ORIGINAL RESEARCH PAPER
Volume - 14 | Issue - 12 | December - 2025 | PRINT ISSN No. 2277 - 8179 | DOI : 10.36106/ijsr
INTERNATIONAL JOURNAL OF SCIENTIFIC RESEARCH

DIAGNOSTIC UTILITY OF CK19 IN DIFFERENTIATING PAPILLARY THYROID CARCINOMA FROM BENIGN PAPILLARY HYPERPLASIA.

Histopathology

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ABSTRACT

Background: Papillary thyroid carcinoma (PTC) is the most common thyroid malignancy and difficult to distinguish from benign papillary hyperplasia and other follicular lesions on morphology alone. Cytokeratin 19 (CK19) immunohistochemistry (IHC) has been proposed as a helpful ancillary marker, with diffuse strong staining favouring PTC whereas weak or focal staining is more common in benign lesions. **Objectives:** To evaluate the diagnostic utility of Cytokeratin 19 (CK19) immunohistochemistry in differentiating papillary thyroid carcinoma from benign papillary hyperplasia, and to compare CK19 expression patterns between these lesions. **Methods:** A retrospective histopathological and immunohistochemical analysis of 50 thyroid specimens with papillary architecture (30 PTC, 20 benign papillary lesions) was performed. CK19 IHC was scored semi-quantitatively by proportion of positive cells (0 to 4+) and correlated with histological diagnosis and clinicopathological features. **Results:** A total of 50 papillary thyroid lesions were studied. The mean age group was 43 years. The male:female ratio in PTC was 1:3.29. Diffuse and strong CK19 positivity (3 to 4+) was found in the majority of PTC cases; 23/30 cases showed 4+ and 7/30 showed 3+ staining. Among benign papillary hyperplasia (n=20), 18 were negative and 2 showed weak (1+) focal staining. The difference in CK19 expression between malignant and benign lesions was statistically significant (p=0.0001). Sensitivity and specificity of CK19 for PTC in this series were approximately 93.7% and 100%, respectively (PPV 100%, NPV 90%). The overall diagnostic accuracy of CK19 was 96.5%. **Conclusions:** CK19 is a useful adjunctive marker for distinguishing PTC from benign papillary lesions when used in the proper morphological context. Diffuse strong membranous/cytoplasmic CK19 staining supports the diagnosis of PTC; focal or absent staining argues against it. CK19 should ideally be used as part of an IHC panel along with other makers and interpreted with histology.

KEYWORDS

Cytokeratin-19, Papillary Thyroid Carcinoma, Benign Thyroid Hyperplasia, Immunohistochemistry.

INTRODUCTION

Thyroid cancer is the most common malignant tumour ranking ninth most diagnosed caner with approximately 5.86 lakhs new cases reported globally. In India contributing 38,574 new cases (29,037 in women and 9,537 in men) in 2025 (Mathew et al., 2025). Thyroid neoplasms represent the most common endocrine malignancies worldwide, and papillary thyroid carcinoma (PTC) is the predominant histologic type, accounting for approximately 80 to 85% of thyroid cancers (Limaiem et al., 2025). PTC is a epithelial malignancy characterized by follicular cell differentiation and distinctive nuclear features. PTC typically affects adults in the third to fifth decades and shows a female predominance (Limaiem et al., 2025)(Seib & Sosa, 2019). PTC generally has an excellent overall prognosis, especially for patients younger than 45 years of age (Limaiem et al., 2025).

The incidence of papillary thyroid carcinoma is increasing worldwide, mainly due to a greater number of papillary thyroid carcinomas. Generally areas where Excess iodine or iodine sufficient diets having the PTC (Ywata de Carvalho et al., 2021). Dietary Iodine found to be influence the morphology and incidence of PTC. Thus there are significant geographic variations, but this wide variability may also be attributed to variations in sampling techniques. Diagnosis is usually established by identifying characteristic nuclear features optically clear nuclei, nuclear grooves, overlapping, and intranuclear cytoplasmic inclusions, often in association with papillary architecture. However, several benign thyroid conditions goiter with papillary hyperplasia, Graves' disease, Hashimoto thyroiditis and certain follicular neoplasms can show papillary formations or nuclear atypia that mimic PTC, complicating morphological interpretation (Forma et al., 2025)(Houten et al., 2023).

Immunohistochemical markers have been evaluated to aid differential diagnosis. CK19 is primarily expressed in papillary thyroid carcinoma (PTC) and has been extensively studied for its diagnostic utility in distinguishing malignant from benign thyroid lesions (Bose et al., 2012)(Idowu et al., 2023). Cytokeratin 19 (CK19) is a low-molecular-weight type I cytokeratin expressed in simple epithelium and widely used in thyroid pathology because of its frequent diffuse strong expression in PTC compared to benign lesions where staining tends to be absent, focal or weak (Prasad & Raju, 2022)(Fadhel, 2023). Other markers frequently considered in panels include HBME-1, galectin-3, TTF-1, RET oncoprotein, and CD56; combining markers often improves diagnostic accuracy compared to single markers alone (Vella et al., 2022)(Abdel-Aziz & Abdallah, 2019). However, few studies reported high sensitivity and specificity for CK19, while others caution about focal expression in benign lesions or variable performance depending on fixation and methodology (Fadhel, 2023)(Laishram et al., 2025).

The purpose of the study is to asses usefulness of CK19 as a marker of papillary carcinoma in relation to other types of papillary hyperplasia.

MATERIALS AND METHODS

A retrospective observational study was conducted in the Department of Pathology, Kakatiya Medical College and Hospital, using thyroidectomy and biopsy specimens from April 2023 to April 2025. Fifty cases with papillary architecture were included: 30 papillary thyroid carcinomas (including classic PTC, follicular variant, microcarcinoma) and 20 benign lesions with papillary hyperplasia (nodular goitre with papillary areas, Hashimoto thyroiditis with papillary changes). Clinical subjects with Papillary carcinoma, its variants and benign lesions of papillary hyperplasia were included in this study. Other malignancies and samples with benign lesions without papillary hyperplasia were excluded from the study. Demographic and clinical information like age, sex, presentation were retrieved from patient records. The study was approved by institution ethics committee (KIEC/2022-23/152) before collecting clinical specimens.

Histology and Immunohistochemistry

Thyroidectomy and subtotal thyroidectomy specimens were received in 10% formalin and fixed within 24 hrs. Formalin-fixed paraffin-embedded (FFPE) tissue blocks were sectioned at 4 to 5 µm and stained with hematoxylin and eosin for routine histology. The slides were studied under light microscopy. CK19 immunohistochemistry was performed using a validated primary antibody and an HRP-DAB

detection kit Manufactured by DAKO™ (Agilent technologies private limited, CA, USA). Antigen retrieval used Tris-EDTA buffer in a microwave as described in the kit protocol. Positive and negative controls were included for each run.

Scoring

CK19 staining was assessed semi-quantitatively by percentage of positive cells: 0 (nil), 1+ (<5%), 2+ (5–25%), 3+ (25–75%), 4+ (>75%). Both membranous and cytoplasmic reactivity were recorded. For diagnostic interpretation, 3+ and 4+ (diffuse/moderate-to-strong) staining was considered supportive of PTC; focal 1+ and 2+ staining was considered equivocal/benign. Scoring reproducibility was enhanced by independent review.

Statistical Analysis

Descriptive statistics summarized clinical and pathological variables. Association between CK19 expression and diagnosis (PTC vs benign) was analysed using Fisher's exact test. Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were calculated for CK19 positivity (3+ and 4+ as positive). Data arrangement and basic statistics and graphs are generated in Microsoft excel spread sheet. Other statistical analyses were performed at openEPI online statistical tool. P value 0.05 or below considered as significant.

RESULTS

Clinicopathological Features

A total of 50 papillary thyroid lesions were studied. Age distribution of PTC showed the majority in the 31–50 years group; mean age was 43 years. Among total study subjects females were 43 (86%) and males were 7 (14%). The male:female ratio in PTC was 1:3.29. Among 50 studies samples, 30 were confirmed as PTC with 24 classic type, 4 follicular-variant, 2 microcarcinoma (Figure-1) . Remaining 20 benign lesions with papillary hyperplasia, 12 were nodular goiter with papillary hyperplasia and 8 Hashimoto thyroiditis with papillary areas. Most PTC presented as solitary nodules 16 (53%), multinodular swellings are 12 (40%) and Diffuse swelling only 2 (6.6%). Out of 12 cases of nodular goiter 7 cases presented as single swelling and 5 cases presented as multinodular swelling. And out of 8 cases of hashimotos thyroiditis 4 cases presented as single nodule, 3 cases as diffuse swelling and 1 case as multinodular swelling.

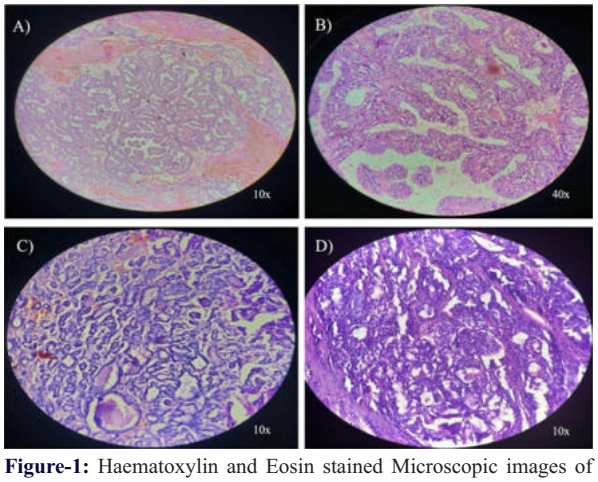

Figure-1: Haematoxylin and Eosin stained Microscopic images of papillary thyroid carcinoma (PTC). A) classical PTC at 10x, B) Classical at 40x, C) Follicular variant of PTC at 10x and D) Microcapillary thyroid carcinoma at 10x. PTC =papillary thyroid carcinoma. CK19= Cytokeratin 19.

CK19 Expression

All 30 PTC samples were processed for CK19 Expression. CK19 scoring in these cases were assessed according to the number of cells showing positivity and graded. Out of 24 cases of classic type papillary carcinoma, 20 cases showed 4+ positivity and 4 cases showed 3+ positivity. Among 4 cases were of follicular variant of papillary carcinoma, 3 cases showed CK19 expression of 4+ positivity and 1 cases showed of 3+ positivity. Similarly 2 cases of micropapillary carcinomas showed CK19 expression of 3+ positivity (in both the cases). Therefore no PTC was negative for CK19 expression (Figure-2). All PTC cases showed diffuse positivity 23/30 (76.7%) had 4+ positivity and 7/30 had 3+ positivity (23.3%). This finding showed borderline significant between percentage of samples and CK19 expression positivity (p=0.07). Among Benign papillary lesions (n=20), CK19 expression showed negative in 18 cases and 2 cases showed focal 1+ positivity.

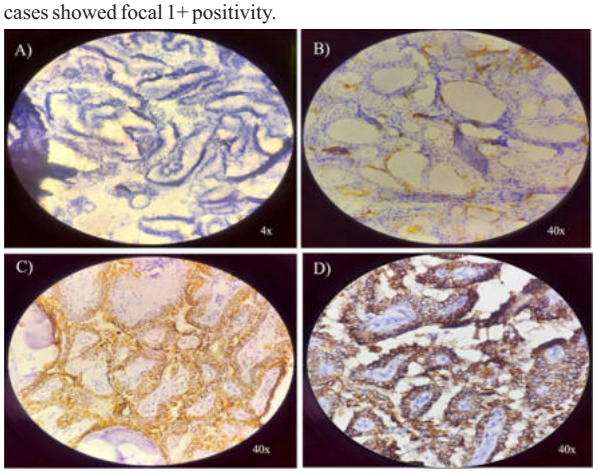

Figure-2: Immunohistochemistry stained microscopic images A) Negative for CK19 expression B) Focal patchy positivity C) Strong Cytoplasmic positivity in PTC and D) Diffuse and strong positivity in PTC. PTC =papillary thyroid carcinoma. CK19= Cytokeratin 19.

The median age for Nil ("0") positivity for CK19 expression was 45, 1+ positivity were 63 age, 3+ positivity were 55 age and 4+ positivity were 50 age. Among 4+ positivity of CK19 expression showed both gender groups (Male + Female), While remaining Negative, 1+ and 3+ positivity of CK19 Expression showed female predominance (Figure-3).

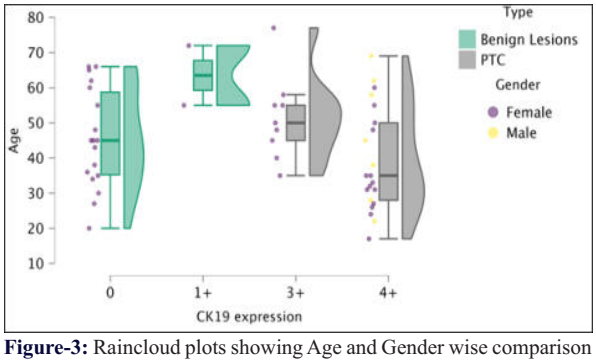

Figure-3: Raincloud plots showing Age and Gender wise comparison between PTC and Benign lesions of hyperplasia. PTC= Papillary thyroid carcinoma. CK19= Cytokeratin 19.

Diagnostic Accuracy

Comparing CK19 strong positivity (3+ and 4+) between malignant and benign papillary lesions produced a statistically significant difference (Fisher's exact, p = <0.0001). Calculated diagnostic metrics were: sensitivity 93.7%, specificity 100%, Positive predictive value, Negative predictive value 90%. Overall diagnostic accuracy 96.5% and contingency ecoefficiency was 0.707.

DISCUSSION

Papillary thyroid carcinoma (PTC) is the most common type of thyroid cancer, and its prognosis is influenced by several factors, including age and gender. Differentiating PTC from benign thyroid lesions demonstrating papillary architecture remains a common diagnostic challenge in endocrine pathology. Diagnostic challenges often arise due to overlapping features with other thyroid lesions, making immunohistochemical (IHC) markers crucial for accurate diagnosis.

Age is recognized as an important prognostic factor in papillary thyroid cancer, with younger patients generally having better survival rates. In our study mean age for PTC was noticed 43 years, our study showed concordance with similar study (Kauffmann et al., 2018). A study with a capacity of 1738 records showed patients with 55 years had a longer survival time (Sun et al., 2020). That's stating age being an individual risk factor for overall survival.

Thyroid cancer predominantly affects women, we displayed men vs female ratio with incident rate more than three times higher than men

(1:3.29). One possible explanation more female incident rate than men because of hormonal differences (Su et al., 2016).

The diagnosis of papillary thyroid carcinoma is challenging, particularly due to the inter- and intra-observer variability in histo-morphological diagnosis and when typical features are not present or overlapping features exist (Singh et al., 2020). Immunohistochemical (IHC) markers play a critical role in the accurate diagnosis and differentiation of papillary thyroid carcinoma, especially in challenging cases (Badini et al., 2022).

Among them CK19 shows strong and diffuse positivity in papillary carcinoma, Often used with other markers (Asghari et al., 2023). Strong CK19 expression is highly associated with PTC, while benign lesions more often show absent or focal weak staining. This study's findings align with numerous published reports showing that diffuse positivity in papillary carcinoma (Fadhel, 2023)(Heidarpour et al., 2024)(Abdou et al., 2019). In the present study, CK19 showed strong 3–4+ reactivity in most PTCs (30/30 diffuse positivity), whereas benign papillary lesions were predominantly CK19-negative (18/20 negative), yielding high sensitivity and specificity in current study. Several studies reported varying diagnostic accuracy of CK19 positivity in PTC ranging from 80 to 100% (Laishram et al., 2025)(Abdou et al., 2019).

Several single-centre studies and meta-analyses have evaluated CK19 Expression. A study from India reported diffuse strong CK19 in all PTCs and weaker focal positivity in some benign lesions, concluding CK19 is valuable but not absolutely specific (Bose et al., 2012). A meta-analysis and other systematic reviews found that CK19, often combined with galectin-3 and HBME-1, increases diagnostic accuracy for PTC both in cytology and surgical specimens (Prasad & Raju, 2022)(Xin et al., 2017)(de Matos et al., 2012). CD56 markers with CK19 provide higher diagnostic accuracy as compared to other marker combinations (Abouhashem & Talaat, 2017).

Recent studies also support CK19's high sensitivity but note variable specificity dependent on cutoffs, antibody clones, and interpretation criteria (Prasad & Raju, 2022)(Abdou et al., 2019)(Kanber et al., 2021). These data support the approach used in this study using semiquantitative thresholds (3+ and 4+) and interpreting CK19 as part of a panel and in morphological context.

In the present study, two benign cases showed focal 1+ staining; these would have been correctly classified if CK19 positivity had been defined strictly as diffuse moderate-to-strong (3–4+). This explains, CK19 expression is not entirely specific: focal or weak CK19 positivity has been described in benign lesions, follicular adenomas, and inflamed thyroid tissue, especially in areas of reactive change or hemorrhage where staining may artifactually appear. A study mentioned that CK19 immunoreactivity should not be used in isolation because nonneoplastic follicles adjacent to tumors may show increased staining (Heidarpour et al., 2024).

Our study recommending, Use of CK19 as part of an IHC panel along with other markers CD56, galectin-3, HBME-1. Define positivity threshold in favour of diffuse 3+ and 4+ pattern for diagnosing PTC and focal/weak staining should prompt cautious interpretation and review of morphology. Correlate with cytology, clinical finding and molecular tests to improve and further assist in ambiguous cases. Recent WHO 2022 guidelines emphasize integrated morphological, immunohistochemical and molecular assessment in thyroid tumor classification (Jung et al., 2022).

Clinical Implications

Accurate differentiation of PTC from benign papillary lesions influences surgical management, follow-up intensity, and prognostication. Overdiagnosis or underdiagnosis can lead to overtreatment or under-treatment. Thus, validated IHC markers such as CK19 used correctly can meaningfully support diagnostic decisions in challenging cases, improving patient care. Meta-analyses and contemporary studies corroborate CK19's utility but recommend panel-based approaches and standardization (Guo et al., 2024).

The study had few limitations, low sample size which may limit the generalizability of the findings. As a retrospective design, a potential selection bias for cases selected for papillary morphology. Single centre study, which may not reflect broader population diversity. Single IHC marker, CK19 alone was evaluated including with two or more markers could have strengthened diagnostic accuracy.

CONCLUSION

This study confirms that CK19 shows diffuse, strong expression in most PTCs while benign papillary hyperplasia is usually negative or only focally positive. CK19, especially when interpreted as diffuse 3+ and 4+ staining and used along with other markers (HBME-1, galectin-3, CD56), is a valuable adjunct in distinguishing PTC from benign papillary thyroid lesions. However, CK19 should not be used in isolation; awareness of focal staining in benign conditions and technical variables is essential. Further multicentre studies, larger sample size and standardized scoring protocols would help refine the role of CK19 in thyroid diagnostics.

Acknowledgements

The authors acknowledge the Department of Pathology staff and technical support personnel at Kakatiya Medical College & MGM Hospital for assistance with histology and IHC, and the supervisors for guidance.

Funding

There is no funding received for this study.

Ethics Consideration

The study was approved by institutional ethics committee approval at Kakatiya medical college, hanamkonda. KIEC/2022-23/152 date: 09-05-2023.

Conflicts of Interest

All authors declares that no conflicts of interest for this article.

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