TERT Outperforms the AGES Score and BRAF in Predicting Recurrence of Papillary Thyroid Carcinoma Following Isthmolobectomy: A Retrospective Study

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ABSTRACT

Background

Recurrence of papillary thyroid carcinoma (PTC) remains a significant clinical challenge despite its generally favorable prognosis. The AGES score is widely used for risk stratification; however, its predictive performance is limited. Molecular biomarkers such as BRAF V600E and TERT may enhance risk prediction, particularly in patients undergoing isthmolobectomy.

Methods

A retrospective cohort study was conducted in patients with PTC who underwent isthmolobectomy at a tertiary referral center between 2019 and 2025. Associations between AGES score, BRAF expression, and TERT expression with recurrence were evaluated using bivariate and multivariate analyses. Binary logistic regression was applied to identify independent predictors.

Results

Seventy patients were included. The AGES score was significantly associated with recurrence in bivariate analysis but not in multivariate analysis ($p = 0.215$). BRAF expression showed a significant association in bivariate analysis but did not remain significant after adjustment. In contrast, TERT expression was significantly associated with recurrence in both bivariate and multivariate analyses and emerged as an independent predictor (OR 6.594; 95% CI 1.603–27.123; $p = 0.009$). The overall model was statistically significant ($p = 0.002$; Nagelkerke $R^2 = 0.371$).

Conclusion

TERT expression is the strongest independent predictor of recurrence in PTC, outperforming both the AGES score and BRAF. Incorporating molecular biomarkers into risk stratification may improve prognostic accuracy and guide postoperative management.

Keywords: papillary thyroid carcinoma; recurrence; AGES score; BRAF V600E; TERT; isthmolobectomy

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INTRODUCTION

Thyroid cancer is an endocrine malignancy with a steadily increasing global incidence, with more than 821,000 new cases reported in 2022, the majority occurring in Asia.[1] In Indonesia, thyroid cancer ranks among the five most common malignancies.[2] Papillary thyroid carcinoma (PTC) is the most prevalent subtype, accounting for 80–85% of cases, and is generally associated with an excellent prognosis, with a 10-year survival rate exceeding 90%.[3,4] Nevertheless, recurrence remains a clinically relevant issue, occurring in up to 20–30% of patients during follow-up.[5]

Accurate risk stratification is essential for guiding treatment decisions and surveillance strategies. Surgical management of PTC includes isthmolobectomy and total thyroidectomy.[7] In low-risk patients, isthmolobectomy is recommended by the American Thyroid Association (ATA) and National Comprehensive Cancer Network (NCCN) guidelines due to its lower complication rates and comparable long-term quality of life.[8,10] However, several studies have reported higher recurrence rates following isthmolobectomy, highlighting the need for more precise risk assessment.

The AGES score (Age, Grade, Extent, Size) is a widely used clinicopathological tool for prognostication.[11] While it correlates with overall outcomes, its ability to independently predict recurrence—particularly in patients undergoing isthmolobectomy—remains limited.[12] Importantly, recurrence can still occur in patients classified as low risk, underscoring the limitations of conventional models.

Recent advances in molecular oncology have identified genetic alterations that contribute to tumor aggressiveness. The BRAF V600E mutation is the most common mutation in PTC and is associated with MAPK/ERK pathway activation; however, its association with recurrence remains inconsistent across studies.[13,14,15] In contrast, TERT promoter mutations have been more consistently linked to aggressive tumor behavior, including recurrence and distant metastasis, and may exert synergistic effects with BRAF mutations.[16,17]

Most previous studies have focused on patients undergoing total thyroidectomy, and evidence regarding patients treated with isthmolobectomy remains limited.

Therefore, this study aimed to evaluate the association of AGES score, BRAF V600E, and TERT expression with recurrence in PTC patients following isthmolobectomy, with the goal of improving risk stratification and informing clinical decision-making.

METHODS

This retrospective analytical study was conducted at a tertiary referral hospital in Indonesia. Medical records of patients diagnosed with papillary thyroid carcinoma between January 2019 and December 2025 were reviewed.

Eligible patients had histopathologically confirmed PTC, underwent isthmolobectomy, and had complete clinical, histopathological, and follow-up data. Patients were excluded if histopathological slides could not be re-evaluated, medical records were incomplete, or there was a history of other malignancies.

Recurrence was defined as disease reappearance at least six months after surgery based on clinical, radiological, or histopathological findings according to ATA guidelines. Independent variables included AGES score, BRAF V600E expression, and TERT expression. Statistical analysis was performed using SPSS version 31. Continuous variables were expressed as mean ± standard deviation, and categorical variables as frequencies and percentages. Bivariate analysis was conducted using appropriate tests, and multivariate analysis was performed using binary logistic regression. A p-value < 0.05 was considered statistically significant.

RESULTS

A total of 70 patients were analyzed. The mean age was 38.84 ± 14.16 years. Most patients were female (85.7%) and classified as low-risk based on AGES score (74.3%).

Table 1. Baseline Characteristics of Study Subjects

Variable	Recurrence (n=35)	Non-recurrence (n=35)	Total (n=70)
Age (years), mean ± SD	42.40 ± 15.14	35.86 ± 12.74	38.84 ± 14.16
Sex			
Male	4 (40.0%)	6 (60.0%)	10 (14.3%)
Female	31 (51.7%)	29 (48.3%)	60 (85.7%)
AGES score, mean ± SD	3.50 ± 1.30	3.00 ± 1.15	3.32 ± 1.25

In bivariate analysis, AGES score was significantly associated with recurrence (p = 0.029), but this association was not maintained in multivariate analysis (p = 0.215). BRAF expression showed a significant association in bivariate analysis (p = 0.025) but was not consistently significant after adjustment.

Table 2. Bivariate Analysis of AGES Score and Recurrence

Variable	Recurrence	Non-recurrence	p-value
AGES (mean rank)	41.30	30.62	0.029*
AGES category			
Low risk (<4)	20 (38.5%)	32 (61.5%)	
High risk (≥4)	12 (66.7%)	6 (33.3%)	0.038*

*Statistically significant (p < 0.05)

Table 3. Association Between BRAF Expression and Recurrence

BRAF Expression	Recurrence n (%)	Non-recurrence n (%)	OR (95% CI)	p-value
Weak (0–8)	17 (48.6)	14 (40.0)	1.417 (0.550–3.652)	0.025*
Strong (9–12)	18 (51.4)	21 (60.0)	—	

*Statistically significant (p < 0.05)

Table 4. Association Between TERT Expression and Recurrence

TERT Expression	Recurrence n (%)	Non-recurrence n (%)	OR (95% CI)	p-value
Weak (0–8)	16 (45.7)	8 (22.9)	2.842 (1.013–7.976)	0.044*
Strong (9–12)	19 (54.3)	27 (77.1)	—	

*Statistically significant (p < 0.05)

TERT expression demonstrated a significant and consistent association with recurrence in both bivariate (p = 0.044) and multivariate analyses. Multivariate logistic regression identified TERT as an independent predictor of recurrence (OR = 6.594; 95% CI 1.603–27.123; p = 0.009). The model was statistically significant (p = 0.002; Nagelkerke $R^2 = 0.371$).

Table 5. Logistic Regression Model Fit

Parameter	Value
Omnibus test (χ^2)	20.811

Parameter	Value
p-value	0.002*
Nagelkerke R^2	0.371
-2 Log likelihood	67.349

*Statistically significant ($p < 0.05$)

Table 6. Multivariate Analysis of Factors Associated with Recurrence

Variable	OR (Exp(B))	95% CI	p-value
AGES score	3.270	0.503 – 21.236	0.215
BRAF	0.127	0.027 – 0.587	0.018*
TERT	6.594	1.603 – 27.123	0.009*

*Statistically significant ($p < 0.05$)

DISCUSSION

This study demonstrates that molecular biomarkers, particularly TERT expression, outperform traditional clinicopathological parameters in predicting recurrence of PTC following isthmolobectomy.

While the AGES score remains useful for initial risk stratification, its limited performance in multivariate analysis suggests that it may not adequately capture tumor biological behavior. Similarly, the inconsistent predictive value of BRAF observed in this study aligns with prior reports indicating variability across populations and disease characteristics.

In contrast, TERT expression showed a strong and consistent association with recurrence, supporting its role as a key determinant of tumor aggressiveness. These findings reinforce the emerging paradigm shift toward integrating molecular markers into risk stratification models.

Clinically, incorporating TERT status may help identify high-risk patients who could benefit from closer surveillance or more aggressive management, even within traditionally low-risk groups.

CONCLUSION

TERT expression is the strongest independent predictor of recurrence in papillary thyroid carcinoma following isthmolobectomy, outperforming both the AGES score and BRAF. Integration of molecular biomarkers into risk stratification may enhance prognostic accuracy and optimize clinical decision-making.

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