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ORIGINAL ARTICLE

The Value of Stanniocalcin1 in Papillary Thyroid Carcinoma and its Correlation with Clinicopathological Parameters: An Immunohistochemical Study

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ABSTRACT

Background: Papillary thyroid carcinoma (PTC) is considered the most prevalent type of thyroid malignancy, exhibiting diverse clinicopathological behaviors. Identifying reliable biomarkers for diagnosis and prognosis remains a clinical challenge. Stanniocalcin 1 (STC1) has been involved in various cancers, but its role in PTC is not fully established. This research aimed to evaluate the expression of STC1 in PTC and its correlation with clinicopathological parameters, including tumor grade and stage.

Methods: A retrospective cross-sectional study was conducted on 90 formalin-fixed, paraffin-embedded thyroid tissue samples categorized into two groups: Group A (PTC group) included 81 cases of PTC, and Group B (Control group) included 9 cases of normal thyroid tissue from the archives of Zagazig University. Immunohistochemical staining for STC1 was performed, and expression was assessed in relation to tumor grade, stage, and other clinicopathological features.

Results: STC1 expression increased from low-grade to high-grade and malignant *PTC* ($P < 0.001$). Higher STC1 expression was significantly correlated with advanced tumor stage, grade, lymph node metastasis, capsular invasion, and lymphovascular invasion (all $P < 0.001$). Diagnostic evaluation revealed that STC1 had a sensitivity of 88.9%, specificity of 92.6%, and an accuracy of 92.2% in distinguishing *PTC* from normal tissue.

Conclusions: STC1 is upregulated in higher-grade and advanced-stage *PTC*, supporting its role in tumor progression and carcinogenesis. Its high sensitivity and specificity suggest that STC1 could serve as a useful diagnostic and prognostic marker among *Papillary thyroid carcinoma* patients.

Keywords: Stanniocalcin1; Papillary Thyroid Carcinoma; Clinicopathological; Immunohistochemical.

INTRODUCTION

Thyroid cancer is recognized as one of the most prevalent endocrine malignancies with an increasing epidemiology across the globe in recent years [1]. The age-standardized incidence rates in 2020 were reported as 10.1 per 100,000 women and 3.1 per 100,000 men worldwide [2]. It is expected to become the fourth most prevalent cancer by 2030 [3]. In Egypt, thyroid cancer is the sixth most prevalent cancer among women and ranks seventeenth among men [4]. Among the various types, Papillary thyroid carcinoma (PTC) stands out as the most diagnosed histological subtype [5].

Immunohistochemical methods have become integral in evaluating malignant

thyroid tumors, yet there is still no highly sensitive or specific biomarker that ensures a clear-cut diagnosis [6]. Accurately predicting the prognosis of papillary thyroid carcinoma is essential for determining the optimal management approach. Given the challenge of identifying PTC cases with aggressive behavior, ongoing research continues to seek out novel prognostic markers. Several proteins, such as galectin-3, cathepsin B, cytokeratin-19, and E-cadherin, have been studied as potential markers, but none have shown definitive utility in forecasting risk or aggressiveness in PTC [7].

Stanniocalcin proteins (STCs) are secreted glycoproteins that play key roles in calcium-phosphate balance, cell growth, programmed cell death, inflammation, and cancer progression [8]. Two main subtypes, STC1 and STC2, are found throughout various mammalian tissues. STC1 is predominantly located in the mitochondria of follicular cells, while STC2 is typically found in the Golgi apparatus and endoplasmic reticulum. These proteins contribute to regulating organelle function mainly through autocrine and paracrine mechanisms [9].

There is growing evidence that STC1 is involved in several cancer-related processes, including enhancing tumor cell survival, supporting tumor growth, aiding in invasion and metastasis, and participating in the epithelial-mesenchymal transition that reshapes the tumor environment [10]. Elevated STC1 expression has been linked to a worse prognosis in various malignancies such as breast, colorectal, esophageal, ovarian, lung, gastric, brain, soft tissue, and laryngeal cancers [11].

Despite accumulating data on the functions of STC1 in other tumor types, its value in *Papillary thyroid carcinoma* remains unclear. Few studies have examined the relationship between STC1 expression and specific clinicopathological features among PTC cases, and the prognostic significance of STC1 in this context has yet to be established. This highlights a need for further investigation into whether STC1 could serve as a reliable biomarker for diagnosis or prognosis in Papillary thyroid carcinoma. So, the current research aimed to evaluate the role of stanniocalcin-1 protein expression in Papillary thyroid carcinoma and to analyze its correlation with clinicopathological parameters such as age, grade, necrosis, mitosis, capsular invasion, and stage in PTC.

METHODS

This retrospective, comparative cross-sectional research was performed in the Pathology Department, Faculty of Medicine, Zagazig University. The study involved ninety formalin-fixed, paraffin-embedded tissue blocks previously diagnosed as Papillary thyroid carcinoma, which were retrieved from the pathology archives covering the period from 2023 to 2025 after receiving approval number (10682/4/4-2023) from the local ethical committee and institutional review board (IRB) of the Faculty of Medicine, Zagazig University. The research was conducted under the World Medical Association's Code of Ethics (Helsinki Declaration) for human research.

The present study was done on 81cases of Papillary thyroid carcinoma (**Group A) (PTC group)** and 9 cases of normal thyroid tissue (**Group B**) added as a control group. Representing 25, 4 %, 20,6% and 54% respectively. The study group consisted of Eighty-one cases representing Papillary thyroid carcinoma of varying grades and lymph node status. Cases included: 30 cases with low-risk Papillary thyroid carcinoma, 24 cases with medium-risk Papillary thyroid carcinoma, and 27 cases with high-risk Papillary thyroid carcinoma. All specimens were obtained from total thyroidectomy procedures.

Inclusion criteria required that cases with Papillary thyroid carcinoma of any grade, or normal thyroid tissue, with available paraffin blocks, complete data sheets, and adequate tissue for diagnosis. **Exclusion criteria** included cases diagnosed with other types of thyroid cancers, all types of thyroiditis, incomplete clinical data, any prior chemotherapy or radiotherapy, or insufficient tissue in the blocks for further processing.

Relevant clinical and pathological information, such as patient age, sex, tumor size, tumor stage, bilaterality, and other gross features, were collected from the medical records associated with each specimen.

Histopathological Assessment

For each case, paraffin-embedded blocks were sectioned at a thickness of 3–4 µm utilizing a rotary microtome. Sections were put on glass slides, then stained with hematoxylin and eosin for histopathological assessment. All slides were checked independently by three experienced pathologists, blinded to each other's findings, for confirmation of the diagnosis and evaluation of the tumor characteristics. Tumor grading was assessed according to the recent WHO classification (5th edition, 2022) for Papillary thyroid carcinoma (PTC) [20]. The PTC risk score was evaluated based on the criteria set by the 2024 Korean Thyroid Association Initial Risk Stratification System (K-RSS), categorizing patients as either low, intermediate, or high risk [13,19]. Tumor staging was assessed using the TNM system, and additional features such as histological variant, lymphovascular invasion, and capsular invasion.

Immunohistochemical Analysis

Immunohistochemistry was performed using the streptavidin-biotin immunoperoxidase technique. Sections (3–5 µm) were deparaffinized at 56°C, rehydrated through graded alcohols, and then rinsed with distilled water. Antigen retrieval was performed in sodium citrate buffer (0.01 M, pH 6) using microwave heating. Endogenous peroxidase activity blockage was done with hydrogen peroxide. Sections were incubated overnight at 4°C with polyclonal rabbit anti-STC1 antibodies (ab229477, Abcam, USA; 1:100 dilution), and then processed with biotinylated secondary antibodies and streptavidin-biotin-peroxidase complex. The chromogen DAB (3,3′-diaminobenzidine) was used for visualization. After counterstaining with hematoxylin and dehydration, the slides were cover-slipped and examined. Photomicrographs were taken using a digital Olympus camera attached to an Olympus CX41 microscope.

Control slides were prepared and stained alongside the study specimens. Positive controls included normal liver tissue, while negative controls consisted of *PTC* tissue sections treated with PBS in place of the primary antibody.

Evaluation of STC1 Immunostaining

Immunostaining for STC1 was evaluated semi-quantitatively according to both the percentage of positively stained cells and staining intensity [14.21]. Cytoplasmic or membranous brown staining was considered positive. Intensity was given a score from 0 (no staining) to 3 (strong staining), while the percentage of positive cells was given a score of 1 (≤10%), 2 (11–50%), 3 (51–80%), or 4 (≥81%). The total immunostaining score for each case ranged from a minimum of 1 to a maximum of 12. (Final IRS = intensity × percentage (range 0–12). Interpretation:0–2 = negative/ 3–5 = weak/6–8 = moderate/9–12 = strong expression [21].

Statistical analysis:

Data was entered and analyzed using SPSS version 23. Qualitative variables were

presented as frequencies and percentages, quantitative variables as mean, standard deviation, and range. Chi-square or Fisher's exact test was used for categorical comparisons. Independent t-test and one-way ANOVA compared means between two or more groups, respectively. Logistic regression analyzed predictors of categorical outcomes. ROC curves assessed diagnostic accuracy, with AUC values ≥0.90 considered excellent, 0.80–0.89 good, 0.70–0.79 fair, 0.60–0.69 poor, and <0.60 failed. Statistical significance was set at $p \leq 0.05$.

RESULTS

The groups did not differ significantly regarding age or sex distribution. STC1 expression demonstrated a highly significant difference between the PTC and control groups ($p < 0.001$). Strong STC1 expression was revealed in nearly half of the PTC cases (48.1%), while none of the controls showed strong expression. Conversely, negative STC1 expression was much more common among controls (66.7%) than PTC cases (12.3%) (Table 1).

Table 2 shows non-significant associations between stanniocalcin1 and the demographic data. In contrast, statistically significant associations were revealed between stanniocalcin1 expression and clinicopathological characteristics, as strong STC1 expression was associated with high T, N, M stages (P<0.001). Also, strong STC1 expressions were associated with lymph vascular invasion, high stage(P<0.001), high grade (P=,03), mitosis (P=0.003), and capsular invasion (P=0.001). (Table 2)

STC1 expression shows a sensitivity of 88.9%, a specificity of 92.6%, and an accuracy of 92.2% in detecting PTC cases with an area under the curve of 0.907 (Table 3).

Univariate analysis showed that older age ($p = 0.01$), nodal stage ($p = 0.04$), metastasis stage ($p < 0.001$), and strong STC1 expression ($p = 0.02$) were significantly associated with lymphovascular invasion in PTC. On multivariate analysis, only age ($p = 0.04$, OR: 1.08) and strong STC1 expression ($p = 0.01$, OR: 1.21) remained independent predictors (Table 4).

Classical variant of low-grade papillary thyroid carcinoma. (A) H&E ×100 shows papillary structures with a connective tissue core infiltrated by inflammatory cells and lined by neoplastic follicular cells demonstrating nuclear crowding, grooving, clearing, and enlargement. (B) H&E ×400 highlights these nuclear features at higher magnification. (C) IHC ×100 reveals moderate membranous STC1 expression in the malignant follicular cells, while the adjacent non-neoplastic thyroid follicles are negative for STC1. (D) IHC ×400 further demonstrates membranous STC1 expression in tumor cells (Figure 1).

Classical variant of high-grade papillary thyroid carcinoma. (A) H&E ×100 shows papillary structures, while (B) H&E ×400 provides a higher magnification of the papillary architecture. (C) IHC ×100 demonstrates strong cytoplasmic STC1 expression in the lining malignant follicular cells, with (D) IHC ×400 confirming this strong cytoplasmic staining at higher magnification. (E) H&E ×100 illustrates lymph node metastasis with papillary structures surrounded by lymphocytes. (F) IHC ×400 shows strong cytoplasmic STC1 expression in the lining follicular cells of the metastatic papillary structures (Figure 2).

Follicular variant of high-grade *Papillary thyroid carcinoma.* (A) H&E ×100 demonstrates a follicular growth pattern without papillary structures. (B) H&E ×400 reveals marked nuclear clearing, crowding, grooving, and enlargement within the follicular cells. (C) IHC ×100 shows strong brownish cytoplasmic STC1 expression in the tumor cells, and (D) IHC ×400 highlights this strong cytoplasmic expression along with prominent nuclear clearing in the lining follicular cells (Figure 3).

Table 1: Demographic, Clinicopathological, and Stanniocalcin1 Expression Data Among the Studied Groups

Variables	PTC Group (n=81)	Control Group (n=9)	P Value
Demographic Data			
Age (years), Mean ± SD	**43.9 ± 8.32**	**38.8 ± 7.36**	**0.081[1]**
Age (years), Range	**(31 – 62)**	**(30 – 50)**	
Sex, n (%)			**0.632[2]**
Male	**21 (25.9%)**	**3 (33.3%)**	
Female	**60 (74.1%)**	**6 (66.7%)**	
Clinicopathological Characteristics			
(PTC only)			
T stage, n (%)			
T I	**21 (25.9%)**	—	
T II	**36 (44.4%)**	—	
T III	**12 (14.8%)**	—	
T IV	**12 (14.8%)**	—	
N stage, n (%)			
N 0	**60 (74.1%)**	—	
N I	**21 (25.9%)**	—	
M stage, n (%)			
M I	**63 (77.8%)**	—	
M II	**18 (22.2%)**	—	
Lymph vascular invasion, n (%)			
Negative	**69 (85.2%)**	—	
Positive	**12 (14.8%)**	—	
Histopathological variant, n (%)			
Classical	**66 (81.5%)**	—	
Follicular	**15 (18.5%)**	—	
Stage, n (%)			
Stage I	**48 (59.3%)**	—	
Stage II	**21 (25.9%)**	—	
Stage III	**6 (7.4%)**	—	
Stage IV	**6 (7.4%)**	—	
Grade, n (%)			
Low	**30 (37.0%)**	—	
Medium	**24 (29.6%)**	—	
High	**27 (33.3%)**	—	
Stanniocalcin1 (STC1) Expression, n (%)			
Negative	**10 (12.3%)**	**6 (66.7%)**	**<0.001[2]**
Weak	**32 (39.5%)**	**3 (33.3%)**	
Strong	**39 (48.1%)**	**0 (0%)**	

PTC: Papillary thyroid carcinoma; SD: Standard deviation; STC1: Stanniocalcin1. Statistical Tests: [1]Independent sample T-test; [2]Chi-square test. P value significance: $P > 0.05$: Non-significant; $P \leq 0.05$: Significant.

Table 2: Association Between Stanniocalcin-1 (STC1) Expression and Demographic, Clinicopathological, and Tumor Characteristics in Papillary Thyroid Carcinoma (PTC) Group

Variables	STC1 Expression			P Value	Statistical Test
	Negative (n=10)	Weak (n=32)	Strong (n=39)		
Age (years)					
Mean ± SD	40 ± 7.63	44 ± 8.94	44.8 ± 7.87		One-way ANOVA
Range	(31–51)	(31–62)	(35–61)		0.231
Sex (n, %)					Fisher Exact Test
Male	2 (20%)	13 (40.6%)	6 (15.4%)		0.062
Female	8 (80%)	19 (59.4%)	33 (84.6%)		
T Stage (n, %)					Fisher Exact Test
T I	5 (50%)	13 (40.6%)	0 (0%)		<0.001
T II	4 (40%)	20 (62.5%)	18 (46.2%)		
T III	0 (0%)	0 (0%)	12 (30.8%)		
T IV	1 (10%)	2 (6.3%)	9 (23.1%)		
N Stage (n, %)					Fisher Exact Test
N 0	10 (100%)	32 (100%)	18 (46.2%)		<0.001
N I	0 (0%)	0 (0%)	21 (53.8%)		
M Stage (n, %)					Fisher Exact Test
M I	10 (100%)	32 (100%)	21 (53.8%)		<0.001
M II	0 (0%)	0 (0%)	18 (46.2%)		
Lymphovascular Invasion (n, %)					Fisher Exact Test
Negative	10 (100%)	32 (100%)	27 (69.2%)		<0.001
Positive	0 (0%)	0 (0%)	12 (30.8%)		
Histopathological Variant (n, %)					Fisher Exact Test
Classical	9 (90%)	24 (75%)	33 (84.6%)		0.52
Follicular	1 (10%)	8 (25%)	6 (15.4%)		
Stage (n, %)					Fisher Exact Test
Stage I	9 (90%)	30 (93.8%)	9 (23.1%)		<0.001
Stage II	1 (10%)	2 (6.3%)	18 (46.2%)		
Stage III	0 (0%)	0 (0%)	6 (15.4%)		
Stage IV	0 (0%)	0 (0%)	6 (15.4%)		
Grade (n, %)					Fisher Exact Test
Low	6 (60%)	21 (65.6%)	3 (7.7%)		<0.001
Medium	3 (30%)	9 (28.1%)	12 (30.8%)		
High	1 (10%)	2 (6.3%)	24 (61.5%)		

PTC: Papillary thyroid carcinoma, STC1: Stanniocalcin-1, SD: Standard deviation, n: Number, %: Percentage, T: Tumor size/stage, N: Nodal stage, M: Metastasis stage. Statistical tests: One-way ANOVA (for age), Fisher exact test (for categorical variables).

Significance threshold: $P \leq 0.05$ (significant); $P > 0.05$ (non-significant).

Table 3: Diagnostic accuracy of STC1 expression to predict PTC among the studied cases

	Sensitivity	**Specificity**	**Accuracy**	**AUC**
STC1 expression	88.9%	92.6%	92.2%	0.907

Table 4: Logistic regression analysis for predictors of lymph vascular invasion among the PTC group

Variables	**Univariate analysis**		**Multivariate analysis**	
	P value	**Odds (CI 95%)**	**P value**	**Odds (CI 95%)**
Age	**0.01**	1.09 (1.009 – 1.17)	**0.04**	1.08 (1.005 – 1.17)
Sex	0.17	0.34 (0.07 – 1.61)	-	-
T stage T Ⅰ T Ⅱ T Ⅲ T Ⅳ	 0.31 0.99 0.36	 2.11 (0.51 – 8.82) 3.04 (0.47 – 8.24) 2.89 (0.29 – 8.07)	 - - -	 - - -
N stage	**0.04**	3.6 (1.01 – 2.79)	0.52	1.02 (0.49 – 1.07)
M stage	**<0.001**	2.08 (1.54 – 8.08)	0.54	1.06 (0.79 – 1.03)
Variant	0.53	1.58 (0.37 – 6.73)	-	-
Stage Stage Ⅰ Stage Ⅱ Stage Ⅲ Stage Ⅳ	 0.34 0.44 0.62	 1.05 (0.71 – 2.31) 1.22 (0.84 – 2.76) 1.29 (0.91 – 2.54)	 - - -	 - - -
Stage Low Medium High	 0.47 0.09	 1.75 (0.39 – 7.88) 1.65 (0.73 – 5.79)	 - -	 - -
STC1 expression Negative Weak Strong	 **0.04** **0.02**	 1.29 (1.07 – 2.01) 1.55 (1.08 – 2.23)	 - **0.01**	 - 1.21 (1.04 – 1.42)

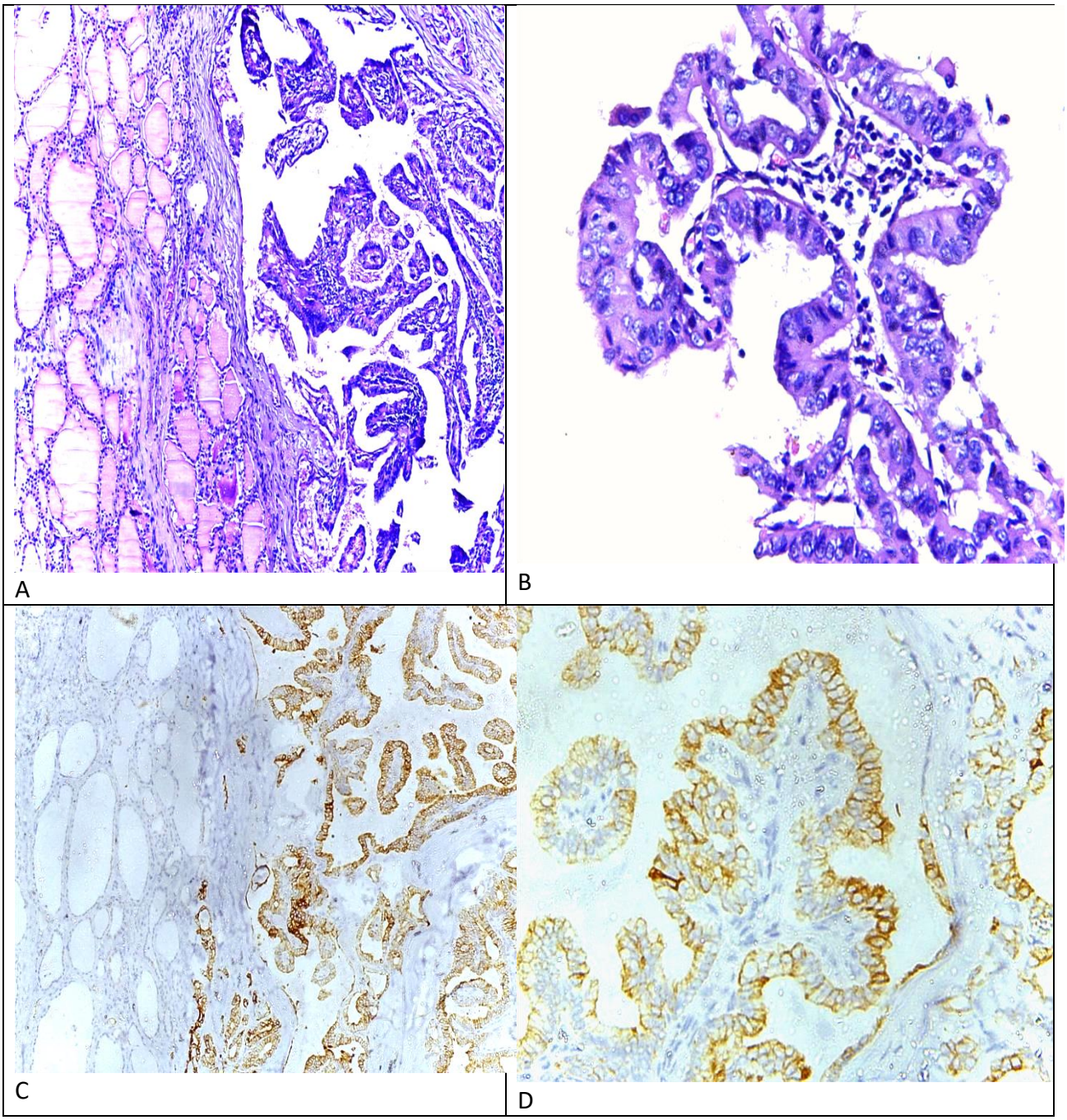

Figure (1): Classical variant of Papillary thyroid carcinoma (low grade)
A:H&E(x100) connective tissue core infiltrated by inflammatory cells and lining follicular cells showing nuclear crowding, grooving, clearing and enlargement**:** H&E(x400) **C:** IBC(x100) moderate membranous STC1 expression in malignant follicular cells while -ve stain in surrounding thyroid follicles with no pathological abnormalities **D:** IHCx400

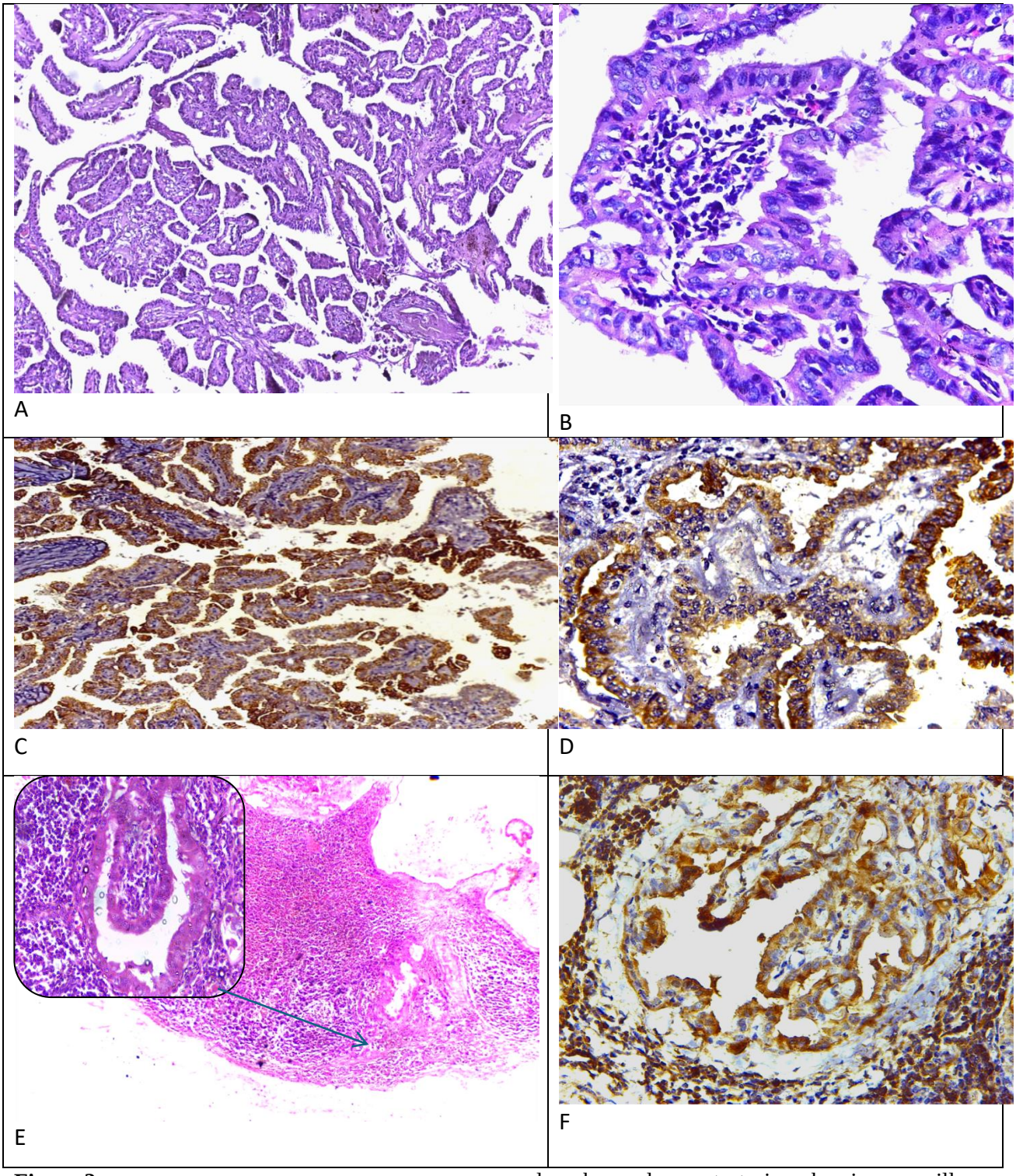

Figure 2: Classical variant of PTC high grade
A: H&Ex100 Papillary structures **B:** H&Ex400 **C:** IHCx100 showing strong cytoplasmic expression of lining malignant follicular cells. **C:** IHC x400 **D:** IHCX400 **E:** H&E x 100 lymph node metastasis showing papillary structure surrounded by lymphocytes**. F:**IHC x 400 papillary structure with lining follicular cells having strong cytoplasmicSTC1 expression

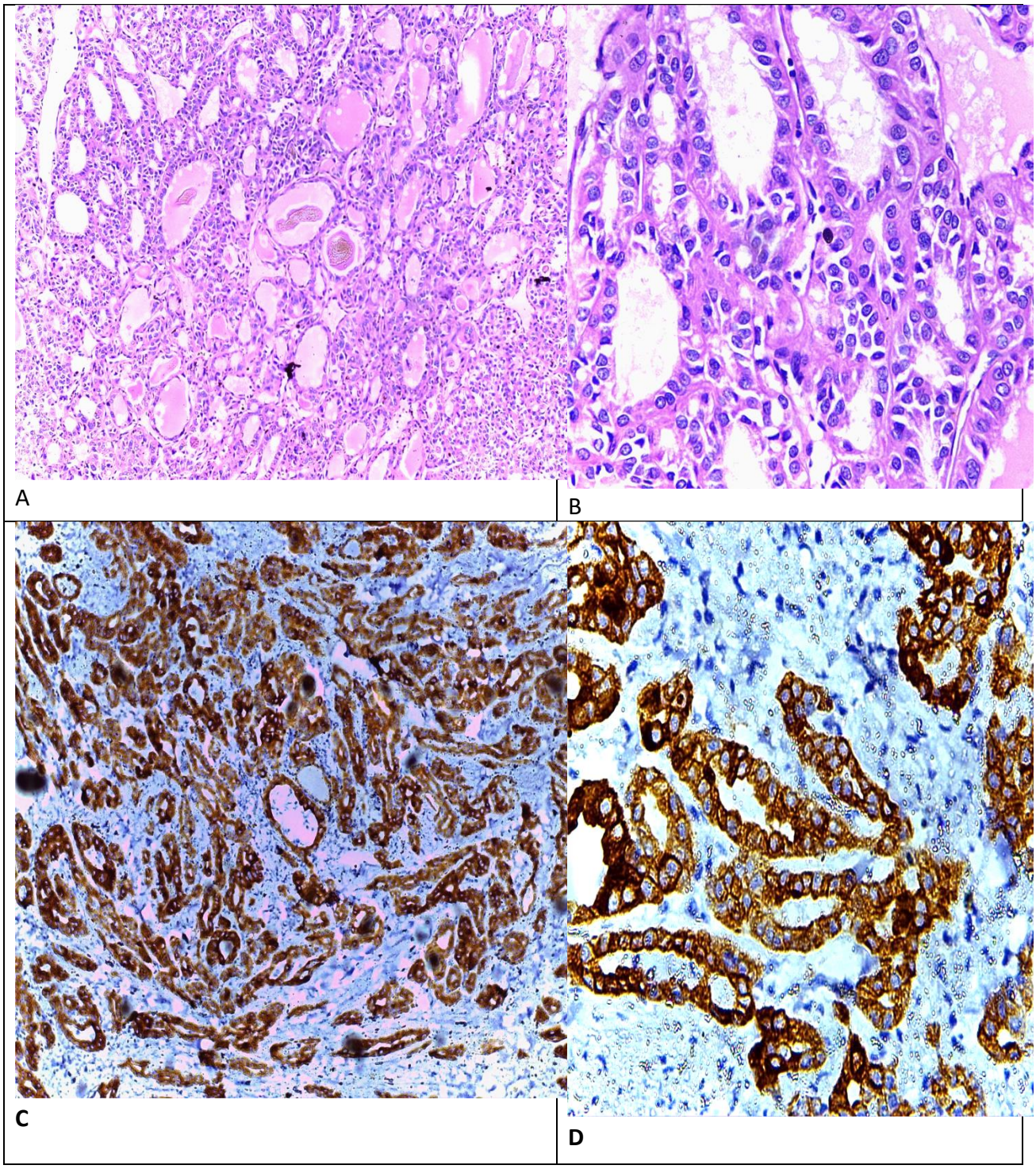

Figure 3: Follicular variant of Papillary thyroid carcinoma, high grade
A: H&Ex100 follicular growth with absence of Papillary structures. **B:** H&Ex400 showing follicular growth with nuclear, clearing, crowding, grooving and enlargement of follicular cells. **C:** IHCx100 strong brownish cytoplasmic expression of STC1. **D:** IHCx400 strong brownish cytoplasmic expression of STC1 and nuclear clearing of lining follicular cells.

DISCUSSION

In the current study, STC1 expression was examined in 90 thyroid samples —81 with PTC and 9 with normal thyroid tissue. A notable finding in the current study was the significant association between tumor size and STC1 expression. Of the 81 PTC specimens, 21 (25.9%) were classified as T1 (≤2 cm), 36 (44.4%) as T2 (>2–4 cm), 12 (14.8%) as T3 (>4 cm or minimal extrathyroidal extension), and 12 (14.8%) as T4 (gross extrathyroidal extension). Increased STC1 expression was observed in larger tumors and more advanced stages ($P < 0.001$). These results are in partial agreement with the staging system of the American Thyroid Association [18]. However, Sengun et al. [13] found no significant correlation between STC1 intensity or percentage of positively stained cells and tumor size, suggesting that this association may be context-dependent or influenced by cohort characteristics.

Regarding staging, the current study found that 48 out of 81 PTC cases (59.3%) were stage I, 21 (25.9%) were stage II, 6 (7.4%) were stage III, and 6 (7.4%) were stage IV. Similar results were reported by Sengun et al. [13], who observed that 77% of PTC cases were diagnosed at stage I and 25% at stage II, with only 1% and 7% at stages III and IV, respectively. This distribution suggests that most *PTC* cases have a favorable prognosis, although a significant minority present with advanced disease.

The current study also demonstrated that higher STC1 expression was significantly correlated with lymph node and distant metastasis, as well as lymphovascular invasion, higher tumor stage, and higher risk score (all $P < 0.001$). These findings are supported by Sengun et al. [13], who reported a positive correlation between STC1 staining score and TNM stage ($r = 0.259$, $p = 0.009$), and identified increased STC1 staining as an independent risk factor for lymph node metastasis in the multivariate analysis. Dai et al. [14] also found that STC1 expression was elevated in less differentiated thyroid cancers, reinforcing the role of STC1 in tumor progression under hypoxic conditions. Conversely, Al-Abdallah et al. [15] reported higher STC1 expression in benign thyroid lesions and lower expression in *PTC*, suggesting that STC1 may have a protective or anti-tumorigenic effect in some contexts—a finding not in agreement with the current results.

Regarding risk score, low risk score was observed in 6/10 (60%) of negative, 21/32 (65.6%) of weak, and 3/39 (7.7%) of strong STC1 expression cases. Intermediate risk was found in 3/10 (30%), 9/32 (28.1%), and 12/39 (30.8%), and high risk in 1/10 (10%), 2/32 (6.3%), and 24/39 (61.5%), respectively. This trend—of increased STC1 expression with increasing risk—mirrors the findings of Sengun et al. [13], who similarly reported that stronger STC1 staining was associated with higher tumor grade and adverse features. Additionally, their study confirmed through Spearman analysis that there is a positive correlation between increased STC1 immunostaining and clinicopathological features like lymph node metastasis, ATA risk score, and TNM stage (*r* = 0.236, *p* = 0.018 and *r* = 0.201, *p* = 0.045, respectively), which aligns with the current study.

Zhao et al. [7] also found that elevated STC1 expression was significantly associated with higher tumor grade, size, invasion, and metastasis in various cancers, including PTC. Their results, showing that increased circulating STC1 mRNA correlates with advanced tumor stage, support the findings of the current study. Additionally, Li et al. [16] reported in a recent meta-analysis that high STC1 expression is an adverse prognostic marker in solid tumors, which further supports the

prognostic significance of STC1 demonstrated here.

An analysis of histological variants in the present study revealed that the classical variant was the most common across all STC1 expression categories, seen in 9/10 (90%) of patients with negative STC1 expression, 24/32 (75%) with weak expression, and 33/39 (84.6%) with strong expression. The follicular variant was identified in 1/10 (10%), 8/32 (25%), and 6/39 (15.4%) of cases with negative, weak, and strong expression, respectively. These distributions align with findings by Sengun et al. [13], who reported that the classical variant predominated among all expression levels of STC1.

In our study, strong STC1 expressions were tracked with multiple indicators of aggressiveness, such as higher histologic grade, elevated mitotic activity, and capsular invasion. The association with tumor necrosis was not significant, likely due to its low prevalence. These patterns align with the emerging view of STC1 as a pro-tumorigenic factor and are concordant with current grading frameworks in thyroid pathology. Regarding tumor grade, we observed a clear enrichment of strong STC1 in high-grade tumors. This dovetails with the 2022 WHO framework, which recognizes high-grade morphology in follicular cell–derived carcinomas and links it to adverse biology and outcomes; our data add that STC1 upregulation co-segregates with this high-risk phenotype. The literature specifically in PTC supports a prognostic role for STC1: a 2022 study reported that higher STC1 expression correlated with adverse clinicopathologic factors and lymph-node metastasis, underscoring its potential as a predictive marker in PTC. [20,22].

Regarding capsular invasion, we found that Capsular invasion clustered with strong STC1; this results match with prior work that shows STC1 overexpression in thyroid tumor tissues (IHC) and links STC1 to invasion/microenvironmental remodeling across cancers (e.g., macrophage-mediated immune evasion), supporting the plausibility that higher STC1 accompanies invasive growth. [23].

While some DTC outcome studies suggest capsular invasion alone has limited long-term prognostic impact when adjusted for other factors, this tempers how strongly STC1–capsular invasion should be interpreted prognostically. Others still identify capsular or angioinvasion as part of broader risk signatures. These mixed results indicate that while STC1 may track with invasion biologically, its independent prognostic weight relative to capsular invasion requires larger, multivariable analyses.[24].

Disagreement / mixed evidence. Some DTC outcome studies suggest capsular invasion alone has limited long-term prognostic impact when adjusted for other factors, which tempers how strongly STC1–capsular invasion should be interpreted prognostically. Others still identify capsular or angioinvasion as part of broader risk signatures. These mixed results indicate that while STC1 may track with invasion biologically, its independent prognostic weight relative to capsular invasion requires larger, multivariable analyses.

Regarding diagnostic performance, the current study found that STC1 immunohistochemistry achieved a sensitivity of 88.9%, specificity of 92.6%, and accuracy of 92.2% (AUC = 0.907) in identifying PTC. These results are consistent with those of Sengun et al. [13], who found that STC1 immunostaining was an efficient diagnostic marker for PTC, reporting a sensitivity of 93%, specificity of 94%, positive predictive value of 93.9%, and negative predictive value of 93.1%.

The current study's main strength lies in its comprehensive assessment of STC1 expression using well-defined PTC cases across different grades and stages. The consistent methodology and detailed clinicopathological data enhance the reliability of the findings, supporting the potential of STC1 as a biomarker in PTC.

The mean age was 43.9 ± 8.3 years in the PTC group and 38.8 ± 7.4 years in the control group, with ranges of 31–62 and 30–50, respectively. There was no significant difference between groups regarding age ($P > 0.05$). Similar demographic patterns have been described by Himabindu et al. [10] and Salmaslioglu et al. [11], while Frates et al. [12] found a higher incidence of thyroid carcinoma in older and male patients, reflecting ongoing controversy regarding demographic risk factors.

However, the retrospective and single-center design limits the generalizability of the results. The modest sample size may reduce statistical power, and the absence of long-term follow-up data prevents assessment of the impact of STC1 on patient outcomes.

CONCLUSIONS

The present study demonstrates that STC1 expression increases progressively from low-grade lesions to high-grade and malignant papillary thyroid carcinoma, suggesting a potential role in PTC carcinogenesis. Given its high sensitivity and specificity, STC1 may serve as a valuable diagnostic marker, particularly in challenging cases lacking classic histopathological features. Furthermore, the observed correlation between STC1 expression and both tumor stage and grade highlights its potential utility as a prognostic indicator in *Papillary thyroid carcinom*a.

Conflict of Interest : None

Financial disclosure: None

Availability of Data: The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Author Contribution: A.M.M.F. conceived and designed the study, performed immunohistochemical staining, collected and analyzed data, and drafted the manuscript. M.I.A. supervised the research, provided critical guidance, and revised the manuscript. O.A.H. contributed to study coordination, offered expert pathological evaluation, and assisted in manuscript editing. H.A. supported the interpretation of findings, contributed to statistical analysis, and took part in preparing and revising the final manuscript. All authors revised and approved the final version of the research.

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