.40 \pm 29.97$  for *FA*,  $142.16 \pm 26.76$  for *FTC*,  $182.80 \pm 38.41$  for *FVPTC*, and  $258.00 \pm 20.92$  for *PTC* (Table 1).

When *FA* was compared with malignant groups, marked differences were observed. The *FA* group had a median H-score of 60.00 (range 0.00–95.00), whereas *FTC*

Table 1. Analysis of the Differences between *TROP-2* IHC Score and Histopathological Feature Groups

| H-Score of<br><i>TROP-2</i> | Histopathology Features |            |              |            | Overall<br>p-value |
|-----------------------------|-------------------------|------------|--------------|------------|--------------------|
|                             | <i>FA</i>               | <i>FTC</i> | <i>FVPTC</i> | <i>PTC</i> |                    |
| Mean                        | 57.4                    | 142.16     | 182.8        | 258        | 0.001              |
| SD                          | 29.97                   | 26.76      | 38.41        | 20.92      |                    |
| Median                      | 60                      | 130        | 170          | 265        |                    |
| Minimum                     | 0                       | 100        | 130          | 210        |                    |
| Maximum                     | 95                      | 190        | 250          | 290        |                    |

Note. Mann–Whitney  $P=0.001$  ( $P<0.05$ ); *FA*, Follicular Adenoma; *FTC*, Follicular Thyroid Carcinoma; *FVPTC*, Follicular Variant of Papillary Thyroid Carcinoma; *PTC*, Papillary Thyroid Carcinoma

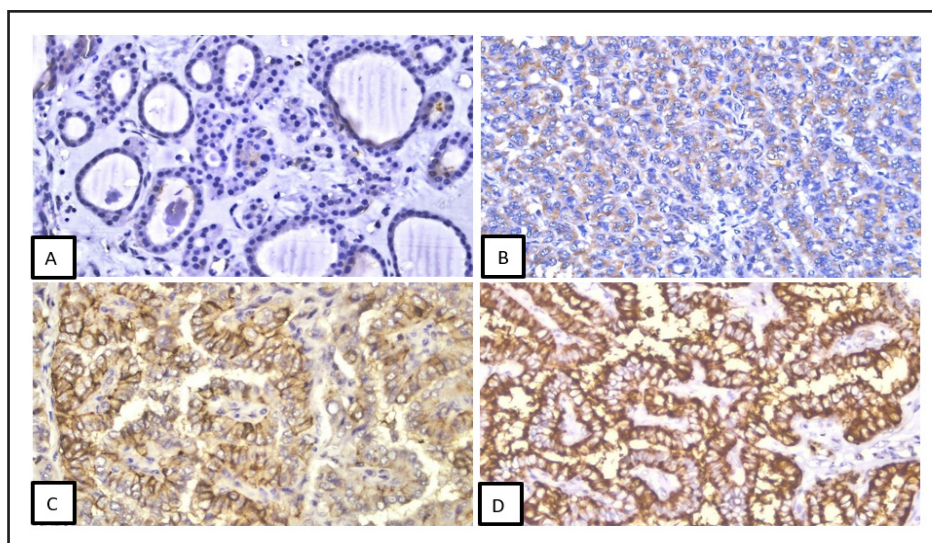


Figure 1. Representative *TROP-2* Expression in Thyroid Neoplasms. A) shows negative expression in *FA*, while B) exhibits weak expression in *FTC*; C) demonstrates moderate expression in *FVPTC*, and D) shows strong expression in conventional *PTC* (Objective 40×; Olympus CX-43)

Table 2. Comparative Study of *TROP-2* Expression Scores between Histopathological Feature Groups

| No | Comparative groups | p-value |
|----|--------------------|---------|
| 1  | FA vs FTC          | 0.001   |
| 2  | FA vs FVPTC        | 0.001   |
| 3  | FA vs PTC          | 0.001   |
| 4  | FTC vs FVPTC       | 0.001   |
| 5  | FTC vs PTC         | 0.001   |
| 6  | FVPTC vs PTS       | 0.001   |

Note. Mann–Whitney  $P=0.001$  ( $P<0.05$ ); FA, Follicular Adenoma; FTC, Follicular Thyroid Carcinoma; FVPTC, Follicular Variant of Papillary Thyroid Carcinoma; PTC, Papillary Thyroid Carcinoma

demonstrated a median of 130.00 (range 100.00–190.00), FVPTC a median of 170.00 (range 130.00–250.00), and PTC a median of 265.00 (range 210.00–290.00). All pairwise comparisons between FA and each malignant group were statistically significant (Mann–Whitney test,  $p = 0.001$ ) (Table 2).

Notably, no overlap in H-score distribution was observed between FA and PTC. The lowest value recorded in PTC (210.00) exceeded the highest value observed in FA (95.00). Similarly, the minimum values in FVPTC (130.00) and FTC (100.00) were substantially higher than the median value of FA. Among malignant lesions, further significant differences were identified. FVPTC demonstrated higher expression than FTC ( $p = 0.001$ ), and PTC exhibited significantly greater expression than both FTC and FVPTC ( $p = 0.001$ ). While limited overlap was present between FTC and FVPTC, *TROP-2* staining intensity and extent were generally more pronounced in FVPTC and most prominent in PTC.

Overall, *TROP-2* expression demonstrated a clear stepwise increase across the spectrum of thyroid neoplasms, from benign follicular adenoma to papillary thyroid carcinoma.

## Discussion

In this study, *TROP-2* expression showed a gradual increase across the spectrum of thyroid neoplasms, with the lowest levels observed in follicular adenoma and the highest in papillary thyroid carcinoma. The stepwise pattern observed in this cohort suggests an association between *TROP-2* expression and histological progression across thyroid neoplasms, although the present design does not permit conclusions regarding causality. This observation is consistent with prior reports describing increased *TROP-2* expression in papillary thyroid carcinoma compared with benign follicular lesions.

The marked difference observed between follicular adenoma and malignant counterparts, particularly FTC, FVPTC, and PTC, reinforces the potential diagnostic relevance of this marker. These findings are consistent with previous studies reporting minimal or absent *TROP-2* expression in benign follicular lesions and significantly elevated expression in papillary thyroid carcinoma [17–19]. Liu et al. demonstrated that *TROP-2* expression was highly prevalent in PTC, while rarely

detected in follicular adenomas [18]. Similarly, Bychkov et al. reported high sensitivity and specificity of *TROP-2* in distinguishing papillary carcinoma from benign follicular lesions [17].

The progressive increase in H-score values observed in this study from FA to FTC, FVPTC, and ultimately PTC may reflect the biological role of *TROP-2* in tumor progression. The observed increase in *TROP-2* expression in malignant tumors may be related to its role in signaling pathways that regulate cellular proliferation, migration, and invasion, particularly those involving the MAPK and PI3K/AKT cascades [11–13]. These pathways are also implicated in thyroid carcinogenesis, particularly in tumors driven by *BRAF* and *RAS* alterations [3, 4]. The highest expression detected in classic PTC aligns with its molecular profile, which is frequently characterized by MAPK pathway activation [3].

Notably, FVPTC exhibited intermediate expression levels between FTC and PTC. This observation may correspond to its biological position between purely follicular tumors and classic papillary carcinoma. Previous literature has emphasized the molecular heterogeneity of FVPTC, with some tumors demonstrating *RAS*-like features and others exhibiting *BRAF*-like profiles [5, 20]. The relatively higher *TROP-2* expression in FVPTC compared to FTC in our cohort may reflect this biological complexity.

From a practical diagnostic perspective, the minimal overlap in H-score distribution between follicular adenoma and papillary thyroid carcinoma suggests potential utility in a supportive diagnostic algorithm. In this cohort, markedly elevated H-scores, particularly those exceeding 200, were observed exclusively in papillary thyroid carcinoma, whereas low scores were characteristic of benign lesions. These findings are consistent with prior reports demonstrating strong *TROP-2* expression in papillary thyroid carcinoma and minimal expression in benign follicular lesions [17–19]. Although formal cut-off analysis was not performed, these observations suggest that high expression levels may favor a diagnosis of PTC over FA in morphologically equivocal cases. The clinical usefulness of *TROP-2* in this setting relates to its contribution to diagnostic interpretation alongside established histopathological criteria and current classification frameworks [8, 9].

Beyond its diagnostic implications, *TROP-2* has emerged as a therapeutic target in several epithelial malignancies [11, 12, 15]. The development of antibody–drug conjugates such as Sacituzumab govitecan has demonstrated the translational potential of *TROP-2*–directed therapies in solid tumors [11, 15]. The strong and consistent expression observed in papillary thyroid carcinoma in this cohort is noteworthy, particularly given that differentiated thyroid cancers are generally less responsive to conventional cytotoxic chemotherapy [7]. Given the established role of *TROP-2* in pathways regulating cellular proliferation and survival, including MAPK and PI3K/AKT signaling [12,13], it is reasonable to consider whether *TROP-2*–directed strategies might have relevance in selected thyroid carcinoma subsets,

especially in radioiodine-refractory or aggressive variants. Nevertheless, such therapeutic considerations remain speculative and would require dedicated translational and clinical investigation.

This study has several limitations. Molecular analysis was not performed to correlate *TROP-2* expression with specific genetic alterations such as *BRAF* or *RAS* mutations, which are known to influence signaling pathways central to thyroid carcinogenesis [3, 4]. Additionally, clinicopathological parameters including tumor size, extrathyroidal extension, lymph node involvement, and other high-risk histologic features were not evaluated, precluding assessment of its potential prognostic significance within established risk stratification systems [7, 8]. Although the H-score method is widely used in immunohistochemical studies, its semi-quantitative nature introduces a degree of subjectivity despite independent blinded evaluation and consensus review. The absence of longitudinal clinical follow-up further limits conclusions regarding survival or predictive implications. Future investigations that incorporate molecular profiling, detailed clinicopathological correlation, and digital image analysis would help clarify the biological and clinical relevance of *TROP-2* expression in thyroid neoplasms.

In conclusion, the findings of this study indicate that *TROP-2* expression is markedly higher in malignant thyroid neoplasms than in benign follicular adenoma, with the highest levels observed in papillary thyroid carcinoma. A progressive increase in H-score values was evident across the spectrum of lesions, from follicular adenoma to follicular thyroid carcinoma, follicular variant papillary thyroid carcinoma, and papillary thyroid carcinoma, suggesting an association between *TROP-2* expression and malignant progression. The minimal overlap in expression between benign and malignant entities, particularly the complete separation observed between follicular adenoma and papillary thyroid carcinoma, underscores the potential adjunctive diagnostic value of *TROP-2* in the evaluation of follicular-patterned thyroid lesions. While *TROP-2* cannot replace conventional histopathological evaluation, it represents a promising adjunctive marker that, with further validation, may be incorporated into diagnostic workflows for challenging follicular-patterned thyroid lesions. Further investigations incorporating molecular profiling and longitudinal clinical follow-up are necessary to clarify the biological significance and possible therapeutic implications of *TROP-2* expression in thyroid neoplasia.

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## Declaration on generative AI and AI-assisted technologies in the writing process

The authors affirm that no generative AI or AI-assisted technologies were used in the preparation of this manuscript; all writing, analysis, and revisions were performed by the authors.

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## Conflict of Interest/Competing interests

The authors declare no conflicts of interest.

## Author Contributor

All authors contributed equally to the article's conception, design, analysis, writing, and editing.

## Ethical Approval

The research has obtained ethical approval and was conducted in accordance with the Declaration of Helsinki. The confidentiality of the research data was guaranteed, and the research procedures and protocols were approved by the Health Research Ethics Commission of the Faculty of Medicine, Hasanuddin University, Makassar, Indonesia (Approval Number: Protocol # UH25090762 – Registry 1013/UN4.6.4.5.31/ PP36/2025).

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