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Original Article

Expression of PD-L1 and CK19 in Thyroid Carcinoma and Their Clinicopathological Significance

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ABSTRACT

Introduction: Thyroid carcinoma is the most common endocrine malignancy, with papillary thyroid carcinoma (PTC) being the predominant subtype. Although most cases have an excellent prognosis, a subset shows aggressive behavior. Cytokeratin 19 (CK19) is a diagnostic marker for PTC, while Programmed Death-Ligand 1 (PD-L1), an immune checkpoint molecule, has its role in tumor progression and prognostic evaluation. This study aimed to assess the expression of CK19 and PD-L1 in thyroid carcinomas and analyze their association with clinicopathological parameters.

Methodology: This combined retrospective and prospective study was conducted at the Institute of Pathology, Madras Medical College, Chennai, over an one-year period (2023–2024). A total of 56 histologically confirmed cases of thyroid carcinoma were included. Immunohistochemical staining for CK19 and PD-L1 was performed on formalin-fixed, paraffin-embedded tissue sections. CK19 expression was evaluated using an immunoreactive scoring system, while PD-L1 expression was assessed using the tumor proportion score. The results were correlated with relevant clinicopathological features.

Results: CK19 showed strong and diffuse expression in the majority of PTC cases, especially classical and follicular variants. Higher CK19 expression was significantly associated with larger tumor size, increased mitotic activity, capsular and vascular invasion, and advanced tumor stage. PD-L1 expression was more commonly associated with tumors showing aggressive pathological features. Dual expression of CK19 and PD-L1 was frequently noted in tumors with adverse histological characteristics.

Discussion: CK19 remains a reliable diagnostic marker for PTC and may reflect tumor aggressiveness. PD-L1 expression, though variable, is associated with unfavorable clinicopathological features, suggesting its potential role in prognostic stratification.

Keywords: *Thyroid carcinoma, Papillary Thyroid Carcinoma, CK19, PD-L1, Prognostic marker*

INTRODUCTION

Thyroid carcinoma is the most common malignancy of the endocrine system and is a heterogeneous grouping of tumor micro-segments mainly originating from follicular epithelial cells with a minor subset derived from parafollicular C cells[1]. In the last few decades, there has been an increasing global incidence of thyroid carcinoma. This change has been mostly explained by technological progress: high-resolution ultrasonography, fine needle aspiration cytology, better histopathological assessment, and improved population surveillance, rather than a true increase in disease-specific mortality[2, 3]. This rising incidence has been accompanied with a need for solid diagnosis and prognostic stratification. Papillary thyroid carcinoma (PTC) is responsible for roughly 80–85% of all thyroid cancers and has a superior prognosis after appropriate surgical and adjuvant treatment[4]. Despite its often sedentary clinical course in majority of cases, some PTC and other subtypes of thyroid carcinoma show aggressive clinicopathological behaviors. These tumors usually display behaviors such as extrathyroidal extension, lymphovascular invasion, regional lymph node involvement, distant metastasis,

recurrence, and tumor resistance to conventional therapies[5, 6]. These aggressive features significantly affect patient prognosis and accentuate the critical importance of consistent biomarkers that can be helpful in prognostication. The following clinical and pathologic markers have a long history as prognostic indicators in the setting of thyroid carcinoma: patient age, sex, tumor size and histological subtype, capsular invasion, vascular invasion, extrathyroidal extension, lymph node involvement and tumor stage[4, 7]. Routine histopathological assessment still provides the basis for diagnosis and classification. Nonetheless, diagnostic complications persist, especially in follicular-patterned lesions, where malignant entities and benign entities can have significant morphological overlap[8]. This diagnostic ambiguity has further validated that immunohistochemistry is being utilised as a complementary approach to enhance the diagnostic efficacy and reproducibility. Cytokeratin 19 (CK19) is a low-molecular-weight intermediate filament protein abundant in simple epithelial tissue and widely known in the field of thyroid pathology. Strong and widespread expression of CK19 is typical in papillary thyroid carcinoma and in benign follicular lesions it may be weak, focal or absent staining[9, 10]. Although CK19 markers are commonly employed as diagnostic markers, recent reports have proposed that elevated CK19 would be associated with pathological characteristics like larger tumor and invasion and in the last stage may be of prognostic relevance[11]. Concurrently, the tumor-induced immune microenvironment of thyroid carcinoma has been receiving a growing focus and interest. Programmed death-ligand 1 (PD-L1) is a type of immune guard against immune evasion in tumors, by inhibiting T-cell–mediated antitumor immunity on the interaction with the programmed death-1 receptor[12]. Abnormal expression of PD-L1 has been implicated in aggressive tumor behavior, advanced stage, and poor prognosis in various malignancies, including thyroid carcinoma[13, 14]. Therapeutic pathways emerged through immune checkpoint inhibitors targeting the PD-1/PD-L1 axis for patients with advanced, poorly differentiated, and radioiodine-refractory thyroid carcinomas[15, 16]. In this novel therapeutic environment, the identification of immunohistochemical markers for diagnosing and prognosticating the progress of immunohistochemical markers providing both prognostic insight will have important clinical significance. As such, the aim of this study was, therefore, to study the expression of CK19 and PD-L1 immunohistochemical markers in thyroid carcinomas and determine their expression to correlate these with established histopathological prognostic parameters.

METHODOLOGY

The present study was a retrospective and prospective observational study involving the Institute of Pathology, Madras Medical College, Chennai, India, for one year from 2023 to 2024. The study population consisted of patients undergoing thyroidectomy and diagnosed with thyroid carcinoma on histopathological examination. The study involved 56 cases of thyroid carcinoma in all. Adult patients aged over 18 years with histologically confirmed thyroid carcinoma with sufficient tissue for immunohistochemical analysis were included. Patients younger than 18 years, cases which had not been reported at the Institute of Pathology, and low-risk thyroid neoplasms according to the WHO 2022 classification were ruled out from the analysis. Patient data including age, gender, clinical presentation, radiological findings, and fine needle aspiration cytology data were retrieved from hospital records. Histopathological parameters assessed were tumor size, histological type and subtype, mitotic activity, tumor necrosis, lymphovascular invasion, perineural invasion, capsular invasion, extrathyroidal extension, and TNM staging. For immunohistochemical processing, a representative formalin-fixed, paraffin-embedded tissue segment was chosen. 4-micron thickness sections were prepared, placed on charged slides and analysed with standard deparaffinization and antigen retrieval techniques. Immunohistochemical staining, with monoclonal antibodies against CK19 and PD-L1, was done. CK19 expression was assessed using an immunoreactive scoring system based on both intensity of staining and percentage of positive tumor cells. The final score was calculated by multiplying intensity through proportion scale and based on that cases were classed as such. We measured PD-L1 expression as the Tumor Proportion Score (TPS), defined as the percentage of viable tumor cells expressing membranous positivity. Statistical analysis was performed through SPSS version 26.0, and a p-value of <0.05 was considered statistically significant

RESULTS

In total, 56 cases of thyroid carcinoma were included in the current study. Patients ranged in age from 10 to 80 years with majority of cases occurring in the fifth (21.43%) and sixth decades (19.64%), respectively. Seventeen per cent (17.86%) of cases came from younger age groups (21–30 years and 31–40 years) and fourteen percent (14.29%) and five percent (5.36%) were found among patients aged 60–70 years and 70–80 years, respectively. Females accounted for 71.43% (n=40), and males 28.57% (n=16). Histologically, papillary thyroid carcinoma (PTC) was the most common tumor type, accounting for 87.5% (n=49) of cases. Other histological types include anaplastic carcinoma (8.93%), medullary carcinoma (1.79%), and dedifferentiated high-grade carcinoma (1.79%). In PTCs, the classical variant was the most common variety (55.36%), followed by the follicular variant (39.29%). Aggressive variants, including diffuse sclerosing, hobnail, and tall cell variants, were uncommon, as demonstrated by 1.79% of cases. The mitotic rate (<3/10 HPF) was lower in 83.93% of tumors, whereas 12.50% of tumors had a moderate mitotic rate (3–5/10 HPF) while 3.57% showed a high mitotic rate (>5/10 HPF). Tumor necrosis was detected in 12.50% of tumors. Capsular invasion occurred in 8.93%, angioinvasion in 30.36%, lymphatic invasion in 35.71%, and perineural invasion in 5.36% of tumors. Tissues showing extrathyroidal extension were observed in 5.36% of the cases. The most common stage of patients was T1b and T3a staging (28.57%), followed by T2 (25.00%), T1a (16.07%), and T3b (1.79%). Strong (3+ to 4+) and weak (1+ to 2+) CK19 expression were detected on immunohistochemical monitoring in 67.86%, 26.79%, and 5.36% of cases, respectively. CK19 expression was strongly detectable in papillary carcinomas, in particular in classical and follicular variants. Increases in CK19 expression

were directly correlated with increases in the size of the tumor, mitotic activity, tumor necrosis, capsular invasion, angioinvasion, perineural invasion, and tumor stage (Figs.1-9). PD-L1 expression (i.e., tumor proportion score [TPS]), was negative (0%) in 37.50%, very low (<1%) in 28.57%, and low (1-9%) in 33.93% of cases. PD-L1 positivity was more common in papillary and anaplastic carcinomas. Figures 10–18 indicate that expanded PD-L1 expression was associated with a larger tumor size, mitotic rate, tumor necrosis, angioinvasion, capsular invasion, and advanced tumor stage. No strong correlates were observed with patient age, sex or perineural invasion. Patients with signs of dual positivity for CK19 and PD-L1 were more likely to be identified with aggressive histopathological features, such as invasive growth and advanced tumor staging, stressing that these markers may possess diagnostic and prognostic significance when combined in their potential usefulness in thyroid carcinoma.

Table 1: Age Distribution (n=56)

Age group (years)	Frequency	Percentage(%)
10-20	2	3.57
21-30	10	17.86
31-40	10	17.86
41-50	12	21.43
51-60	11	19.64
61-70	8	14.29
71-80	3	5.36

Table 2: Gender Distribution

Gender	Frequency	Percentage(%)
Female	40	71.43
Male	16	28.57

Table 3: Histological Types

Histological Type	Frequency	Percentage(%)
Papillary carcinoma	49	87.50
Anaplastic carcinoma	5	8.93
Medullary carcinoma	1	1.79
Dedifferentiated high-grade carcinoma	1	1.79

Table 4: Subtypes of Papillary Thyroid Carcinoma

Subtype	Frequency	Percentage(%)
Classic	31	55.36
Follicular Variant	22	39.29
Diffuse sclerosing	1	1.79
Hobnail	1	1.79
Tall Cell	1	1.79
Total	56	

Table 5: Frequency Distribution of Mitotic Rate (n =56)

Mitotic Rate	**Frequency**	**Percent**
High (>5/10 HPF)	2	3.57%
Low (<3/10 HPF)	47	83.93%
Moderate (3–5/10 HPF)	7	12.50%
Total	**56**	**100%**

Table 6: Frequency Distribution of Tumor Necrosis (n =56)

Tumor Necrosis	**Frequency**	**Percent**
Identified	7	12.50%
Not Identified	49	87.50%
Total	**56**	**100%**

Table 7: Frequency Distribution of Capsular Invasion (n =56)

Capsular Invasion	**Frequency**	**Percent**
Present	5	8.93%
Absent	51	91.07%
Total	**56**	**100%**

Table 8: Frequency Distribution of Angioinvasion (n =56)

Angioinvasion	Frequency	Percent
Identified	17	30.36%
Not Identified	39	69.64%
Total	**56**	**100%**

Table 9: Frequency Distribution of Perineural Invasion (n =56)

PNI	Frequency	Percent
Identified	3	5.36%
Not Identified	53	94.64%
Total	**56**	**100%**

Table 10: Frequency Distribution of Lymphatic Invasion (n =56)

Lymphatic Invasion	Frequency	Percent
Identified	20	35.71%
Not Identified	36	64.29%
Total	**56**	**100%**

Table 11: Frequency Distribution of Extrathyroidal Extension (n =56)

Extrathyroidal Extension	Frequency	Percent
Present	3	5.36%
Absent	53	94.64%
Total	**56**	**100%**

Table 12: Frequency Distribution of Staging (T Stage) (n =56)

T Stage	Frequency	Percent
T1a	9	16.07%
T1b	16	28.57%
T2	14	25.00%
T3a	16	28.57%
T3b	1	1.79%
Total	**56**	**100%**

Table 13: Frequency Distribution of CK19 Expression (n =56)

CK19 Expression	Frequency	Percent
Strong (3+ to 4+)	38	67.86%
Weak (1+ to 2+)	15	26.79%
Negative	3	5.36%
Total	**56**	**100%**

Table 14: Frequency Distribution of PDL1 Expression (n =56)

PDL1 Expression	Frequency	Percent
Negative (0%)	21	37.50%
Very Low (<1%)	16	28.57%
Low (1–9%)	19	33.93%
Total	**56**	**100%**

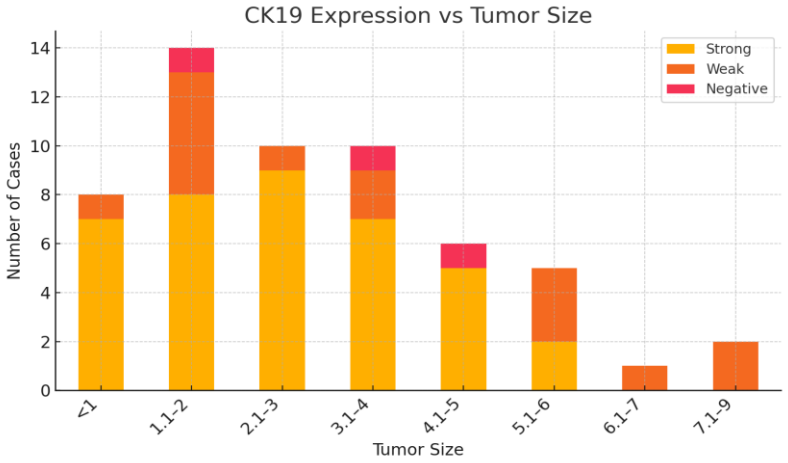

Figure:1 CK19 expression in relation to tumor size.

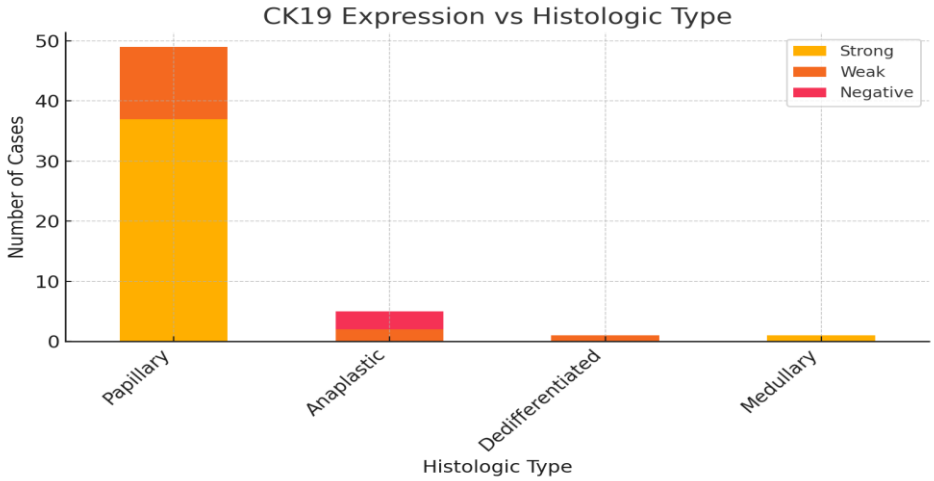

Figure2: CK19 expression in relation to histologic type.

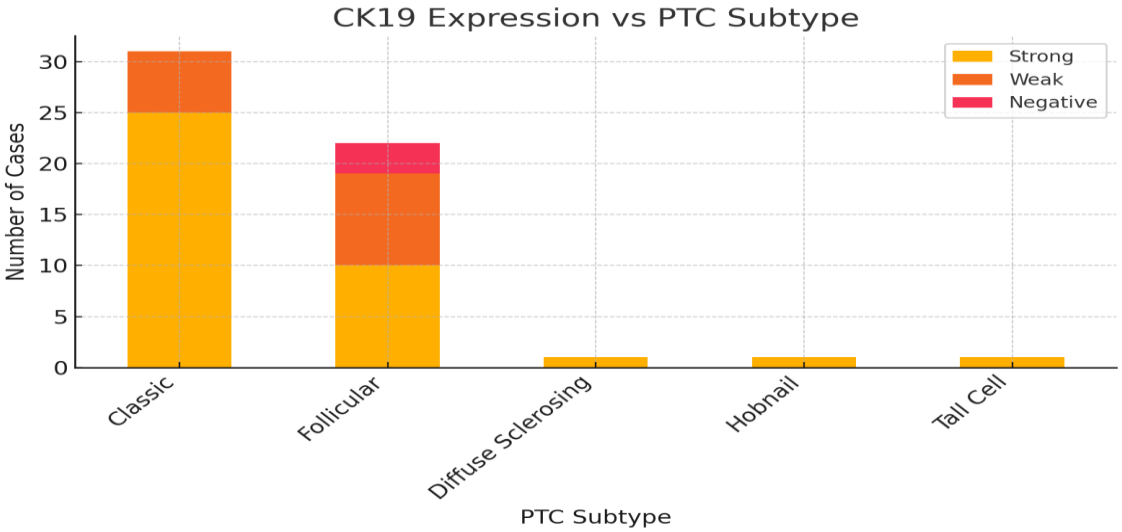

Figure:3 CK19 expression in relation to PTC subtype.

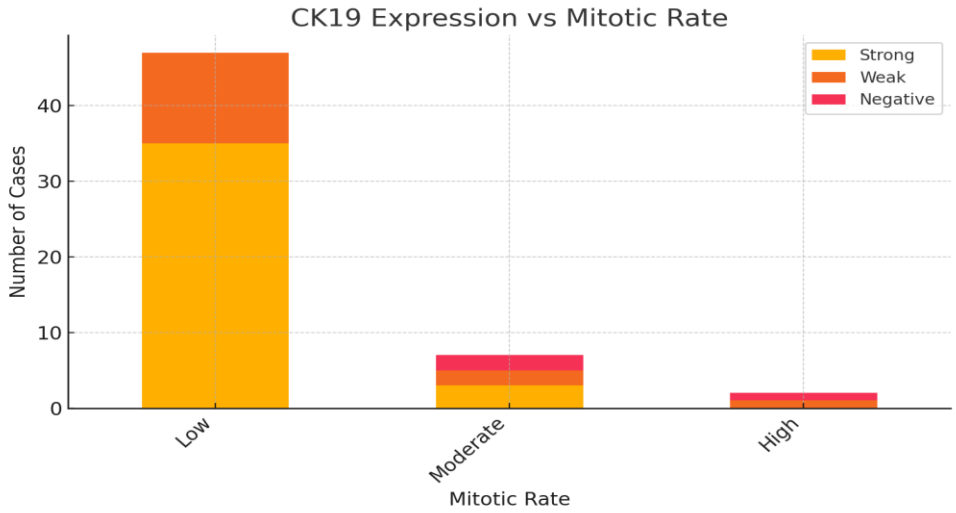

Figure:4 CK19 expression in relation to mitotic rate.

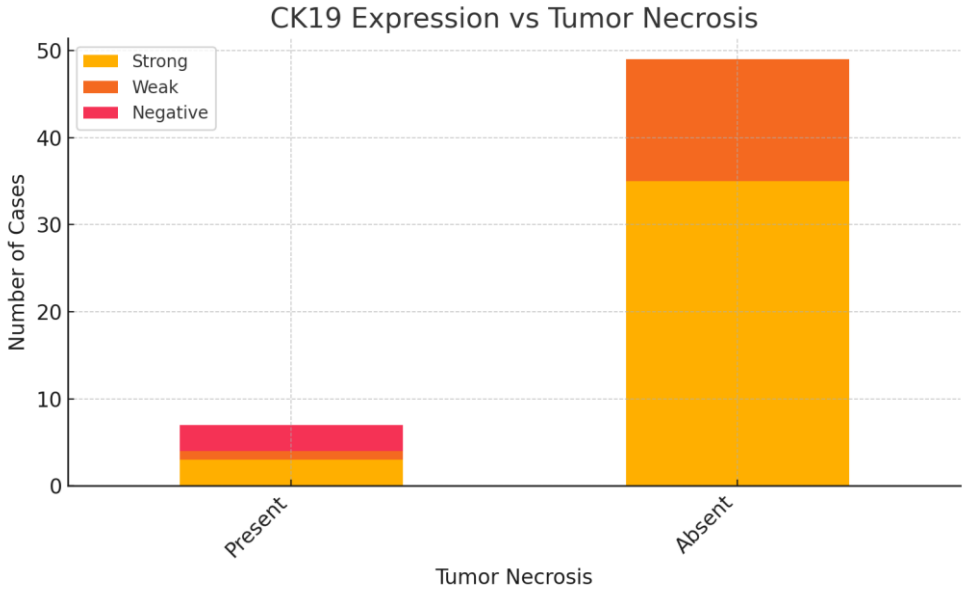

Figure:5 CK19 expression in relation to tumor necrosis.

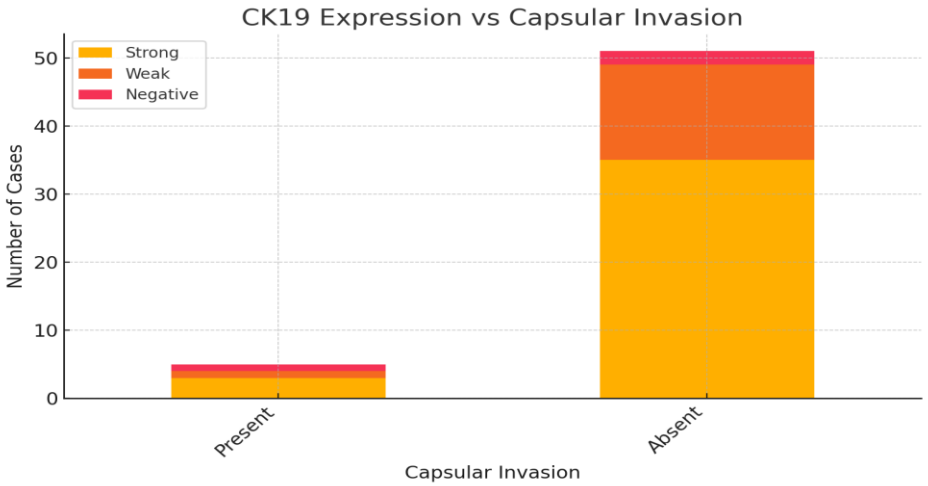

Figure:6 CK19 expression in relation to capsular invasion.

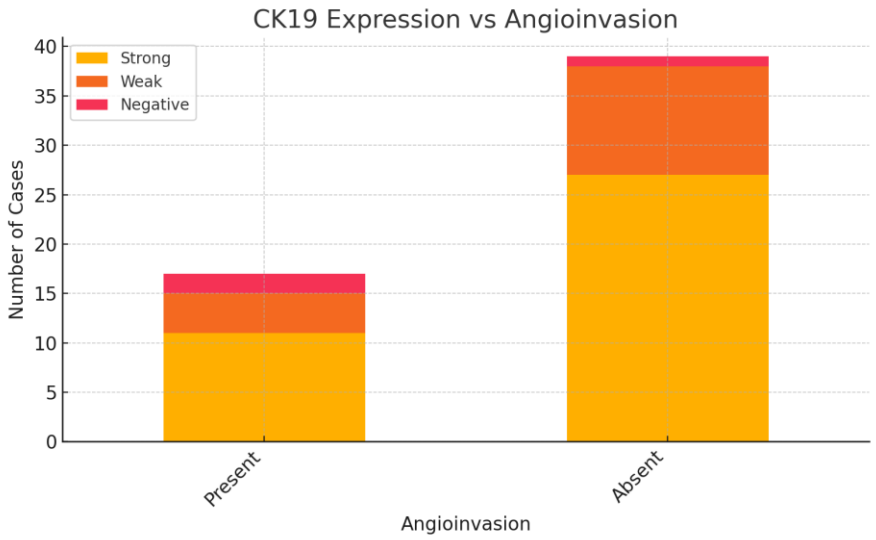

Figure:7 CK19 expression in relation to angioinvasion.

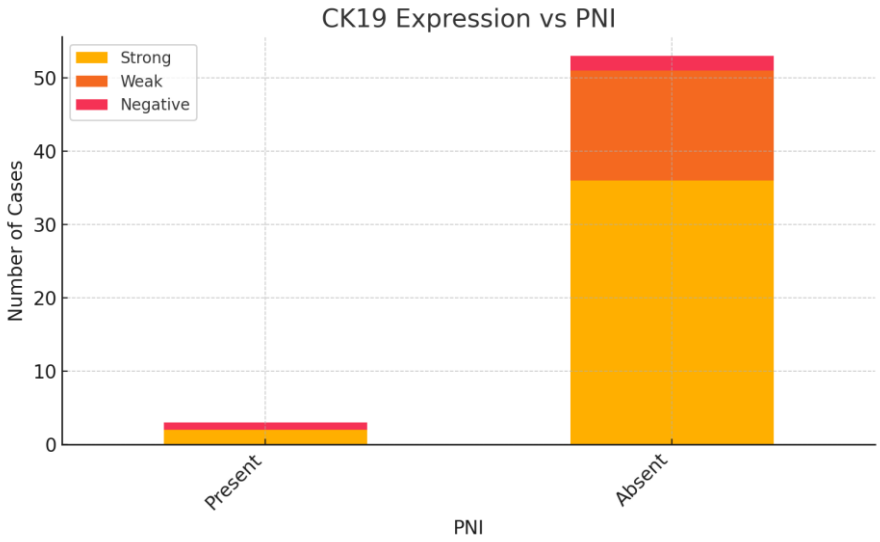

Figure:8 CK19 expression in relation to PNI(Perineural invasion).

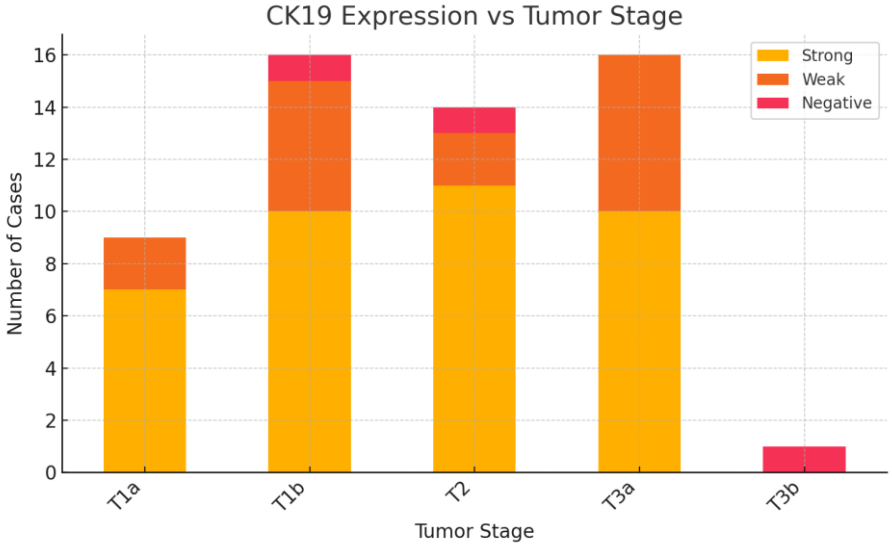

Figure:9CK19 expression in relation to tumor stage.

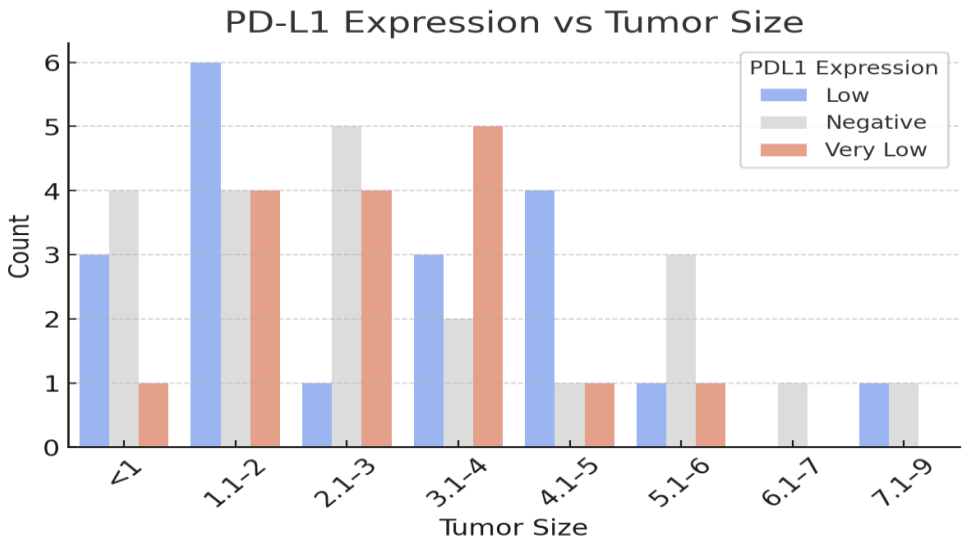

FIG:10 PD-L1 Expression vs Tumor Size

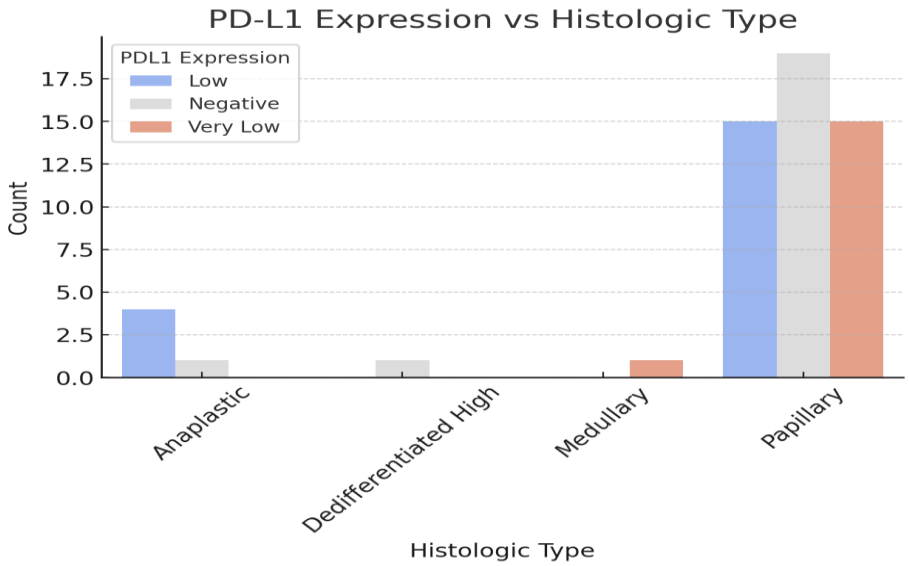

FIG:11PD-L1 Expression vs Histologic Type

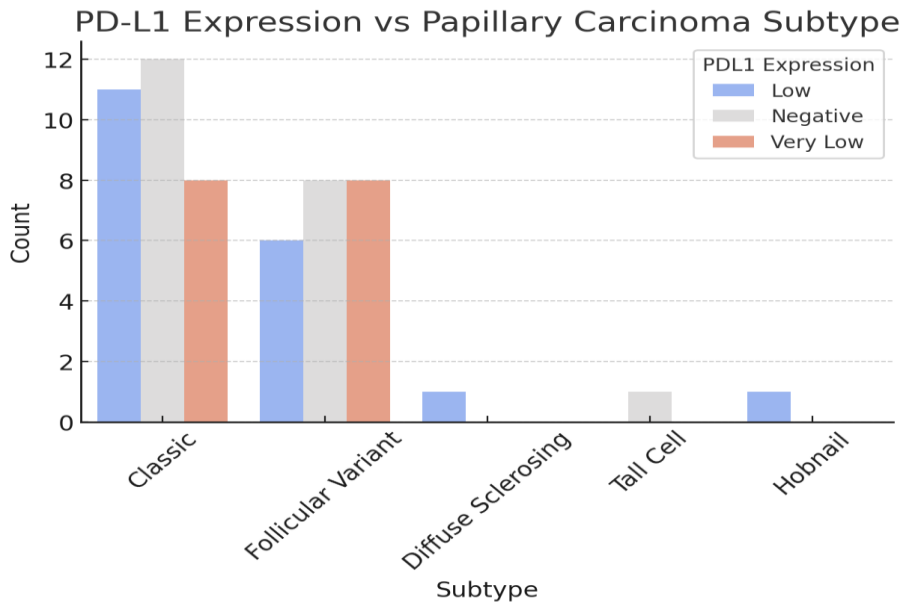

FIG:12 PD-L1 Expression vs Papillary Carcinoma Subtype

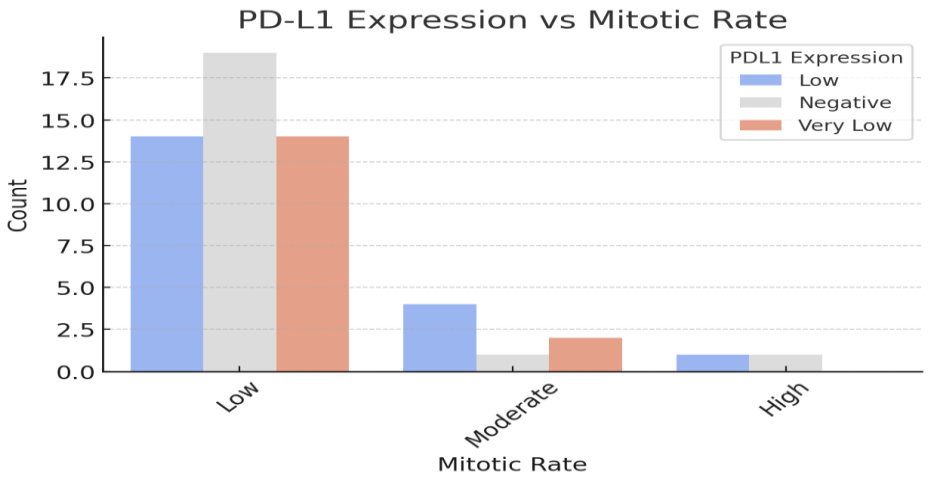

FIG:13PD-L1 Expression vs Mitotic Rate

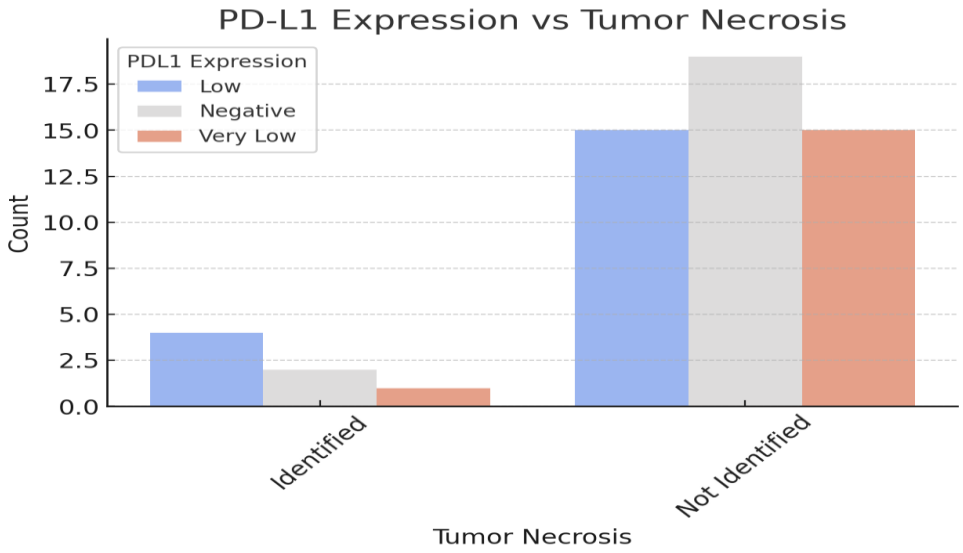

FIG 14:PD-L1 Expression vs Tumor Necrosis

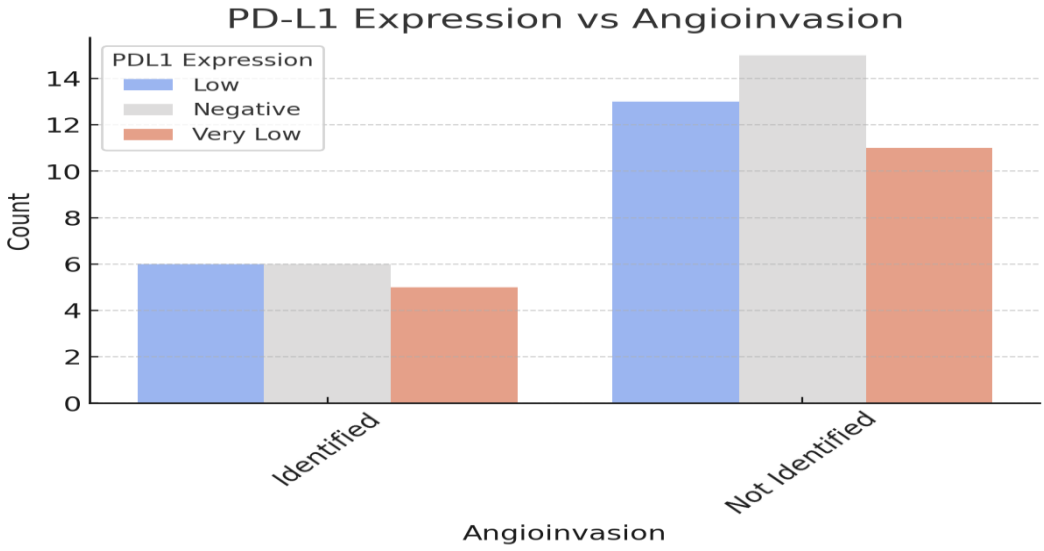

FIG 15:PD-L1 Expression vs Angioinvasion

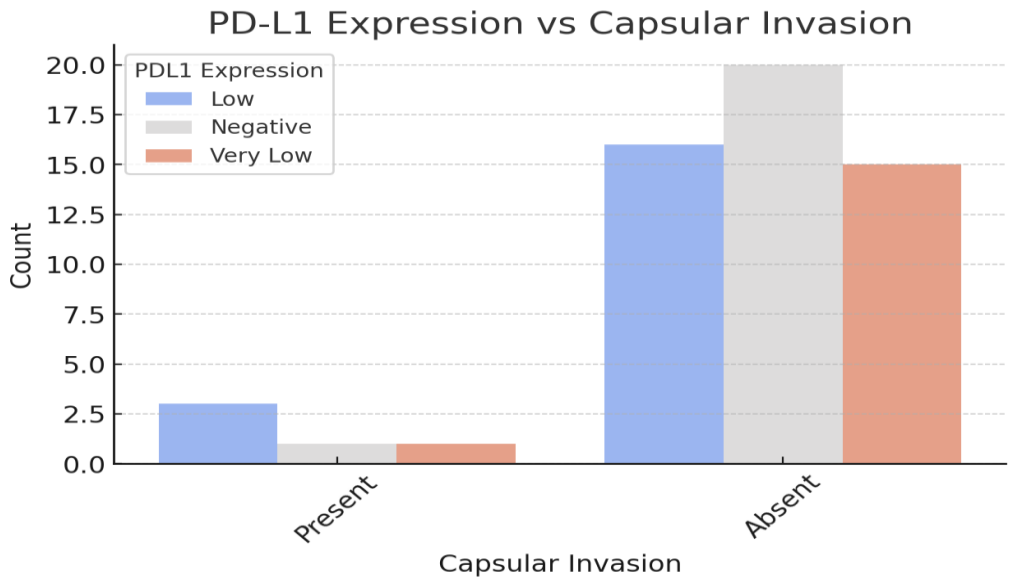

FIG 16:PD-L1 Expression vs Capsular Invasion

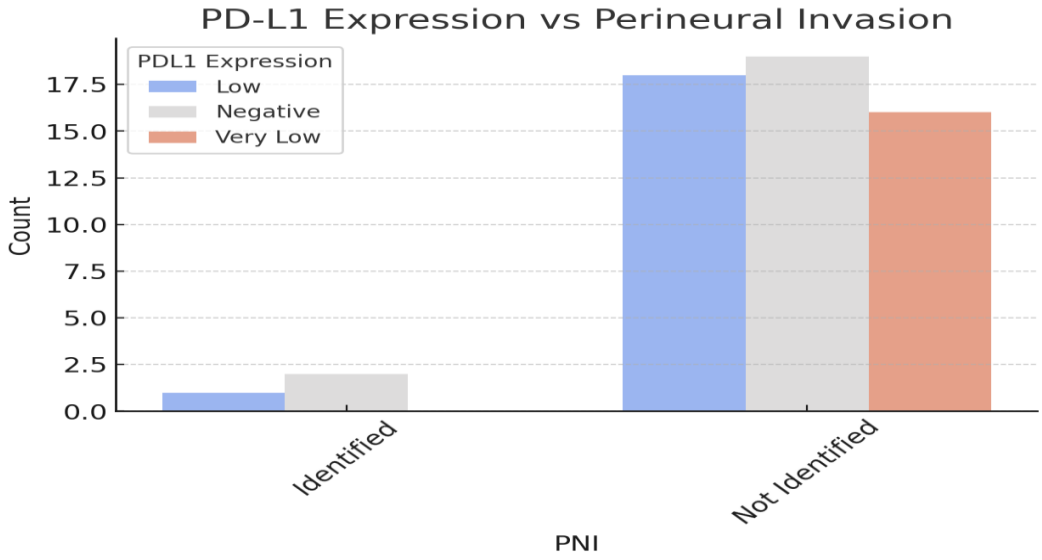

FIG 17:PD-L1 Expression vs Perineural(PNI) Invasion

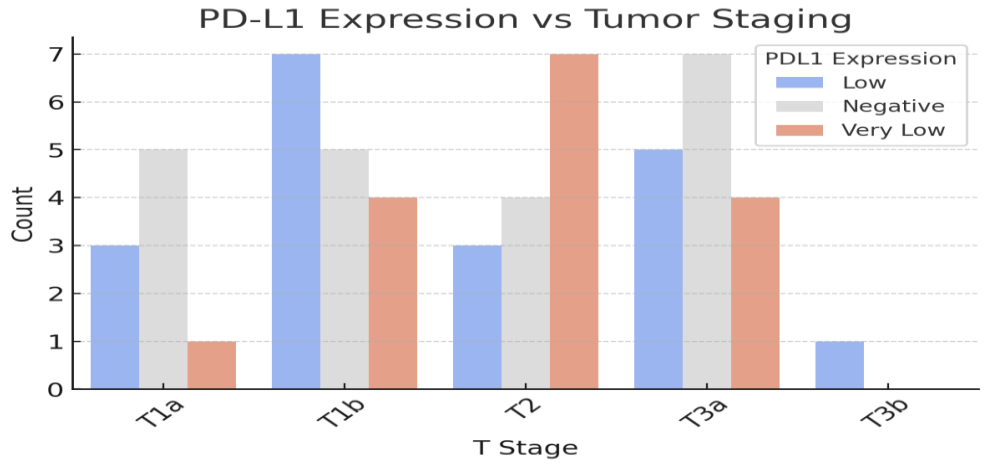

FIG: 18 PD-L1 Expression vs Tumor Staging

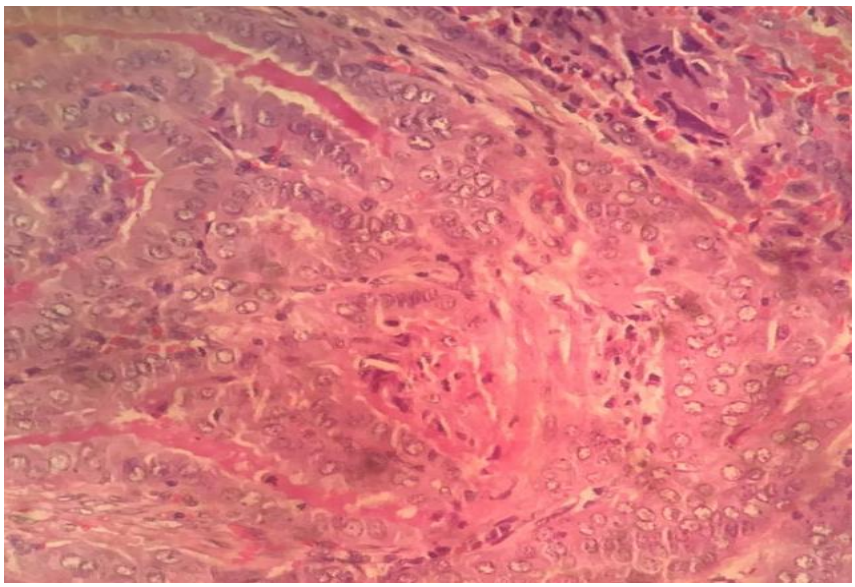

FIG: 19A) CLASSIC PTC

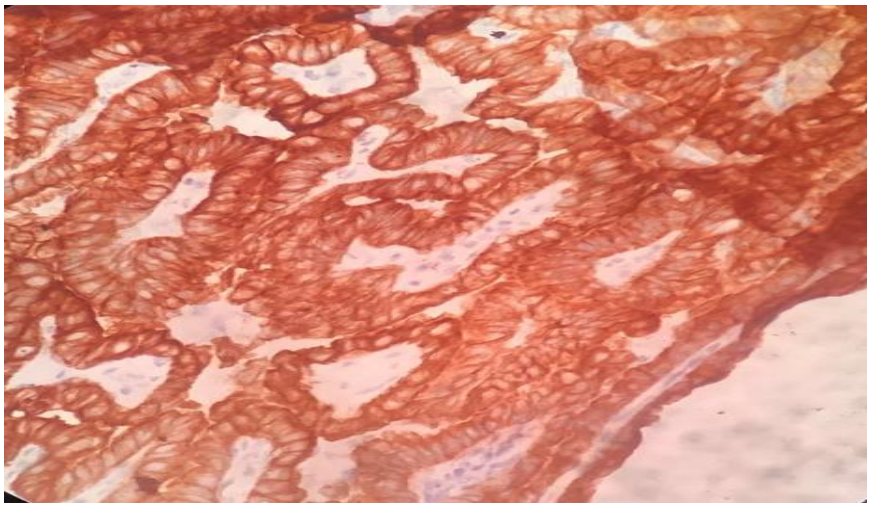

FIG: 19B) STRONG DIFFUSE CYTOPLASMIC AND MEMBRANOUS POSITIVITY BY CK19

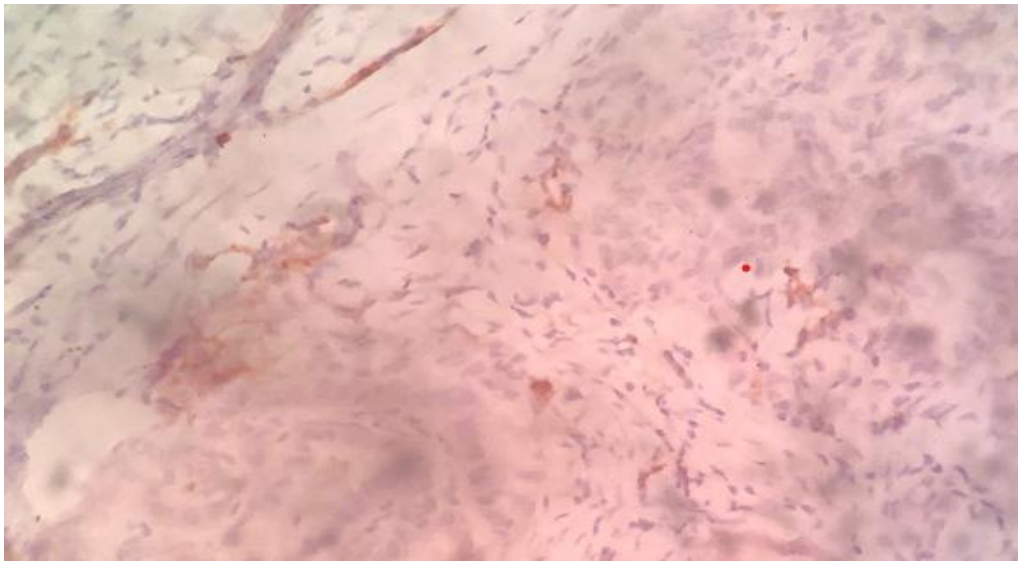

FIG 19C) PDL WEAK POSITIVITY (TPS SCORE 10%)

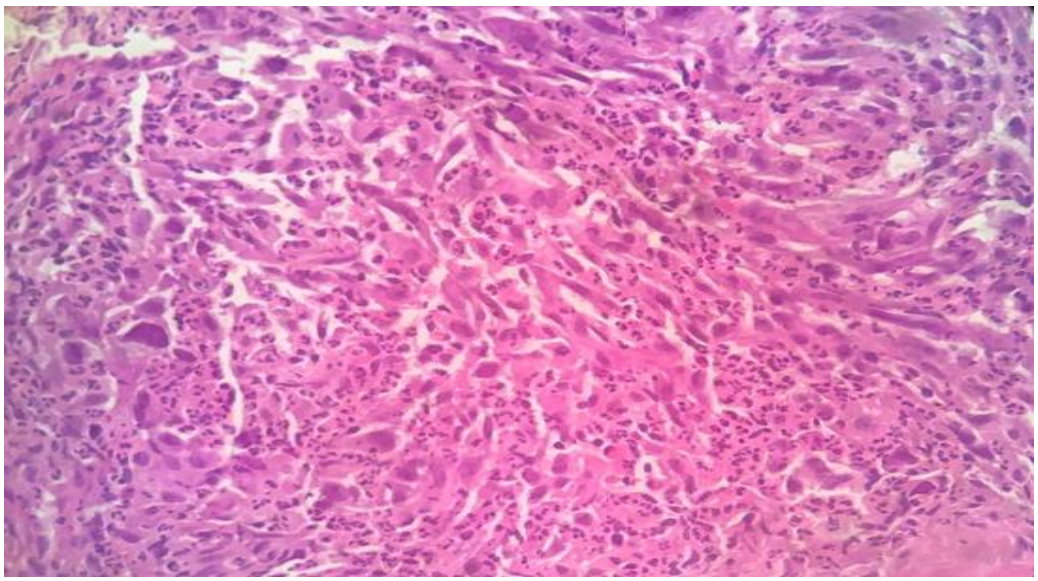

FIG: 20A) ANAPLASTIC CARCINOMA

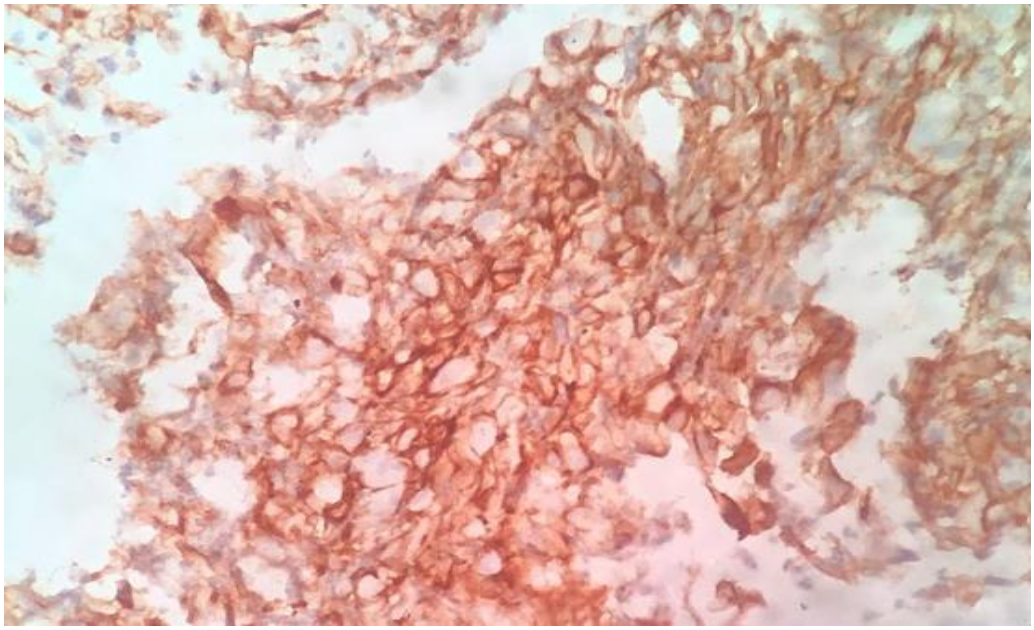

FIG: 20B) PDL 1 STRONG STRONG MEMBRANOUS POSITIVITY IN TUMOR CELLS(TPS SCORE 70%)

DISCUSSION

Papillary thyroid carcinoma represents the majority of endocrine malignancies encountered in routine pathology practice and generally carries a favorable prognosis[4]. Nevertheless, a clinically significant subset of thyroid carcinomas exhibits aggressive biological behavior that contributes to increased risk of invasion, recurrence, metastasis, and treatment resistance. The heterogeneity of tumor behavior illustrates the need for immunohistochemical markers, necessary for diagnostic confirmation but also helping with prognostic stratification. Here, we evaluated the expression of CK19 and PD-L1 in thyroid carcinomas and examined their relationship with established histopathological prognostic parameters.

CK19 Expression and Its Diagnostic Significance

Significantly, CK19 expression was observed mostly in papillary thyroid carcinoma in this study with strong and diffuse staining patterns. This pattern is particularly pronounced in classical and follicular varieties. These findings are consistent with earlier and recent studies which have established CK19 as a highly sensitive immunohistochemical marker for PTC, assisting in its differentiation from benign follicular lesions[9, 10, 11]. The characteristic diffuse cytoplasmic and membranous staining pattern of CK19 in PTC contrasts with the weak, focal, or absent staining seen in benign follicular nodules, thus increasing the diagnostic confidence required for morphologically demanding cases. Although it is very sensitive, CK19 expression is not exclusive to malignant lesions, as focal positivity may occasionally be seen in benign conditions. This reinforces the need to interpret CK19 expression in the context of histomorphological features and other immunohistochemical markers, rather than using CK19 alone[8]. However, its robust expression in papillary thyroid carcinoma emphasizes the importance of this immunohistochemical panel used to assess thyroid pathology.

Prognostic Implications of CK19 Expression

Apart from diagnostic utility, the present study found significant associations of increased CK19 expression with adverse histopathological parameters including larger tumor size, greater mitotic activity, tumor necrosis, capsular invasion, angioinvasion, perineural invasion, and advanced tumor stage. Similar associations have also been observed in the literature over the last years, indicating that it is possible that diffuse CK19 expression may be related to higher proliferative capacity and invasive potential of tumor cells[11, 17]. Biologically, the mechanism for this relationship may be through CK19 to help to preserve epithelial cell integrity and cytoskeletal organization. More recent studies have associated high expression of CK19 with increased tumor cell motility, invasion, and metastatic potential in many epithelial cancers. Accordingly, diffuse CK19 expression in thyroid cancer might not only be a diagnostic finding but also be a phenotypic index of tumor aggressiveness. This is consistent with the possibility of CK19 as a prognostic feature next to its known diagnostic significance.

PD-L1 Expression and Tumor Aggressiveness

We identified PD-L1 expression in a subgroup of thyroid carcinomas in our study, and found higher levels of PD-L1 expression in papillary and anaplastic carcinomas. This observation is consistent with recent reports in the literature that report variable but clinically relevant PD-L1 expression in thyroid carcinoma, particularly in tumors with aggressive clinicopathological characteristics[13, 14, 18]. This variation in PD-L1 expression across tumor subtypes indicates a complex effect of tumor cell expression in conjunction with the immune microenvironment. In the present study, PD-L1 positivity showed a significant correlation with larger tumor size, increased mitotic rate, tumor necrosis, capsular invasion, angioinvasion, and advanced tumor stage. The associations indicate PD-L1 upregulation is associated with biologically aggressive tumor behavior. Similar correlations have been reported in recent studies, which have demonstrated that PD-L1–positive thyroid carcinomas are more likely to present invasive growth patterns and advanced disease at presentation[13, 14].

Biological Role of PD-L1 in Thyroid Carcinoma

One biological implication of PD-L1 expression is the mechanism by which immune escape occurs. PD-L1 binds to the PD-1 receptor on activated T lymphocytes to suppress antitumor immune responses, allowing tumor cells to evade immune surveillance[12]. This immune suppression promotes tumor growth and invasion with resistance to standard therapies. PD-L1–positive thyroid carcinomas are also associated with a more immunosuppressive tumor microenvironment, which is marked by impaired T-cell cytotoxicity and compromised immune cell infiltration[16, 18]. This immunologically 'cold' microenvironment might explain the aggressive clinical behavior in PD-L1-expressing tumors and may account, in part, for their association with late stage and poor prognostic traits.

Combined Evaluation of CK19 and PD-L1

One of key observations in the current study was the relationship by which it was found that CK19 and PD-L1 were linked to aggressive histopathological features by dual positivity. Tumors positive for both markers had more common invasive growth, increased mitotic activity and advanced tumor stage. These results imply a biologically aggressive tumor phenotype, in that the epithelial differentiation (epithelial differentiation as detected by CK19 expression) and immune evasion (PD-L1 expression) are accompanied by each other. All these aspects emphasize that CK19 and PD-L1 are complementary in the evaluation of thyroid carcinoma[14, 17]. CK19 contributes most to diagnostic accuracy and epithelial tumor features, while PD-L1 provides prognostic information on immune evasion and tumor aggressiveness. Integrated approaches based on epithelial and immune markers have also been recommended in recent studies to enhance the risk stratification in thyroid carcinoma[14, 17].

Therapeutic Implications

PD-L1 is of particular relevance in the current era of immunotherapy from a therapeutic perspective. Immune checkpoint inhibitors targeting the PD-1/PD-L1 axis have demonstrated encouraging results in various solid tumors and are emerging as potential treatment options for selected patients with advanced, poorly differentiated, or radioiodine-refractory thyroid carcinoma[15, 16]. Although none of those surveyed received immunotherapy, the observed association between PD-L1 expression and aggressive histopathological features provides reason to explore PD-L1 as a predictive biomarker for immunotherapy response in thyroid carcinoma.

Limitations of the study

There are some limitations concerning the current study that should be recognized. A relatively small sample size could compromise the statistical power and generalizability of the results, especially those of the rare histological subtypes. Referral bias may be introduced due to the single-center design. Molecular profiling for genetic alterations such as BRAF and TERT promoter mutations was not performed, limiting correlation with known molecular drivers of aggressive disease[6,7]. Further, long-term follow-up data regarding recurrence and survival outcomes were unavailable, precluding direct assessment of prognostic significance. Finally, the semi-quantitative approach of immunohistochemical scoring may be subject to inter-observer variation, even if evaluated according to the same criteria.

CONCLUSION

Thyroid carcinoma consists of a variety of tumors in which morphology and clinical signs as well as prognosis differ and are classified as such. To evaluate the diagnostic and prognostic value of CK19 and PD-L1 immunohistochemistry expression, we analyzed 56 histologically verified thyroid cancer patients. The results of our investigation indicated CK19 to be a very sensitive protein to differentiate between PTC, particularly in classical and tall cell subtypes. Its intense and diffuse expression was strongly correlated with key adverse histopathological variables of tumor size, mitotic activity, capsular and vascular invasion, and tumor staging. This supports the concept that CK19 can be not only used as a diagnostic tool to differentiate PTC from other follicular-patterned lesions, but as a possible marker of tumor aggressiveness. Another fraction of thyroid carcinomas were found to express PD-L1, and in tumors with aggressive characteristics such as advanced stage tumors, high mitotic index, and capsular and angioinvasion the PD-L1 expression was also present. An association of PD-L1 expression to histologic aggressiveness has significant implications for immune escape mechanisms in thyroid carcinoma. This might help us to select patients for immunotherapy for cases of poorly differentiated or resistant thyroid cancer. CK19 and PD-L1 expression together can contribute to the classification of the disease and risk stratification, particularly in borderline or indeterminate lesions. PD-L1 may aid in prognostication and new therapeutic planning while CK19 improves morphological diagnosis. Finally, an additional immunohistochemistry panel for thyroid carcinomas appears to be especially interesting for CK19 and PD-L1. Expression of these markers in combination with standard histopathological and clinical data could contribute to greater diagnostic confidence and to further personalized patient care. More studies in larger cohorts and longer follow-up will be required to confirm these findings and explore their potential therapeutic applications.

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