Original Article

Diagnostic utility of CK19 and galectin-3 in differentiating papillary thyroid carcinoma from nonneoplastic lesions of thyroid

ABSTRACT

Background: Thyroid neoplasm is one of the most common endocrine neoplasms. The diagnosis and the distinction between malignant and benign neoplasms can be difficult, but it has clinical, therapeutic, and prognostic significance. Hence, it is necessary to make precise diagnosis by using biomarkers.

Materials and Methods: This is a laboratory observational study considering histologically diagnosed cases of papillary thyroid carcinoma (PTC) and nonneoplastic thyroid lesions. Immunohistochemistry (IHC) staining was done on tissue sections of all cases for CK19 and galectin-3 using appropriate positive and negative controls. The expression of immunomarkers was evaluated by a semi-quantitative method as negative, weak positive, moderate positive, and strong positive. The data were entered in Microsoft Excel sheet and were analyzed using SPSS 22 version software.

Results: A total of 52 cases were considered for the study, of which 26 cases each were PTC and nonneoplastic lesions of thyroid. Among the 26 PTC cases, 6 were classical variant of PTC (CVPTC) and 20 were follicular variant of papillary thyroid carcinoma (FVPTC). Among 26 nonneoplastic cases, 13 each were nodular hyperplasia cases and lymphocytic thyroiditis. There was a statistically significant ($P < 0.01$) association of CK19 and galectin-3 expression between CVPTC and FVPTC. There was no statistically significant association ($P = 0.271$) of CK19 expression between PTC and nonneoplastic cases. There was a statistically significant association ($P = 0.003$) of galectin-3 expression between PTC and nonneoplastic cases.

Conclusion: Galectin-3 expression can be used to differentiate PTC from nonneoplastic lesions of thyroid in ambiguous cases. Galectin-3 and CK19 expression can be used to classify PTC into CVPTC and FVPTC.

KEY WORDS: CK19, galectin-3, papillary thyroid carcinoma, thyroid

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INTRODUCTION

Thyroid neoplasm is one of the most common endocrine neoplasms. The incidence of thyroid neoplasm varies worldwide. Most countries have reported an upward trend in its incidence.[1] A similar trend in the incidence is seen in southern India.[2] According to the National Cancer Registry of India, thyroid cancers show an upward trend from 2.3/100,000 population in 1990 to 3.8/100,000 population in 2014.[1] The common carcinomas of thyroid are papillary thyroid carcinoma (PTC), follicular carcinoma, poorly differentiated carcinoma, and anaplastic carcinoma, the incidence of which is 80%, 15%, <1%, and <2%, respectively.[3]

The distinction of classical cases with follicular patterned thyroid lesions is considerably easy. However, many a times, the diagnosis and the distinction between malignant and benign neoplasms can be difficult, even with histopathological examination.[1] General nuclear features of malignancy may not be applicable to endocrine tumors as benign endocrine tumors, and some of the nonneoplastic lesions may exhibit the same. The only reliable criteria of malignancy in endocrine tumors are invasion and metastasis.[2]

PTCs are the most commonly encountered thyroid malignancies. PTC diagnosis is based on the special nuclear features such as anisonucleosis,

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overlapping of nuclei, intranuclear inclusions, optical clearing, and nuclear grooves. However, some of these features may also be seen in benign thyroid lesions secondary to degeneration. As differentiation between benign or malignant lesions has clinical, therapeutic, and prognostic significance, it is necessary to make precise diagnosis by using biomarkers.[2]

In recent years, a large number of immunohistochemical (IHC) markers have been studied to assist in differentiating nonneoplastic lesions from malignant thyroid lesions. CK19, galectin-3, TG, Ki67, BRAF, calcitonin, HBME-1, TTF-1, and RET are some of the examples of these IHC markers.[3] In spite of several studies being done related to the utility of these markers in single as well as in various combinations, a uniform consensus is yet to be reached. Moreover, a minimum number of biomarkers required to make a distinction have not been established. Hence, the present study using CK19 and galectin-3 has been taken up.

MATERIALS AND METHODS

This is a laboratory observational study done on thyroidectomy cases received in the department of pathology from January 2019 to September 2020. As per the sample size calculated by statistics, 52 cases were considered for the study. The objectives of the study were to determine the expression of CK19 and galectin-3 in PTC and nonneoplastic lesions of thyroid and then to compare the expression of these two markers in PTC and nonneoplastic lesions of thyroid. The inclusion criteria were to consider cases that are histologically diagnosed as nonneoplastic thyroid lesions (lymphocytic thyroiditis and nodular goiter) and PTC. The exclusion criteria were the thyroid cases that had undergone chemotherapy or radiotherapy including recurrent cases. Clinical details of the cases such as the age, gender, clinical diagnosis, and radiological and other relevant investigations were collected from case files.

All the histopathology slides stained with hematoxylin and eosin of the selected cases were retrieved and reviewed. Tissue sections of 4–5 μ thickness were cut from representative formalin-fixed paraffin blocks, and IHC staining was done for CK19 (Biogenex) and galectin-3 (Master Diagnostics) using appropriate positive and negative controls as per the instructions by the manufacturers. Membranous as well as cytoplasmic staining of CK19 and cytoplasmic staining of galectin-3 in epithelial cells were considered as positive. The expression of immunomarkers was evaluated by a semi-quantitative method as described in a study done by Wa Kammal *et al*. as follows.[4] The percentage of staining was scored from 1 to 4 as 0%–25% staining in the area of the lesion as score 1, 26%–50% staining as score 2, 51%–75% staining as score 3, and 76%–100% staining as score 4. The intensity of staining was scored from 0 to 3 as no or negative staining in the area of the lesion as score 0, mild staining as score 1, moderate staining as score 2, and strong staining as score 3. The final immunohistochemical score was obtained by multiplying scores of percentage of staining and intensity of staining as score 0 = negative, score 1–4 = weak positive, score 5–8 = moderate positive, and score 9–12 = strong positive [Figures 1-4].

Data were entered into the Microsoft Excel datasheet and were analyzed using SPSS 22 version software (IBM SPSS Statistics, Somers, NY, USA). The categorical data were represented in the form of frequencies and proportions. Chi-square test was used for the test of significance for qualitative data. Continuous data were represented as mean and standard deviation. *P* value (probability that the result is true) of <0.05 was considered as statistically significant. Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and diagnostic were calculated.

RESULTS

A total of 52 cases were considered for the study, of which 26 cases were PTC and 26 cases of nonneoplastic lesions of thyroid. Majority of PTCs were in the fifth and third decades (8 cases each), and in nonneoplastic lesions, it was in the fifth decade (11 cases) followed by the third decade (7 cases). In PTC, there was female preponderance with a male-to-female ratio of 1:12 [Table 1]. In nonneoplastic lesions, all 26 cases were female. Among the 26 PTC cases, 6 were classical variant of PTC (CVPTC) and 20 were follicular variant of papillary thyroid carcinoma (FVPTC). Among 26 nonneoplastic cases, 13 were nodular hyperplasia cases and 13 lymphocytic thyroiditis.

Among 26 PTC cases, 23 (88.5%) and 3 (11.5%) cases showed positive and negative expression for CK19, respectively. All 6 cases (100%) of CVPTC showed strong positive CK19 expression. Among 20 cases of FVPTC, 3 (15%), 7 (35%), 4 (20%), and 6 (30%) cases showed negative, weak positive, moderate positive, and strong positive expression for CK19, respectively. There was a statistically significant ($P < 0.01$) association of CK19 expression between CVPTC and FVPTC. Among 26 nonneoplastic cases, 20 (76.9%) and 6 (23.1%) cases showed positive and negative expression for CK19, respectively. Among 13 lymphocytic thyroiditis cases, 2 (15.4%), 9 (69.2%), and 2 (15.4%) cases showed negative, week positive, and moderate positive expression of CK19, respectively. Among 13

Table 1: Age and sex distribution of cases in the present study

Age range (years)	PTC, *n* (%)	Nonneoplastic, *n* (%)	Total, *n* (%)
10-19	1 (3.8)	0	1 (1.9)
20-29	8 (30.7)	7 (26.9)	15 (28.8)
30-39	4 (15.3)	3 (11.5)	7 (13.4)
40-49	8 (30.7)	11 (42.3)	19 (36.5)
50-59	2 (7.6)	3 (11.5)	5 (9.6)
60-69	3 (11.5)	2 (7.6)	5 (9.6)
Total	26 (100)	26 (100)	52 (100)
Male: female	1:12	0:26	1:25

PTC=Papillary thyroid carcinoma

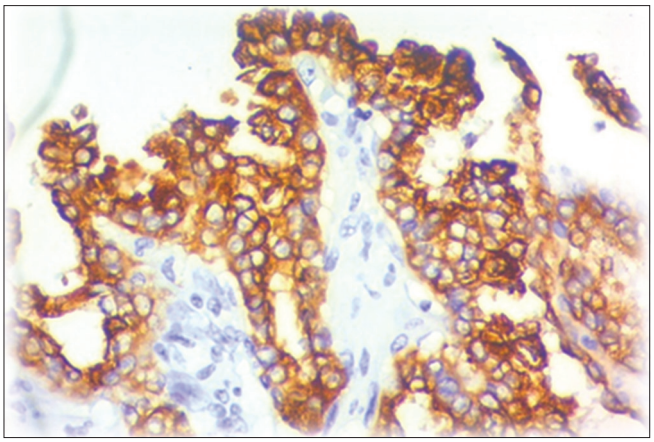

Figure 1: CK19 marker in classical variant of papillary thyroid carcinoma showing strong positive expression (CK 19, x 400)

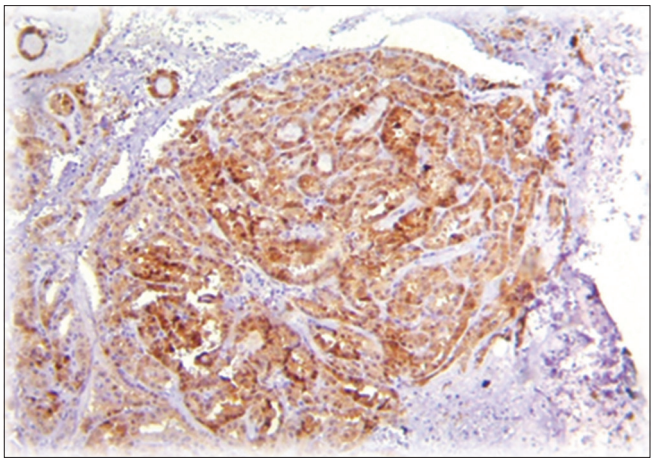

Figure 2: Galectin-3 marker in classical variant of papillary thyroid carcinoma showing strong positive expression (Galectin-3, ×100)

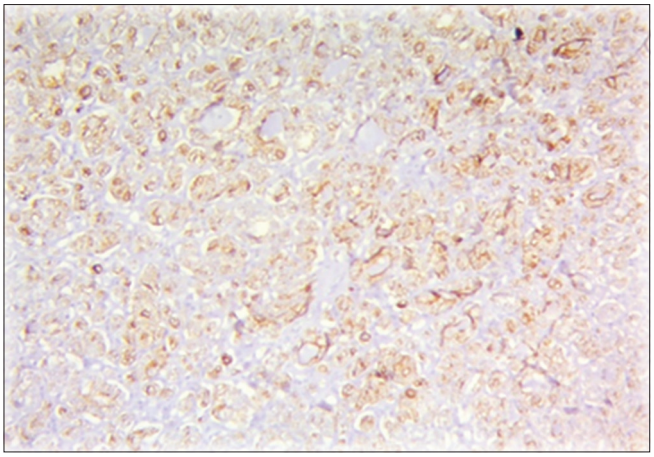

Figure 3: CK19 marker in follicular variant of papillary thyroid carcinoma showing moderate positive expression (CK19, ×100)

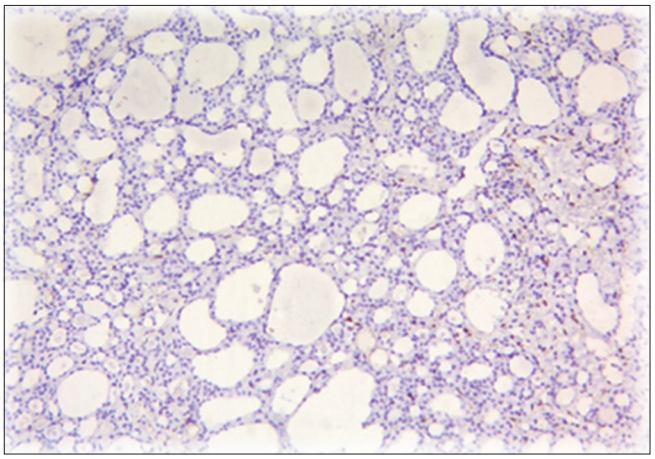

Figure 4: Galectin-3 marker in lymphocytic thyroiditis showing negative expression (Galectin-3, ×100)

nodular hyperplasia cases, 4 (30.7%), 8 (61.5%), and 1 (7.7%) cases showed negative, week positive, and moderate positive expression for CK19, respectively. There was no statistical association ($P = 0.58$) of CK19 expression between lymphocytic thyroiditis and nodular hyperplasia. None of the nonneoplastic cases showed strong positive CK19 expression. There was no statistically significant association ($P = 0.271$) of CK19 expression between PTC and nonneoplastic cases [Table 2].

Among 26 PTC cases, 23 (88.5%) and 3 (11.5%) cases showed positive and negative expression for galectin-3, respectively. All 6 cases (100%) of CVPTC showed strong positive galectin-3 expression. Among 20 cases of FVPTC, 3 (15%), 9 (45%), 3 (15%), and 5 (25%) cases showed negative, weak positive, moderate positive, and strong positive expression for galectin-3, respectively. There was a statistical significant ($P < 0.01$) association of galectin-3 expression between CVPTC and FVPTC. Among 26 nonneoplastic cases, 13 (50%) cases each showed positive and negative expression for galectin-3. Among 13 lymphocytic thyroiditis cases, 3 (23.1%) and 10 (76.9%) cases showed negative and week positive expression of galectin-3, respectively. Among 13 nodular hyperplasia cases, 10 (77%), 2 (15.3%), and 1 (7.7%) cases showed negative, week positive, and moderate positive expression for galectin-3, respectively. There was a statistical significant association ($P = 0.01$) of galectin-3 expression between lymphocytic thyroiditis and nodular hyperplasia. None of the nonneoplastic cases showed strong positive galectin-3 expression. There was a statistically significant association ($P = 0.003$) of galectin-3 expression between PTC and nonneoplastic cases [Table 3].

Among 26 PTC cases, lymph nodes were retrieved in 10 cases, of which 2 cases of CVPTC and 2 FVPTC cases showed tumor metastatic deposits. All the 4 cases with metastatic deposits showed strong positive expression (100%) for CK19 and galectin-3. In nonmetastatic cases, there was variable expression of the two biomarkers. There was no statistically significant association in CK19 ($P = 0.78$) and galectin-3 ($P = 0.62$) expression between the PTC cases with and without lymph node metastasis [Table 4]. Among 26 PTC cases, 8, 13, and 5 cases were of 1–2 cm, 2–4 cm, and more than 4 cm in size, respectively. The different sizes of the lesions

Table 2: Distribution of CK19 expression score in papillary thyroid carcinoma and nonneoplastic cases

CK19 score	PTC			Nonneoplastic lesions		
	CVPTC, *n* (%)	FVPTC, *n* (%)	Total, *n* (%)	Lymphocytic thyroiditis, *n* (%)	Nodular hyperplasia, *n* (%)	Total, *n* (%)
Negative	0	3 (15)	3 (11.5)	2 (15.4)	4 (30.7)	6 (23.0)
Weak	0	7 (35)	7 (26.9)	9 (69.2)	8 (61.5)	17 (65.3)
Moderate	0	4 (20)	4 (15.3)	2 (15.4)	1 (7.7)	3 (11.5)
Strong	6 (100)	6 (30)	12 (46.1)	0	0	0
Total	6 (100)	20 (100)	26 (100)	13 (100)	13 (100)	26 (100)

PTC=Papillary thyroid carcinoma, CVPTC=Classical variant of papillary thyroid carcinoma, FVPTC=Follicular variant of papillary thyroid carcinoma

Table 3: Distribution of galectin-3 expression score in papillary thyroid carcinoma and nonneoplastic cases

Galectin-3 Score	PTC			Nonneoplastic lesions		
	CVPTC, *n* (%)	FVPTC, *n* (%)	Total, *n* (%)	Lymphocytic thyroiditis, *n* (%)	Nodular hyperplasia, *n* (%)	Total, *n* (%)
Negative	0	3 (150	3 (11.5)	3 (23.1)	10 (77)	13 (50)
Weak	0	9 (45)	9 (34.6)	10 (76.9)	2 (15.3)	12 (46.1)
Moderate	0	3 (15)	3 (11.5)	0	1 (7.7)	1 (3.8)
Strong	6 (100)	5 (25)	11 (42.3)	0	0	0
Total	6 (100)	20 (100)	26 (100)	13 (100)	13 (100)	26 (100)

PTC=Papillary thyroid carcinoma, CVPTC=Classical variant of papillary thyroid carcinoma, FVPTC=Follicular variant of papillary thyroid carcinoma

Table 4: CK19 and galectin-3 expression with lymph node metastasis in papillary thyroid carcinoma cases in the present study

Lymph node status	CK19 expression			Galectin-3 expression		
	Weak, *n* (%)	Moderate, *n* (%)	Strong, *n* (%)	Weak, *n* (%)	Moderate, *n* (%)	Strong, *n* (%)
Metastasis	0	0	4 (100)	0	0	4 (100)
No metastasis	2 (33.3)	1 (16.7)	3 (50)	2 (33.3)	0	4 (66.7)

PTC=Papillary thyroid carcinoma

showed variable expression of CK19 and galectin-3. There was no statistically significant association in CK19 ($P = 0.312$) and galectin-3 ($P = 0.678$) expression between the PTC cases of various sizes of the lesion.

The sensitivity, specificity, PPV, NPV, and diagnostic accuracy at 95% confidence interval for CK19 were 88.46%, 23.08%, 53.49%, 66.67%, and 55.77%, respectively; for galectin-3 was 88.46%, 50.00%, 63.89%, 81.25%, and 69.23%, respectively; and combining both the markers 84.62%, 61.54%, 68.75%, 80.00%, and 73.08%, respectively [Table 5].

DISCUSSION

Thyroid nodule is a common presentation in general population and yet it is a major concern worldwide. The thyroid lesion can range from nonneoplastic to benign to malignancy. Most of the thyroid nodules are benign, however, thyroid carcinoma is the concern.[5] The prevalence of thyroid malignancy reported in Kolar (southern part of Karnataka) was 3.43%.[6]

Worldwide, the incidence rate of PTC in women is about three times higher than in men (male: female = 1:3).[7] Similar reports were published in a study at Kolar by Kalyani *et al*.[6] The male-to-female ratio for PTC in the present study was 1:12.

Many immunohistochemical markers are used to diagnose the thyroid nodules. Several studies have been conducted to know the expression of individual markers as well as in combination for differentiating these lesions into nonneoplastic, benign, and malignant when ambiguity arises to diagnose histomorphologically. Meticulous use of these markers in thyroid nodules can help in arriving at correct diagnosis to plan treatment regimen and assess prognosis.[7] In the present study, CK19 and galectin-3 markers were studied in PTC and nonneoplastic lesions of thyroid.

In the present study, among the FVPTC cases, 30%, 20%, 35%, and 15% showed strong positive, moderate positive, and week positive and negative CK19 expression, respectively. For galectin-3 expression, 25%, 15%, 45%, and 15% showed strong positive, moderate positive, and week positive and negative galectin-3 expression, respectively. Studies done by Sumana *et al*., Borkar PV *et al*., and Bose *et al*. found similar results.[1,8,9] All (100%) CVPTC cases in the present study showed strong positive expression for both biomarkers. Studies done by Abdou *et al*., Borkar *et al*., and Bose *et al*. found similar results and that by Sumana BS *et al*. showed variable expression.[1,8-10] The present study demonstrates a significant statistical association in expression of CK19 and galectin-3 between the FVPTC and CVPTC. A study done by Abdou *et al*. demonstrates similar results.[10] Hence, CK19 and galectin-3 can be used to classify PTC into CVPTC and FVPTC.

In the present study, majority of the nodular hyperplasia cases stained weak positive for CK19 and negative for galectin-3. None of the nodular hyperplasia cases had strong positive expression for both the biomarkers. Similar studies of Balci and

Table 5: Sensitivity, specificity, positive predictive value, negative predictive value, and diagnostic accuracy of CK19 and galectin-3 in the present study

Statistics	CK19		Galectin-3		CK19 + Gal-3
	Value (%)	95% CI	Value (%)	95% CI	Value (%)
Sensitivity	88.46	69.85-97.55	88.46	69.85-97.55	84.62
Specificity	23.08	8.97-43.65	50.00	29.93-70.07	61.54
PPV	53.49	47.19-59.68	63.89	54.04-72.70	68.75
NPV	66.67	35.85-87.74	81.25	58.29-93.07	80.00
Diagnostic accuracy	55.77	41.33-69.53	69.23	54.90-81.28	73.08

PPV=Positive predictive value, NPV=Negative predictive value, CI=Confidence interval, Gal-3=Galectin-3

Seckin and Bose *et al*. have demonstrated variable expression of CK19 and galectin-3 in nodular hyperplasia.[9,11] The results of our study were comparable to the study done by Mehdi *et al*.[12]

Majority of lymphocytic thyroiditis cases stained weak positive for both CK19 and galectin-3. None of the lymphocytic thyroiditis cases had strong positive expression for both the biomarkers. A study done by Barroeta demonstrated predominantly weak positive expression of these markers in lymphocytic thyroiditis.[13] Similar studies by Balci and Seckin and Mehdi *et al*. reported variable expression of CK19 and galectin-3.[11,12] Technical errors in the procedure of IHC staining can lead to variability in expression of the biomarkers.

CK19 showed 76.9% positivity in nonneoplastic cases and 88.5% in PTC in the present study. There was no statistically significant association in CK19 expression between PTC and nonneoplastic cases. Similar reports are published in the study done by Abdou *et al*. and Scognamiglio *et al*.[10,14] Hence, CK19 is not a useful biomarker for differentiating nonneoplastic lesions and PTC cases.

Galectin-3 showed 50% week positivity in nonneoplastic cases and 88.5% positive in PTC in the present study. There was a statistical significant association in galectin-3 expression between PTC and nonneoplastic cases. Similar reports were noted in the study done by Huang *et al*. and Barroeta JE *et al*.[11,15] Hence, galectin-3 is a useful biomarker for differentiating nonneoplastic lesions and PTC cases.

There was no statistically significant association in CK19 and galectin-3 expression between PTC cases with and without metastasis to lymph nodes in the present study. This suggests that there is a strong possibility of lymph node metastasis if the tumor expresses strong positivity for both the biomarkers. Similar results had been obtained by a study done by Abdou *et al*.[10]

A study done by Dencic *et al*. speculated the role of CK19 in the prognosis of the disease and its association with extrathyroidal extension and pathological Tumour Node Metastasis staging (pTNM) staging.[16] Variable biomarker expressions of both markers were seen in PTC cases of different tumor sizes in the present study, and there was no statistically significant association in the expression of biomarkers in different tumor sizes. Similar reports were noted in studies by Wa Kammal *et al*. and Cho and *et al*.[4,17]

The present study showed a sensitivity of 88.46% for both CK19 and galectin-3 biomarkers to detect PTC cases. The specificity for CK19 and galectin-3 was 23.08% and 50.00%, respectively. This result was comparable to the result in the study by Balci and Seckin.[11] However, studies by Abdou *et al*. and Dunderovic *et al*. have reported high specificity in their studies.[10,18] The PPV, NPV, and diagnostic accuracy of the present study were comparable to that of Balci and Seckin.[11] The discrepancy may be due to different antibody kits and different techniques used in different studies. Hence, there should be global standardization of the techniques for comparing the results in different studies.

CD56 and CD57 are other common immunohistochemical markers used in thyroid lesions. CD56 shows diffuse positivity in benign and malignant follicular lesions, and CD57 shows diffuse positivity in malignant follicular lesion.[19] CD56 and CD57 immunoexpression is found to be useful in distinguishing follicular thyroid lesions from PTC.[20] In the present study, we have used CK19 and galectin-3 to differentiate PTC from nonneoplastic lesions of thyroid.

The limitations of the present study were as follows. The present study comprised a smaller sample size. Cases with larger sample have to be studied to validate and confirm the results so that the information can be used for regular diagnostic purpose. Only two variants of PTC (CVPTC and FVPTC) and two nonneoplastic lesions (lymphocytic thyroiditis and nodular hyperplasia) were available and considered for the study. The scoring system followed in the present study was as per the study of Wa Kammal *et al*.[4] Different scoring systems are used to evaluate the positive and negative expression of the biomarkers in various published studies. Possibility of interpersonal observer bias in subjective assessment of the expression of biomarkers can be one of the reasons for variable results in different studies. A global standard scoring system is suggested for better comparison and uniformity of the results.

CONCLUSION

Galectin-3 is a useful biomarker to differentiate PTC from nonneoplastic lesions of thyroid. CK19 and galectin-3

expression can be used to classify PTC into CVPTC and FVPTC. Strong positive expression of both CK19 and galectin-3 in PTC has a high possibility of metastasis.

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Conflicts of interest
There are no conflicts of interest.

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