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**Original Research Article**

# The impact of Hashimoto's thyroiditis on the diagnostic utility of P63 and CK19 immunohistochemistry markers in predicting thyroid cancer

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## ABSTRACT

**Background:** The incidence of thyroid cancer (TC) and Hashimoto's thyroiditis (HT) is increasing worldwide. Coexisting HT adds to diagnostic confusion in establishing TC on histopathological examination (HPE). Studies have shown the promising role of immunohistochemistry markers in predicting cancer, but the impact of coexisting HT is unclear. This prospective study determined the impact of HT on the diagnostic utility of p63 and CK19 in predicting thyroid cancer.

**Methods:** Out of 103 patients undergoing total thyroidectomy for benign or malignant thyroid nodules, 31 patients (mean age=39.7 years; Male:Female=4:27) with elevated thyroid autoantibodies were studied. HPE of formalin-fixed paraffin-embedded tissue from surgical specimens confirmed the final diagnosis. Sections 2-4µ were stained for immunohistochemistry using the standard avidin-biotin complex method with antibodies against P63 and CK19. Expression in 10% or more of neoplastic cells qualified as positive while expression in less than 10% was considered negative. Receiver Operating Characteristic (ROC) assessed the diagnostic accuracy.

**Results:** Histopathology comprised 58.1% benign and 41.9% malignant lesions. CK19 exhibited membranous expression in 87.1%, while p63 exhibited focal nuclear expression in 35.5% of cases. In ROC analysis predicting TC for entire cohort, the area under curve (AUC) of P63 was 0.6 and CK19 was 0.532. In subgroup with HT, the AUC of p63 was 0.8. Each P>0.05.

**Conclusions:** P63 expression had better predictability for thyroid cancer with co-existent Hashimoto's thyroiditis but was not statistically significant. Whereas, CK19 was non-specific and unreliable. Histomorphological features on HPE are the gold standard for diagnostic decisions.

**Keywords:** CK19, Hashimoto's thyroiditis, Immunohistochemistry markers, p63, Thyroid cancer

## INTRODUCTION

Thyroid cancer is the most common endocrine malignancy and its incidence is increasing worldwide.[1] Papillary thyroid carcinoma (PTC) is the most common cause of thyroid malignancy worldwide.[2–4] In the past few decades, not only PTC but also benign thyroid conditions including Hashimoto's thyroiditis (HT) and

thyrotoxicosis have increased incidence globally, particularly in iodine-replete areas.[1,5] India is no exception. In contrast to the northern iodine-deficient sub-Himalayan endemic goiter belt, iodine-replete southern India has reported an increasing incidence of papillary thyroid cancer, Hashimoto's thyroiditis, and thyrotoxicosis.[6,7] PTC is a follicular-derived thyroid neoplasm with characteristic nuclear features, which are of diagnostic importance. The diagnosis of PTC is well-established with cytology and histopathological examination (HPE) of thyroidectomy specimens.

However, follicular thyroid carcinoma cannot be diagnosed with cytology as capsular and vascular invasion can be demonstrated only with HPE. Recently, with increasing incidence of follicular patterned benign thyroid lesions including non-invasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP), it is difficult to rule out thyroid carcinoma on HPE. Similarly, it is difficult to distinguish encapsulated follicular thyroid carcinoma from the follicular variant of PTC.

In contrast to many benign thyroid disorders, surgical eradication remains the mainstay of treatment for malignancy. Additionally, the radicality of total thyroidectomy (TT) allows follow-up surveillance with tumour markers including thyroglobulin, and improved efficacy of subsequent radioiodine scans and therapy. On the other hand, HT is a benign auto-immune thyroid disease often requiring thyroxine supplementation for hypothyroidism.

Moreover, studies recommend a higher threshold for TT in HT patients due to higher rates of postoperative recurrent laryngeal nerve palsy and hypoparathyroidism.[8] For this reason, it is necessary to distinguish benign and malignant thyroid lesions to decide on appropriate treatment strategies. However, histopathological examination is challenging, cumbersome, and subjective.

A few studies have shown the promising role of immunohistochemistry (IHC) markers in establishing the diagnosis of thyroid cancers.[9,10] Nevertheless, the co-existent Hashimoto's thyroiditis adds to diagnostic confusion.[11] There is a paucity of data on the influence of HT on the diagnostic utility of IHC markers in discriminating benign and malignant thyroid lesions, which needs elucidation. Therefore, we conducted this single institutional prospective observational cohort study with the aim to determine the impact of Hashimoto's thyroiditis on the diagnostic utility of IHC markers p63 and CK-19 in predicting follicular-derived thyroid cancer.

## METHODS

### *Study type*

Prospective observational cohort study.

### *Study place*

Consecutive patients with benign or malignant thyroid nodules who were surgical candidates for total thyroidectomy admitted to the Department of Endocrine Surgery, Government Mohan Kumaramangalam Medical College Hospital, Salem, India.

### *Study duration*

The study period was from October 2020 to September 2022 were enrolled in the study.

### *Inclusion criteria*

Serologically detected Hashimoto's thyroiditis patients with elevated thyroid auto-antibodies and concomitant follicular cell-derived thyroid lesions were included.

### *Exclusion criteria*

Patients with medullary thyroid carcinoma of C-cell origin, re-operative cases and those with lesser resective surgery including hemithyroidectomy or lobectomy were excluded.

### *Ethical study*

This prospective observational cohort study was done in line with STROBE guidelines, adhering to the ethical standards of the Institutional Ethics Committee and 1964 Helsinki Declaration and its later amendments.

### *Data collection*

Demographic data and clinicopathological profiles including thyroid profile, anti-thyroperoxidase antibody, anti-thyroglobulin antibody, neck ultrasound, and cytology were noted. The absolute surgical indication was cytology suspicion of malignancy. Relative indications were large volume goiter with pressure symptoms, toxic goiter resistant to anti-thyroid drugs, thyroid eye disease, cosmesis and the patient's preference for surgery. A single surgeon performed TT as per Institutional standards safeguarding the parathyroids and laryngeal nerves. The final diagnosis was confirmed with histopathological examination (HPE) of surgical specimens, in accordance with the WHO classification of endocrine tumors.[12]

Formalin-fixed paraffin-embedded tissue sections were carried out as per institutional standards and histomorphology was studied in detail. Two main histopathological features confirmed HT. First, the stromal or parenchymal infiltration of lymphoplasmacytic cells with germinal centre formation, occasional histiocytes and scattered multinucleated giant cells. Mere infiltration of lymphocytic cells was not considered HT. Secondly, the presence of Hurthle or Ashkenazi cells (large polygonal cells with granular eosinophilic

cytoplasm and large nuclei with prominent nucleoli) paving the thyroid follicle. Patients with histologically confirmed HT and those without were included in HT and non-HT subgroups respectively.

### *Immunohistochemistry*

Immunohistochemistry was performed on 2-4 µ thick sections using the labelled streptavidin-biotin peroxidase complex system (LSAB2) from Dako, USA. Antibodies were directed against P63 and CK19 using the standard avidin-biotin complex method as per the manufacturer's instruction. Evaluation of the immunohistochemical staining was performed by light microscopy using a 10x objective lens with the selective use of a 40x objective lens for confirmation. A positive expression of IHC markers in 10% or more of neoplastic cells qualified the case as "positive (+)", while expression in less than 10% of the neoplastic cells/lesion was considered negative.

Two independent pathologists confirmed the HPE and IHC reports. Consensus was reached in controversial cases. The patients, pathologists and the investigator were all blinded.

### *Statistical analysis*

Categorical data were expressed as frequency and percentage. Continuous data were mostly non-normal on the Kolmogorov-Smirnov normality test and were expressed as median (interquartile range). SPSS software was used for statistical analysis. Fischer's exact tests, independent student's T test and ANOVA were employed where appropriate.

Mann-Whitney non-parametric test was used for non-normal data. The receiver operating characteristic (ROC) curve assessed the diagnostic accuracy of IHC markers p63 and CK19. Classifiers with up and leftward shifts had better predictability while classifiers closer and parallel to the diagonal had poor predictability. A p value of less than 0.05 was considered significant.

## RESULTS

Out of 103 patients undergoing TT for benign or malignant thyroid nodules, a total of 31 patients (n=31) with elevated thyroid auto-antibodies were eligible for the analysis (Figure 1). The study included 4 male (12.9%) and 27 female (87.1%) patients. Their age, antithyroglobulin antibody and anti-thyroperoxidase antibody levels were 39(20, 13-65) years, 56(433.8, 3.2-1000) IU/mL and 224.6(817.6, 12-1000) IU/ml. In our cohort, the frequency of histologically confirmed differentiated thyroid cancer and HT was 41.9% (n=13) and 54.8% (n=17) respectively. Demographics of patients with and without thyroid cancer (Table 1) and those with and without thyroiditis (Table 2) were compared. There was no significant difference with regard to age and sex in either of the groups.

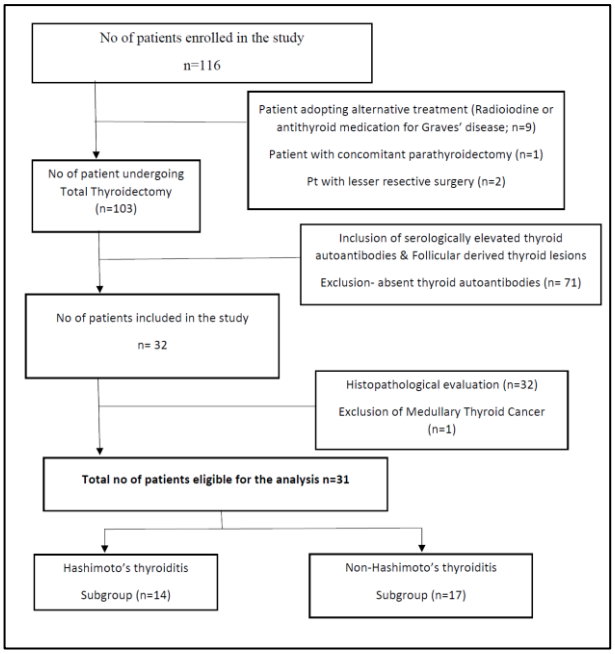


**Figure 1: Patients included in the study and those eligible for the analysis.**

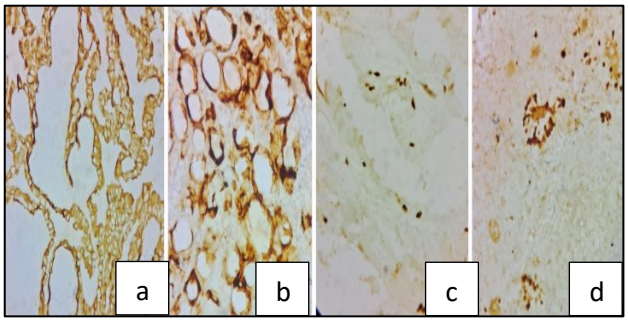


**Figure 2: Immunohistochemistry on high power (40X) showing CK19 membranous positivity in (a) PTC) and (b) Hashimoto's thyroiditis (HT). P63 nuclear positivity in (c) PTC and (d) HT.**

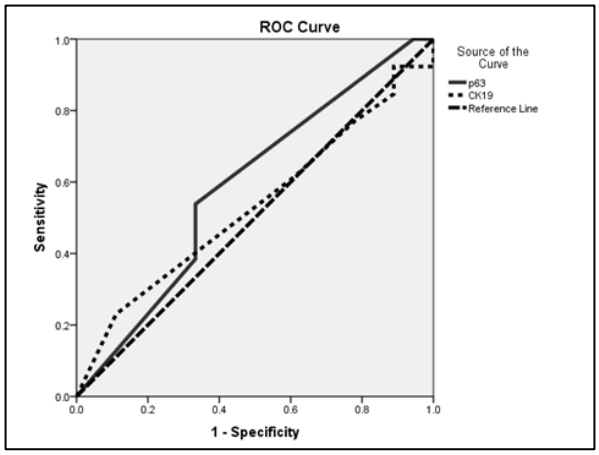


**Figure 3: ROC curve showing p63 and CK19 predicting thyroid cancer in the entire cohort.**

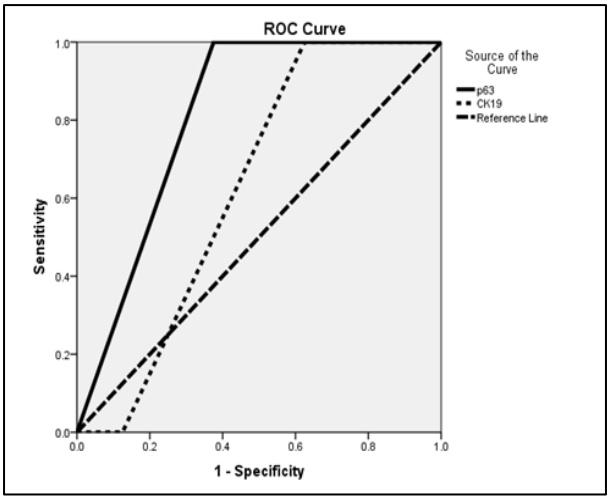


**Figure 4: ROC curve showing p63 and CK19 predicting thyroid cancer in the subgroup with coexistent Hashimoto's thyroiditis.**

Histopathology comprised 16.1% colloid goiter (n=5), 25.8% Hashimoto's thyroiditis (n=8), 3.2% nodular hyperplasia (n=1), 3.2% follicular adenoma (n=1), 3.2% Graves' disease (n=1), 6.4% adenomatous hyperplasia (n=2), 32.3% papillary thyroid carcinoma (n=10), 6.4% follicular thyroid carcinoma (n=2) and 3.2% poorly differentiated thyroid carcinoma (n=1). A positive CK19 membranous expression with or without cytoplasmic staining was observed in 87.1% (n=27) of our study population. CK19 expression profile was non-discriminatory, exhibiting positivity in both benign (59.3%, n=16) and malignant (40.7%, n=11) thyroid lesions. CK19 had a higher sensitivity rate of 84.6% for TC, exhibiting positivity in eleven of the thirteen patients with cancer but poor specificity of 11.1% (2/18) with a large number of false positives.

Both the positive predictive value (PPV) of 40.7% (11/27) and the negative predictive value (NPV) of 50% (2/4) were limited. Furthermore, CK19 failed to achieve statistical significance (p=0.737). On the other hand, focal nuclear p63 staining pattern was observed in 35.5% (n=11) of the cases, including 5 malignant and 6 benign thyroid lesions (Figure 2). Immunohistochemistry on high power (40X) showing CK19 membranous positivity in (a) Papillary Thyroid Carcinoma (PTC) and (b) Hashimoto's thyroiditis (HT). P63 nuclear positivity in (c) PTC and (d) HT.

P63 exhibited a relatively higher specificity of 66.7% (12/18) for TC with a limited number of false positive cases. However, the sensitivity rate of 38.5% (5/13) was poor. PPV, NPV and p value were 45.5% (5/11), 60% (12/20) and 0.482 respectively. P63 expression was observed in 30% (3/10) of PTC, 50% (1/2) of FTC, and 100% (1/1) of PDTC cases.

***Receiver operating characteristic analysis***

ROC curve was constructed to assess the diagnostic accuracy of IHC markers in predicting thyroid cancer. The area under the curve (AUC) values closer to 1 indicate better predictability, while values closer to 0.5 indicate poorer predictability. In ROC analysis for the entire cohort (Figure 3), the AUC for the test variable p63 was 0.6 (p=0.401) and that for CK-19 was 0.532 (p=0.764).

In subgroup analysis, among cohorts with histologically proven HT, AUC for p63 was 0.813 (P=0.307). The sensitivity, specificity, PPV and NPV were 100%, 62.5%, 14.3%, and 100% respectively. Whereas, for CK-19 predicting cancer in HT subgroup (n=17), AUC, sensitivity and specificity was 0.625 (p=0.683), 100%, and 6.3% respectively (Figure 4). In subgroup without HT (n=14), p63 predicted TC with AUC, sensitivity and specificity of 0.75 (p=0.273), 33.3% and 100% and values for CK19 were 0.667 (p=0.465), 83.3% and 50% respectively.

**Table 1: Comparison of demographic data of patients with and without thyroid cancer.**

| Parameter | Thyroid cancer | | P value |
|---|---|---|---|
| | Yes (n=13) | No (n=18) | |
| **Age in years, median (IQR)** | 40 (28) | 36 (20) | 0.879 |
| **Male: Female (N, %)** | 2 (15.4%): 11 (84.6%) | 2 (11.1%): 16 (88.9%) | 0.737 |
| **CK-19 (N, %)** | 11 (84.6%); 2 (15.4%) | 16 (88.9%): 2 (11.1%) | 0.990 |
| **P63 (N, %)** | 5 (38.5%): 8 (61.5%) | 6 (33.3%): 12 (66.7%) | 0.354 |
| **Anti-thyroglobulin antibody IU/ml, median (IQR)** | 22.2 (32.5) | 342 (836.4) | 0.042 |
| **Anti-thyroperoxidase antibody IU/ml, median (IQR)** | 78.8 (118.3) | 885.2 (799.9) | 0.006 |

**Table 2: Comparison of demographic data of patients with and without Hashimoto's thyroiditis.**

| Parameter | Hashimoto's thyroiditis | | P value |
|---|---|---|---|
| | Yes (n=17) | No (n=14) | |
| **Age in years (median (IQR))** | 35 (20) | 39.5 (26) | 0.843 |
| **Male: Female, (N, %)** | 2 (11.8%): 15 (88.2%) | 2 (14.3%): 12 (85.7%) | 0.842 |
| **CK-19 (N, %)** | 16 (94.1%): 1 (5.9%) | 11 (78.6%): 3 (21.4%) | 0.393 |
| **P63 (N, %)** | 7 (41.2%): 10 (58.8%) | 4 (28.6%): 10 (71.4%) | 0.983 |
| **Anti-thyroglobulin antibody IU/ml median (IQR)** | 348 (831.9) | 18.5 (29.6) | 0.002 |
| **Anti-thyroperoxidase antibody IU/ml, median (IQR)** | 874 (824.4) | 83.1 (179) | 0.018 |

## DISCUSSION

Hashimoto's thyroiditis is the leading autoimmune disease and is the most common cause of hypothyroidism in iodine-sufficient areas worldwide.[13] HT is characterized by thyromegaly, aseptic chronic inflammation and elevated thyroid autoantibodies. There is growing evidence of the association between HT and thyroid cancer. However, the causal relationship remains controversial. Many studies have shown that chronic inflammation is an indispensable component in cancer development. The reported rate of thyroid cancer in HT patients ranges from 0.6% to 58.4%, with a mean rate of 25%.[13] Consistent with published reports, the incidence of thyroid cancer in our HT patients was 41.9%, though relatively high.

The co-existence of HT can add to diagnostic confusion during HPE of thyroidectomy specimens. The histological hallmarks of HT are the presence of lymphoplasmacytic infiltrate with germinal centre formation, Ashkenazi cells, follicular atrophy and fibrosis. However, HT may contain cells with optically clear nuclei that tend to overlap follicular epithelium or other nuclear alterations, similar to that seen in PTC.[11,14]

Studies on the utility of IHC markers including CK19 and p63 to improve diagnostic accuracy of thyroid cancer have reported conflicting results.[9,10,14,15] Cytokeratin polypeptide-19 (CK19) is a 40 kDa smallest known keratin, often co-expressed with CK7 in simple and complex epithelium. CK19 is a type I intermediate filament involved in the organization of myofibers. Several studies have shown CK19 positivity with varying intensity in both benign and malignant thyroid lesions.[9,16]

In our cohort, IHC studies demonstrated positive CK19 membranous expression in 87.1% of the cases. CK19 had a higher sensitivity of 84%, staining positive in 11 of 13 cancer patients. However, CK19 had poor specificity (11.1%), PPV (40%) and NPV (50%) for cancer. A specificity of 11.1% implies that only 11 eleven out of 100 patients who do not have cancer, will stain negative for CK-19 (true negatives), indicating a large number of false positives. PPV of 40% implies that only 40% of the patients who test positive are likely to have the disease (cancer) while NPV of 50% implies that 50% of the patients with negative test results are unlikely to have cancer.

In ROC showing CK19 predicting cancer, the classifier was parallel to the diagonal indicating poor diagnostic accuracy. Thus, CK19 was non-discriminatory between benign and malignant thyroid lesions and was inconsistent in predicting thyroid cancer. On the other hand, P63 protein is a p53 homologous nuclear transcription factor involved in the regulation of epithelial proliferation and differentiation. Mutation in p53 tumour suppressor gene is a late-step event in carcinogenesis and is associated with cancer progression from well-differentiated thyroid cancers to undifferentiated forms.[17] P63 with six different isoforms may exert either a transactivating or dominant negative effect on p53 and its tumour suppressor effect in thyroid cancer is controversially reported.[18–20] Perhaps, studies have shown that p63 expression in thyroid cancers ranges widely from 6.9% to 74% with a higher positive rate towards the undifferentiated end of the spectrum.[21]

Our present study demonstrated a focal p63 nuclear staining pattern in 3 PTC (30%), 1 FTC (50%) and 1 PDTC (100%) patient. Our observations corroborated with published reports. P63 expression had a higher specificity for thyroid cancer compared to CK-19 (66.7% vs 11.1%). It implied that 66.7% of the patients who do not harbour cancer are likely to have negative p63 staining patterns. Likewise, p63 had better NPV (60%) compared to CK-19. Nevertheless, NPV of 60% (12/20) was limited. It implied that 12 out of 20 patients who did not have cancer had negative test results with p63 IHC staining, while the remaining 8 patients actually had cancer but tested negative, indicating a false negativity of 40%.

In ROC analysis showing p63 predicting cancer, the AUC was 0.6 implying poor predictability. Our subgroup analysis revealed that p63 and CK-19 had better predictability of TC (with AUC of 0.8 and 0.7) in patients with coexistent HT compared to those without HT. However, both p63 and CK-19 failed to achieve statistical significance in the ROC analysis. Thus, we conclude that thorough HPE shall be the standard of care and histomorphological features are of prime importance in establishing the diagnosis of thyroid cancer.

The improved diagnostic value of both the IHC markers p63 and CK-19 in the subgroup with histologically confirmed HT may be attributed to the increased cancer risk in this subset.[22–24] Consistent with our observation, many studies have shown that chronic inflammation is an indispensable component in cancer development.[13,25] The proposed mechanism of tumorigenesis in HT is the release of reactive oxygen species and inflammatory chemokines from the damaged tissues in the inflammatory milieu. Subsequent damage to DNA, proteins and lipids can result in unregulated cellular proliferation, cellular transformation, tumour development and progression. DNA methylation is another proposed mechanism of tumorigenesis involved in inflammatory milieu.

Additionally, elevated TSH, thyroid autoimmunity and iodine can impact the immune microenvironment in HT.[5,13,25] Hence, it is probable that HT may be the cause as well as the effect and thereby confound the outcome of test variables in predicting cancer. Other limitations include the small sample size. The relatively high frequency of HT and thyroid cancer in our study population may be attributed to the referral bias, as it is a tertiary care centre. The study is population-specific and hence could not extrapolated to the general population. There could be other confounding factors not included in our analysis which could have influenced some of our observations.

## CONCLUSION

IHC marker P63 expression had higher specificity and better predictability for thyroid cancer in patients with co-existent Hashimoto's thyroiditis but failed to achieve statistical significance. CK19 expression was non-specific and unreliable in distinguishing benign and malignant thyroid lesions. Histomorphological features on HPE shall always be the gold standard for establishing the diagnosis of thyroid cancer.

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*Ethical approval: The study was approved by the Institutional Ethics Committee*

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