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Association of TROP-2 expression with clinicopathological features in papillary thyroid carcinoma

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Abstract

Background: Papillary thyroid carcinoma (PTC) is the most common endocrine malignancy, with increasing global incidence. Although most cases have favorable outcomes, some tumors exhibit aggressive clinicopathological features associated with recurrence and disease progression. Trophoblast cell surface antigen-2 (TROP-2), a transmembrane glycoprotein involved in MAPK and PI3K/AKT signaling pathways, has emerged as a potential biomarker in various malignancies. However, its clinicopathological significance in PTC remains unclear.

Objective: To evaluate the association between TROP-2 expression and clinicopathological features of papillary thyroid carcinoma.

Methods: A retrospective cross-sectional study was conducted involving 30 histologically confirmed PTC cases from thyroidectomy specimens at Dr. Soetomo General Hospital, Surabaya, Indonesia, collected between January 2022 and December 2024. TROP-2 expression was assessed by immunohistochemistry using a semi-quantitative H-score. Associations between TROP-2 expression and clinicopathological features were analyzed using non-parametric statistical tests.

Results: Membranous TROP-2 expression was observed in all PTC cases. No significant association was observed between TROP-2 H-score and pT stage ($\rho = -0.061$, $p = 0.750$), nodal status ($\rho = 0.050$, $p = 0.794$), age ($\rho = 0.256$, $p = 0.171$), sex ($p = 0.491$), or multifocality ($p = 0.769$).

Conclusion: TROP-2 was consistently expressed in papillary thyroid carcinoma; however, its expression level was not associated with clinicopathological features related to tumor aggressiveness. These findings suggest that TROP-2 may represent a molecular feature of PTC rather than an independent indicator of aggressive tumor behavior. Further studies incorporating molecular profiling and long-term clinical outcomes are required to clarify its prognostic significance.

Keywords: Papillary Thyroid Carcinoma; Trop-2; Immunohistochemistry; Clinicopathological Features.

1. Introduction

Thyroid carcinoma is the most common malignancy of the endocrine system. Papillary thyroid carcinoma (PTC) represents approximately 80–90% of thyroid carcinoma cases. According to the Global Cancer Observatory (GLOBOCAN) 2022, thyroid carcinoma was the seventh most commonly diagnosed cancer worldwide, with 821,214 new cases, and the highest incidence was reported in Asia (1,2).

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PTC generally has a favorable prognosis, with a 10-year disease-specific survival rate of approximately 90% (3,4). However, its biological behavior is heterogeneous, and some patients develop aggressive features such as locoregional recurrence and cervical lymph node metastasis. These variations highlight the importance of identifying biomarkers that can provide additional information regarding tumor biological behavior and risk stratification (3–5).

Trophoblast cell surface antigen-2 (TROP-2) is a transmembrane glycoprotein that functions as an oncogenic cell surface receptor involved in tumor cell proliferation, migration, invasion, and epithelial–mesenchymal transition. TROP-2 regulates tumor progression through several signaling pathways, particularly MAPK and PI3K/AKT pathways, which promote cellular proliferation and survival (6–8). Increased TROP-2 expression has been reported in various epithelial malignancies and has been associated with aggressive clinicopathological features and unfavorable outcomes (9).

Previous studies have demonstrated TROP-2 expression in PTC, mainly focusing on its potential diagnostic role in distinguishing PTC from benign thyroid lesions. However, the association between TROP-2 expression and clinicopathological features of PTC remains unclear. Therefore, this study aimed to evaluate the relationship between TROP-2 expression and clinicopathological features of PTC to determine its potential role as a biomarker reflecting tumor biological behavior.

2. Material and methods

This retrospective cross-sectional study was conducted at the Department of Anatomical Pathology, Dr. Soetomo General Hospital, Surabaya, Indonesia. The study included 30 papillary thyroid carcinoma (PTC) cases from thyroidectomy specimens collected between January 2022 and December 2024. Samples were selected using a purposive sampling technique based on the following criteria: formalin-fixed, paraffin-embedded (FFPE) tissue blocks with confirmed histopathological diagnosis of PTC, adequate tissue preservation, and representative tumor areas for immunohistochemical evaluation. Cases with other thyroid malignancies or patients who had received chemotherapy or radiotherapy prior to surgery were excluded.

Histopathological diagnoses were reviewed based on the 2022 World Health Organization (WHO) Classification of Thyroid Tumours. TROP-2 expression was evaluated by immunohistochemistry using 4-µm-thick FFPE tissue sections and a rabbit monoclonal anti-TROP-2 antibody (Clone A20824, ABclonal Technology, Wuhan, China) at a dilution of 1:6000. Immunoreactivity was assessed using the semi-quantitative Histochemical Score (H-score) method based on membranous staining intensity and the percentage of positive tumor cells, resulting in scores ranging from 0 to 300. Evaluation was performed independently by two anatomical pathologists.

Statistical analysis was performed using IBM SPSS Statistics version 29.0. The Shapiro–Wilk test was used to assess data distribution. The association between TROP-2 expression and clinicopathological features was analyzed using Spearman's rank correlation coefficient and the Mann–Whitney U test. A two-tailed p-value <0.05 was considered statistically significant.

This study was approved by the Research Ethics Committee of Dr. Soetomo General Hospital, Surabaya, Indonesia (ethics approval code: 1640/KEPK/VII/2026). Patient confidentiality was maintained, and all data were used solely for research purposes.

3. Results

3.1. Clinicopathological Features

A total of 30 patients with histopathologically confirmed papillary thyroid carcinoma (PTC) were included in this study. The clinicopathological features of the patients are presented in Table 1. The mean age of patients was 44.43 ± 15.68 years (range, 13–72 years). Most patients were female (22 cases, 73.3%). Based on pathological tumor stage, pT3 was the most frequent category (14 cases, 46.7%), followed by pT2 (11 cases, 36.7%) and pT1 (5 cases, 16.7%). Regional lymph node metastasis (N1) was identified in 20 cases (66.7%), while unifocal and multifocal tumors were equally distributed (15 cases each, 50.0%).

Table 1 Clinicopathological features of the study population (n = 30)

Variable	Value
Age (years)	
Mean ± SD	44.43 ± 15.68
Range	13–72
Sex, n (%)	
Male	8 (26.7)
Female	22 (73.3)
Pathological tumor stage, n (%)	
pT1	5 (16.7)
pT2	11 (36.7)
pT3	14 (46.7)
Nodal status, n (%)	
N0	10 (33.3)
N1	20 (66.7)
Multifocality, n (%)	
Unifocal	15 (50.0)
Multifocal	15 (50.0)

3.2. TROP-2 Expression in Papillary Thyroid Carcinoma

Immunohistochemical evaluation demonstrated membranous TROP-2 expression in all PTC cases. The intensity and distribution of staining varied among cases, with H-score values ranging from 0 to 300. Representative immunohistochemical staining patterns showing weak, moderate, and strong membranous expression are presented in Figure 1.

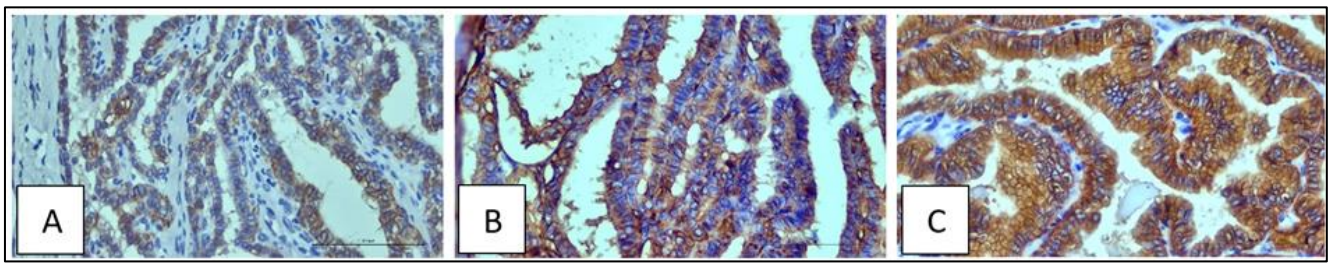

Figure 1 TROP-2 membranous expression in papillary thyroid carcinoma: (A) weak, (B) moderate, and (C) strong staining intensity.

3.3. Association Between TROP-2 Expression and Clinicopathological Features

The association between TROP-2 expression and clinicopathological features is presented in Tables 2 and 3. Spearman's rank correlation analysis showed no significant correlation between TROP-2 H-score and pathological tumor stage ($\rho = -0.061$; $p = 0.750$), nodal status ($\rho = 0.050$; $p = 0.794$), or patient age ($\rho = 0.256$; $p = 0.171$).

Furthermore, Mann–Whitney analysis demonstrated no significant differences in TROP-2 H-score according to sex ($p = 0.491$) or tumor multifocality ($p = 0.769$).

Table 2 Correlation between TROP-2 expression and clinicopathological parameters

Variable	Spearman's ρ	p-value
Pathological tumor stage (pT)	-0.061	0.75
Nodal status (N stage)	0.05	0.794
Age	0.256	0.171

Table 3 Comparison of TROP-2 expression according to sex and tumor multifocality

Variable	Category	p-value
Sex	Male vs Female	0.491
Tumor focality	Unifocal vs Multifocal	0.769

4. Discussion

This study evaluated the association between TROP-2 expression and clinicopathological features in PTC. TROP-2 expression was observed in all PTC cases, demonstrating consistent membranous immunoreactivity. However, no significant associations were identified between TROP-2 expression and pathological tumor stage, lymph node status, age, sex, or multifocality. These findings indicate that although TROP-2 is consistently expressed in PTC, its expression level may not directly reflect tumor aggressiveness or disease progression.

The consistent expression of TROP-2 observed in the present study may be explained by its involvement in the molecular pathogenesis of papillary thyroid carcinoma. TROP-2 is a transmembrane glycoprotein that functions as an oncogenic cell-surface receptor regulating intracellular signaling pathways involved in cell proliferation, survival, migration, and invasion. Following activation, TROP-2 promotes intracellular calcium release and protein kinase C (PKC) activation, leading to stimulation of the MAPK/ERK and PI3K/AKT signaling pathways, which enhance cellular proliferation and survival (6,10). Activation of these signaling cascades increases cyclin D1 and cyclin E expression while suppressing the cell-cycle inhibitor p27, thereby facilitating G1/S cell-cycle progression and tumor cell proliferation (7,11,12). In papillary thyroid carcinoma, constitutive activation of the MAPK pathway, primarily driven by BRAF, RAS, RET/PTC, and ALK alterations, represents a key molecular event in thyroid tumorigenesis (9). Previous studies have suggested a potential association between BRAF V600E mutation and increased TROP-2 expression in PTC; however, the biological relationship between these molecular alterations requires further investigation (14). Conversely, TROP-2 can further potentiate MAPK and PI3K/AKT signaling through activation of downstream effectors, including cyclin D1, NF-κB, and STAT1/3, creating a feed-forward loop that sustains oncogenic signaling and promotes tumor cell survival (6,10,15). The interaction between TROP-2 expression and oncogenic signaling pathways may explain the widespread expression of TROP-2 observed in PTC, suggesting its potential role as a marker of tumorigenesis rather than a marker of tumor progression (16).

In the present study, TROP-2 expression was not significantly associated with pathological tumor stage, lymph node status, or multifocality. These findings are consistent with previous studies by Bychkov et al., Attia et al., and Kong et al. Bychkov et al. reported that TROP-2 expression was not correlated with patient age, sex, tumor size, nodal disease, or pathological stage (17). Similarly, Attia et al. demonstrated that TROP-2 immunohistochemical expression was not significantly associated with tumor size, lymph node metastasis, distant metastasis, or extrathyroidal extension (16). Likewise, Kong et al. found no significant association between TROP-2 expression and patient age, sex, tumor size, lymph node metastasis, or extrathyroidal extension (18). In contrast, Guan et al. demonstrated that high TROP-2 expression was significantly associated with advanced TNM stage and lymph node classification, suggesting a potential role of TROP-2 in tumor progression (9).

One possible explanation for the absence of a significant association is that TROP-2 expression may reflect malignant transformation rather than the extent of tumor progression. TROP-2 is activated by oncogenic signaling pathways, particularly MAPK/ERK and PI3K/AKT, resulting in enhanced cellular proliferation, survival, migration, and invasion (6,9,10). Once overexpressed during thyroid carcinogenesis, TROP-2 expression may remain relatively stable throughout tumor development, thereby serving primarily as a marker of malignancy rather than increasing proportionally with pathological tumor stage, lymph node metastasis, or multifocality. This interpretation is supported

by several immunohistochemical studies, including those by Bychkov et al., Kong et al., and Attia et al., which consistently demonstrated no significant association between TROP-2 expression and most clinicopathological features despite its high diagnostic performance in papillary thyroid carcinoma (16–18). Furthermore, clinicopathological features such as tumor stage and lymph node metastasis are influenced by multiple molecular and microenvironmental factors beyond TROP-2 alone, including alterations in BRAF, RAS, RET/PTC, and TERT promoter genes. Therefore, TROP-2 protein expression alone may be insufficient to reflect the biological complexity underlying tumor aggressiveness (6,9)

In the present study, TROP-2 expression was not significantly associated with patient age or sex. These findings are consistent with those reported by Bychkov et al., Kılınc et al. and Kong et al., who likewise found no significant correlation between TROP-2 expression and patient age or sex in papillary thyroid carcinoma (17–19). Although increasing age is a well-established prognostic factor and is incorporated into the AJCC eighth edition staging system for differentiated thyroid carcinoma, its prognostic significance primarily reflects patient outcomes rather than intrinsic tumor biology. Likewise, papillary thyroid carcinoma occurs more frequently in women than in men; however, sex has not been shown to directly regulate the oncogenic signaling pathways responsible for TROP-2 expression. Instead, TROP-2 overexpression is largely driven by tumor-specific molecular alterations, including activation of the MAPK/ERK and PI3K/AKT pathways, which occur independently of patient demographic features (6,9,10). Therefore, the absence of an association between TROP-2 expression and patient age or sex observed in the present study is biologically plausible and further supports the concept that TROP-2 reflects tumor-specific molecular alterations rather than patient-related prognostic factors.

Taken together, the findings of this study suggest that TROP-2 expression is a consistent molecular feature of PTC but has limited value as an independent indicator of tumor aggressiveness. Although TROP-2 has been implicated in oncogenic signaling pathways and tumor progression in various malignancies, its prognostic significance in PTC remains uncertain. The lack of association between TROP-2 expression and clinicopathological parameters in this study suggests that TROP-2 alone may not be sufficient to predict aggressive tumor behavior. Future studies involving larger cohorts, molecular profiling, and long-term clinical follow-up are needed to further clarify the prognostic significance of TROP-2 in papillary thyroid carcinoma.

This study has several strengths. First, TROP-2 expression was evaluated using immunohistochemistry in histopathologically confirmed PTC specimens. Second, expression assessment was performed using the H-score method, which incorporates both staining intensity and the proportion of positive tumor cells, providing a semi-quantitative evaluation of protein expression. Third, the relationship between TROP-2 expression and multiple clinicopathological parameters was comprehensively assessed, providing additional information regarding the potential biological relevance of TROP-2 in PTC.

Several limitations should be acknowledged. This study was conducted at a single institution with a relatively limited sample size, which may have reduced the ability to detect weak associations between TROP-2 expression and clinicopathological parameters. In addition, molecular alterations associated with PTC progression, including BRAF and TERT promoter mutations, were not evaluated. The absence of long-term follow-up data also limited assessment of the relationship between TROP-2 expression and clinical outcomes, such as recurrence and disease-specific survival. Further multicenter studies incorporating molecular analysis and longitudinal follow-up are warranted to determine the prognostic role of TROP-2 in PTC.

5. Conclusion

Based on a study conducted on 30 patients with papillary thyroid carcinoma at Dr. Soetomo General Hospital during the period from January 2022 to December 2024, the clinicopathological and immunohistochemical findings of TROP-2 expression were obtained as follows:

TROP-2 immunohistochemical expression was observed in all papillary thyroid carcinoma cases, demonstrating consistent membranous staining. The H-score assessment showed variable levels of TROP-2 expression; however, no significant association was identified between TROP-2 expression and clinicopathological parameters, including pathological tumor stage, lymph node status, multifocality, age, and sex.

These findings indicate that TROP-2 expression is a common molecular feature of papillary thyroid carcinoma but does not appear to reflect tumor aggressiveness based on conventional clinicopathological parameters. Therefore, TROP-2 may have a role in thyroid tumor biology, although its potential as an independent prognostic biomarker in papillary

thyroid carcinoma remains uncertain and requires further investigation involving larger cohorts, molecular analysis, and clinical follow-up.

Compliance with ethical standards

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Disclosure of conflict of interest

The authors declare that there is no conflict of interest regarding the publication of this manuscript.

Statement of ethical approval

This study was conducted in accordance with the ethical standards of the institutional research committee and the Declaration of Helsinki. Ethical approval was obtained from the Health Research Ethics Committee of Dr. Soetomo General Hospital, Surabaya, Indonesia (Ethical Approval Number: 1640/KEPK/VII/2026).

Statement of informed consent

As this study used archived formalin-fixed paraffin-embedded tissue specimens and involved retrospective analysis of existing pathological data, informed consent was waived by the ethics committee.

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