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Systematic Review

Immunohistochemical Biomarkers in Thyroid Pathology- A Systematic Review

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Abstract

Background: Thyroid nodules is one of the important health issues addressed globally. Distinguishing benign and malignant thyroid lesions by histopathological examination remains a diagnostic challenge. This review provides a comprehensive account of various markers useful in identification of thyroid tumours.

Objectives: To systematically review the diagnostic performance of various immunohistochemical markers that are used in differentiating benign from malignant thyroid lesions.

Methods: A systematic search of PubMed and Google scholar was conducted for studies done on IHC expression in thyroid pathology, published between 2010 and 2024. Based on the inclusion and exclusion criteria, twenty studies were finally included in the review. Data on study characteristics and sensitivity and specificity of IHC markers were collected and analysed.

Results: Comparative statistics of various studies showed that Galectin3, CK19, HBME1, TROP2 & CD56 were the most useful markers in differentiating benign and malignant thyroid nodules. They were found to achieve improved sensitivity, specificity and diagnostic accuracy when used in two marker combinations.

Conclusion: Galectin3, CK19, HBME1, TROP2 & CD56 are valuable IHC markers in thyroid pathology. Combined marker panels improved diagnostic performance.

Keywords: Immunohistochemistry (IHC), Galectin3, CK19, HBME1, TROP2, CD56.

Introduction

Thyroid nodules are common clinical entity. Although most of them are benign,5% of the nodules are malignant [1]. Thyroid carcinomas is the most common endocrine malignancy [2] with most common histological subtype being Papillary Thyroid Carcinoma [5].

To solve the diagnostic dilemma that is encountered during the histopathological examination of these tumours, recent studies have focussed on identifying an optimal IHC marker with high specificity and sensitivity [3].

Various IHC markers used in the diagnosis of thyroid tumours are as follows-CD56, CD57, Galectin-1,3,7,8, HBME1, TROP2,p63,CK19, CITED1, VE1, Ret.

CD56 is a glycoprotein which is expressed on the neurons, glia and skeletal muscle. CD56 is found to be expressed in normal thyroid follicular cells and in nearly all benign thyroid tumor cells. Frequently, decreased immune expression of CD56 has been found in malignant thyroid tumors, especially in PTC. [1]

Galectin [3] are a family of lectins that are predominantly localized in the cytoplasm. They possesses affinity for beta galactoside containing glycoconjugates and thus participates in cellular functions like cell proliferation, apoptosis, cellular transformation, tumour progression and metastasis of cancer cells. In the recent studies, Galectin-3 has received notable recognition for its usefulness as a diagnostic marker for thyroid cancer. [2]

HBME-1 is a monoclonal antibody directed against an antigen on the mesothelial cell membrane. Several studies have demonstrated its preferential reactivity in malignant thyroid tumors [3]

Human trophoblast cell surface marker (TROP-2) is a cell surface glycoprotein .It is over-expressed in certain human carcinomas. In view of this, TROP-2 IHC staining may play a role in diagnosing PTC. [4]

CD57 was first identified in lymphocytes showing Natural Killer activity.

There are studies showing that CD57 is expressed in thyroid tumors and other carcinomas. [6] P63 is p53 homologous nuclear transcription factor. It has a negative dominant effect on the P53 gene.

P63 is expressed in basal cells, squamous and myoepithelial cells, and the tumor suppressor feature is controversial [6].

CK19 has been found to exhibit strong and diffuse expression in thyroid malignancies and focal weak staining in benign nodules [7] This review provides a comprehensive account of various markers useful in identification of thyroid carcinoma.

Research Question (PICO):

Population: Patients with thyroid nodules.

Intervention: IHC Markers (Galectin3, CK19, HBME1, TROP2, CD56).

Comparator: Benign vs malignant thyroid lesions.

Outcome: Diagnostic accuracy (sensitivity, specificity).

Objective: To systematically review the diagnostic performance of various immunohistochemical markers that are used in differentiating benign from malignant thyroid lesions.

Methodology

Eligibility Criteria: Included studies which evaluated Immunohistochemical expression of markers in thyroid pathology, which were published between 2010-2024 in indexed journals, and in English language.

Exclusion Criteria: Review articles, duplicates and studies using non-IHC methods were excluded.

Information Sources: PubMed and Google scholar were searched.

Search strategy: Search terms included 'thyroid nodules', 'immunohistochemistry', 'Galectin3', 'CK19', 'HBME1', 'TROP2', 'CD56'.

Selection process: Titles and abstracts were screened for relevance of the study. Full texts were assessed for inclusion of the study in this review. Studies not satisfying inclusion criteria were excluded.

Data collection process: Data collected from each study included author, year of publication, country, sample size, age range of study population, IHC markers analysed and diagnostic performance of IHC markers.

Risk of bias: Risk of bias was not assessed in included studies. However, limitations such as difference in sample sizes of the studies analyzed and single center designs were noted.

Results

Study Selection: A total of 20 studies were included in the final review. (Table 1)

Table 1: Immunohistochemical markers in thyroid pathology that are analysed in various studies

Sl No	Studies	Markers Studied
1.	Mohammed R F et al	CD56
2.	Sumana BS et al	Galectin 3
3.	Raouf SMA et al	HBME1 Galectin3
4.	Simms A et al	TROP2
5.	Abu-Seadah SS et al	HBME1 TROP2
6.	Tastekin E et al	CD56 CD57 HBME1 CK19 Galectin3 P63
7.	Sadiq et al	CK19 HBME1
8.	Chuang et al	CK19 CD56 Galectin 3 CITED1 HBME1 VE1 TROP2
9.	Chen YJ et al	HBME1

10.	Cho et al	HBME1 CK19 Galectin3 CD56
11.	MurtezaogluAR et al	TROP2 HBME1 Galectin 3 CK19
12.	Zargari N et al	TROP2 HBME1
13.	Saleh H A et al	Galectin3 HBME1 CK19 Ret
14.	Kilinc E et al	TROP2
15.	Abouhashem N S et al	CK19 CD56
16.	Alshenawy H A	CD56 HBME1 Galectin 3 CK19
17.	Bychkov A et al	TROP2
18.	Abdou A G et al	TROP2 CK19
19.	Arcolia V et al	Galectin1, 3,7,8 TPO CK19 HBME1
20.	Raman J et al	Galectin 3 CK19 CD56

Study Characteristics: The studies were conducted across multiple countries. The country of origin for the studies were as follows- 2 from India, 6 from Egypt, 1 from Georgia, 3 from Turkey, 2 from US, 1 from Taiwan, 1 from China, 1 from Korea, 1 from Iran, 1 from Thailand, 1 from France.(Table 2) Thyroid tumours were more common in women aged 20-60 years in the studies reviewed. All the studies had variable sample sizes. The minimum sample size was reported by Raman J et al (47 cases), while the maximum was reported by Kilinc E et al (270cases). (Table 2)

Table 2: Details of the studies analysed in this review

SL No	Studies	Country of origin	Age range in years	Total no of cases
1	Mohammed RF et al	Egypt	29-50 years	70
2	Sumana BS et al	India	20-60 years	50
3	Raouf SMA et al	Egypt	Not mentioned	50
4	Simms A et al	Georgia	Not mentioned	137
5	Abu-Seadah SS et al	Egypt	23-71 years	50
6	Tastekin E et al	Turkey	18-75 years	120
7	Sadiq Q et al	US	21-80 years	73
8	Chuang HW et al	Taiwan	37-50 years	63
9	Chen YJ et al	China	13-56 years	206
10	Cho H et al	Korea	18-77 years	207
11	MurtezaogluAR et al	Turkey	Not mentioned	102
12	Zargari N et al	Iran	Not mentioned	102
13	Saleh HA et al	US	Not mentioned	98
14	Kilinc E et al	Turkey	34-65 years	270
15	Abouhashem NS et al	Egypt	17-78 years	80
16	Alshenawy HA	Egypt	13-78 years	70
17	Bychkov A et al	Thailand	13-93 years	226
18	Abdou AG et al	Egypt	19-75 years	77

19	Arcolia V et al	France	13-76 years	132
20	Raman J et al	India	26-57 years	47

Table 3: Results of the studies with single IHC marker analysis on thyroid pathologies

Sl No	Study	IHC Marker	Sensitivity	Specificity
1	Mohammed RF et al	CD56	95%	90%
2	Sumana BS et al	Galectin 3	86%	85%
3	Simms A et al	TROP2	95.31%	89%
4	Chen YJ et al	HBME1	94.5%	77%
5	Kilinc E et al	TROP2	55.5%	98.4%
6	Bychkov A et al	TROP2	98.1%	97.5%

Table 4: Summary of results of the studies with two IHC marker expression on thyroid pathologies

Sl No	Study	IHC Marker	Sensitivity	Specificity
1	Raouf SMA et al	Galectin 3	92.9%	90.9%
		HBME1	89.3%	72.7%
2	Abu-Seadah SS et al	TROP2	74.2%	84.2%
		HBME1	87.1%	78.9%
3	Zargari N et al	HBME1	84%	98%
		TROP2	93%	74%
4	Abdou AG et al	TROP2	71%	81%
		CK19	78.6%	66.7%

Table 5: Summary of results of the studies with 3-4 IHC marker expression on thyroid pathologies

Sl No	Study	IHC Marker	Sensitivity	Specificity
1	Saleh HA et al	Galectin3	85.2%	72.4%
		Ret	83.3%	69.4%
		HBME1	87%	64.3%
		CK19	85.2%	68.4%
2	Raman J et al	Galectin3	84.6%	90.5%
		CK19	100%	66.7%
		CD56	92.3%	80.9%

Table 6: Summarised results of the study done by Cho H et al with various combinations of 4 IHC marker panel [10]

Marker Panel	IHC marker	Sensitivity	Specificity
SINGLE MARKER	HBME1	100%	42.1%
	CK19	60.5%	86.9%
	Galectin3	83.7%	81.7%
	CD56	90.7%	59.8%
DOUBLE MARKERS	HBME1 & CK19	60.5%	90.9%
	HBME1 & Galectin3	83.7%	85.4%
	HBME1 & CD56	90.7%	72%
	CK19 & Galectin3	55.8%	91.5%
	CK19 & CD56	55.8%	90.9%
	Galectin3 & CD56	76.7%	90.9%
TRIPLE MARKERS	HBME1,CK19, Galectin3	55.8%	93.3%
	HBME1,CK19,CD56	55.8%	93.9%
	HBME1,Galectin3,CD56	76.7%	92.1%
	CK19,Galectin3,CD56	51.2%	95.1%
ALL 4 MARKERS	HBME1,CK19,Galectin3,CD56	51.2%	95.7%

Table 7: Summarised results of the study done by Murtezoaglu AR et al with various combinations of 4 IHC marker panel [11]

Marker Panel	IHC marker	Sensitivity	Specificity
Single Marker	HBME1	73.8%	100%
	CK19	83.3%	60%
	Galectin3	69%	100%
	TROP2	50%	100%
Double Markers	HBME1 & CK19	85.7%	60%
	HBME1 & Galectin3	76.2%	100%
	Ck19 & Galectin3	88.1%	60%
	TROP2 & HBME1	76.2%	100%
	TROP2 & CK19	85.7%	60%
	TROP2 &Galectin3	71.4%	100%
Triple Markers	TROP2, HBME1, CK19	88.1%	60%
	TROP2 , HBME1, Galectin3	78.6%	100%
	TROP2,CK19,Galectin3	90.5%	60%
	HBME1, CK19, Galectin3	88.1%	60%
All 4 Markers	HBME1,CK19,Galectin3,TROP2	90.5%	60%

In the study done by Mohammed RF et al, decreased CD56 immunohistochemical expression was much higher in malignant tumors, such as follicular carcinoma and papillary thyroid carcinoma, than in nodular hyperplasia and follicular adenoma(p value <0.001).(Table 3).Therefore, they suggested that CD56 immunohistochemistry can be a helpful marker in discriminating benign from malignant thyroid lesions. [1]

According to the study done by Sumana BS et al,Galectin-3 expression was significantly higher in malignant thyroid neoplasms as compared to benign neoplasms (p<0.0001). (Table 3).No statistical significance was observed (p=0.4718) when comparing PTC and other malignant lesions in terms of Galectin-3 expression. [2]

The results of the study done by Raouf S M A et al indicate that galectin-3 and HBME-1 immunohistochemical markers are significantly more expressed in malignant thyroid tumors compared to benign lesions. Galectin-3 showed higher sensitivity and specificity of immunoexpression in thyroid malignancy than HBME-1, and the combined use of galectin-3 and HBME-1 showed increase in specificity of immunoexpression in malignant tumors. [3] (Table 4) TROP2 expression in thyroid pathologies were evaluated by Simms et al,Kilinc E et al and Bychkov A et al.(Table 4) Simms A et al observed that TROP-2 play aimportant role in diagnosing classic PTC, as it showed high sensitivity (95.31%) and specificity (89%) for classic PTC. [4]

Kilinc E et al observed that TROP-2 is a marker for aggressive behaviour rather than detecting malignancy. They also suggested that, if it is TROP2 stained and not malignant, it may also have potential for determining precursor lesion. [14] Bychkov A et al observed that non-neoplastic thyroid, follicular adenomas, follicular carcinomas, and medullary carcinomas were negative for TROP-2 immunostaining. The majority of papillary thyroid carcinoma (PTC) were positive for TROP-2; however, the pattern of staining differed between the histopathological variants of PTC. All papillary microcarcinomas, PTC classic variant, and tall cell variant were TROP-2 positive, with mainly diffuse staining pattern. In contrast, less than half of the PTC follicular variant specimens were positive for TROP-2, with only focal immunoreactivity. None of the baseline (age, gender) and clinical (tumour size, nodal disease, stage) parameters were correlated with TROP-2 expression in the study. They concluded that TROP-2 membranous staining is a very sensitive and specific marker for PTC – classical variant, tall cell variant, and micro PTC, with high overall specificity for PTC. [17]

The results of the study done by Abu-Seadah SS et al suggest that with high sensitivity and specificity, both HBME-1 and TROP-2 are beneficial in identifying thyroid cancer, particularly papillary carcinoma, and in separating malignant follicular-derived thyroid lesions from benign ones.[5](Table4)

Tastekin E et al studied immunohistochemical expression of 6 markers in thyroid tumours. He observed that, although the expression of CD56 was high in benign follicular lesions, Follicular Carcinoma could not be excluded. CD57 was high in malignant follicular group and NIFTP. p63 was found highly expressed in FVPTC, which might be promising to predict invasiveness in follicular group of lesions. CK19, Galectin-3 and HBME1 were found prominent in CVPTC. [6]

The study done by Sadiq Q et al indicated that HBME1 and CK19 are valuable markers in differentiating NIFTPs from morphologic mimics like follicular adenoma and adenomatoid nodules/multinodulargoiter. While HBME1 and

CK19 are both sensitive in diagnosing lesions with PTC-like nuclear features, CK19 stains a higher number of benign lesions than HBME1. No increase in sensitivity or specificity in diagnosis of NIFTP, PTC, or FVPTC was noted in this study on combining both the immunohistochemical markers. [7] Chuang H W et al observed that the IHC results for NIFTP and NEFVPTC exhibited no statistically significant differences using CK19, CD56, galectin-3, CITED1, HBME 1, VE1, and TROP-2 markers. In differentiating IFVPTCs from BFNs and NIFTPs/NEFVPTCs, galectin-3 and TROP-2 were found to be useful markers with the highest sensitivity and high specificity, respectively. In various combinations, panel co-expression of two markers, including galectin-3 and/or HBME-1 and/or TROP-2, and the combination of galectin-3 and TROP-2 co-expression could achieve high diagnostic accuracy. In terms of discrimination of BFNs from NIFTP/NEFVPTC, CK19 was found to be the single most sensitive marker (81.3%), while CD56 was the most specific (100%). The panel consisting of CK19 and/or HBME-1 exhibited the highest sensitivity (96.9%), but the panel with CD56 and/or HBME-1 exhibited the highest specificity (90.5%). [8]

Chen YJ et al studied HBME-1 expression in thyroid tumours. HBME1 was positively immunostained in PTC tissue, which was significantly higher than that in benign thyroid nodules (77.1 vs. 5.77 %). HBME1 immunoexpression was also correlated with infiltration levels in PTC tissues, and it was found that it can be used as a potential biomarker in the diagnosis of PTC. [9] (Table 3)

In the studies done by Cho H et al and Alshenawy HS et al HBME1, CK19, CD56 and Galectin3 expression were evaluated. According to study done by Cho H et al, Immunohistochemical expression of these above markers was not significantly different in invasive EFVPTC and NIFTP, except for that of HBME-1. Immunoexpression of all the four above markers were significantly higher in IFVPTC than in EFVPTC. [10] Combination panel of the above markers showed increased diagnostic accuracy in the study (Table 6).

The study results of Alshenawy HS et al also suggested that the combination of IHC marker panel comprising of CD56, HBME-1, Gaectin-3 and CK19 attained high sensitivity and specificity in diagnosis of thyroid tumours. [16] Murtezaoglu AR et al studied 4 markers (HBME1, Galectin3,CK19 & TROP2) in thyroid pathology. In distinguishing cases of follicular variant-papillary carcinoma from follicular nodular diseases and follicular adenoma, HBME1 and Galectin3 were found to be statistically significant ($p<0.001$).In determining malignancy, HBME1 had the highest diagnostic accuracy and CK19 had highest sensitivity. The sensitivity increased when combination panel of markers were used. [11] (Table 7) The study done by Zargari N et al demonstrated that combination usage of TROP-2 and HBME-1 can reliably diagnose thyroid carcinoma with equivocal morphology with high sensitivity and specificity.(Table4) These 2 markers specifically showed higher immunoreactivity in PTCs and its variants than in Follicular Carcinomas. Carcinomas showed diffuse strong membranous immunoreactivity for TROP2 in contrast to benign lesions, in which the reactivity was focal or weak. One exception to this above finding was found to be Hurthle cell neoplasms which were strongly positive for TROP-2, so this marker was found to be not useful in the differential diagnosis of benign and malignant lesions with oncocytic morphology. [12]

Staining results in the study done by Saleh HA et al showed that malignant tumors express galectin-3, HBME-1, CK19 and Ret oncoprotein significantly more than benign nodules. (Table 5) The sensitivity of these markers for the distinction between benign and malignant lesions ranged from 83.3% to 87%. The sensitivity of two-marker panels was not significantly different in this study. Immunoexpression of the above markers was found to be diffuse and strong in malignant tumors, and focal and weak in the benign lesions. [13]

Abouhashem N S et al studied CK19 and CD56 immunoexpression in thyroid pathologies. They observed that on comparing papillary carcinoma with papillary hyperplasia, CK19 was the most sensitive marker and CD56 was the most specific one. Better diagnostic accuracy was obtained on combining both immunostains. Co-expression of CK19&CD56 obtained 100% sensitivity and 92% diagnostic accuracy in differentiating follicular variant of PTC from follicular adenoma. Sensitivity and diagnostic accuracy increased to 100% and 91.7% respectively on comparing FVPTC with Follicular Carcinoma. On comparing between papillary carcinoma -Hurthle cell variant and Hurthle cell adenoma, sensitivity, specificity, and diagnostic accuracy were 100%, 75% and 83.3% respectively, with combination of both above markers. They concluded that the combined use of CK19 and CD56 is helpful in discriminating papillary thyroid carcinoma and its variants from other mimicking thyroid lesions. [15]

Alshenawy HS et al studied the immunohistochemical expression of CD56, HBME-1, Galectin-3 and CK19 in thyroid pathologies. The sensitivity and specificity for each marker and their combination were calculated. They suggested that although no single marker is completely sensitive and specific for follicular thyroid lesions, the combination of CD56, HBME-1, Gaectin-3 and CK19 could attain high sensitivity and specificity in diagnosis. [16] Abdou AG et al studied immunoexpression of TROP2 & CK19 in PTC. They observed that TROP2 is a specific rather than

sensitive marker, while CK19 is a sensitive rather than specific marker in differentiating PTC from other mimickers.(Table 4)The diagnostic validity of both markers was found to be superior in diagnosis of Classical variant of PTC compared with follicular variant of PTC. Positive expression of these 2 markers was also found to be associated with lymphnode metastasis. [18]

In the study done by Arcolia V et al, identification of optimal cut-off levels and the diagnostic value of single immunomarkers or combinations were evaluated using the receiver operating characteristic curve analysis. Galectin-3 and CK19 were the most sensitive markers (97 and 98%, respectively), whereas galectin-1 was the most specific (97%). The combination of gal-3, CK19 and HBME-1 were found to be the most efficient and informative marker panel reaching the highest specificity (97%) and sensitivity (95%) for the diagnosis of PTCs. The findings of the study suggested that this combination of markers could improve the reliability of thyroid cancer diagnosis. [19]

Raman J et al studied immunoexpression of Galectin3, CK19 and CD56 in thyroid neoplasms. (Table 5)Galectin-3 was the only marker with diagnostic Odd's ratio >1 (2.31) indicating a good test performance level. Galectin-3 was found to be a reliable marker for thyroid papillary carcinoma and for differentiating malignancy. The panel of Galectin-3 & CD56 combination, was found to be valuable and complementary, with improved sensitivity and specificity in differentiating malignant from benign neoplasms. [20]

Findings

Single markers: Galectin-3, CK19, HBME-1, TROP2 and CD56 showed good sensitivity and specificity.

Combination panels of IHC Markers achieved improved diagnostic accuracy compared to single markers.

Notable outcome: Galectin-3 and HBME1 combination improved specificity .CK19 and CD56 combination improved sensitivity.

Discussion

This systematic review highlights the diagnostic utility of various IHC markers in thyroid pathology. Galectin-3, CK19, HBME1, TROP2 and CD56 were most commonly used markers in distinguishing benign from malignant thyroid lesions. Combined panels showed improved diagnostic accuracy compared to single markers.

Strengths of the study: Comprehensive analysis of 20 studies from multiple regions. Detailed assessment of single and combined IHC marker diagnostic performance.

Limitations of the study: Restriction to English language studies. Potential publication bias

Conclusion

The present review concludes that the Immunohistochemistry play an integral role in ensuring the correct diagnosis of thyroid nodules.

Galectin3, CK19, HBME1, TROP2 & CD56 were found to be the most useful markers in differentiating benign and malignant thyroid nodules. They werefound to be valuable and complementary when used in two marker combinations which could achieve improved sensitivity, specificity and diagnostic accuracy.

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