Significance of Insulin-Like Growth Factor II Mrna-Binding Protein 3 (IMP3) Expression in Selected Thyroid Lesions

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Abstract:

Background: Differentiation of benign from malignant follicular thyroid lesions remains difficult and the ability of molecular markers to differentiate between them still unclear. The aim of this study was to evaluate the usefulness of *IMP3* expression to distinguish benign from malignant thyroid lesions. **Methods**: This is a retrospective study upon selected 57 thyroid lesions designated as; 7 cases of Hashimoto thyroiditis (HT), 10 cases of hyperplastic nodules (HN), 15 cases of follicular thyroid adenoma (FTA), 13 cases of conventional papillary thyroid carcinoma (PTC), 6 cases of follicular variant of papillary thyroid carcinoma (FV-PTC), and 6 cases of follicular thyroid carcinoma (FTC). Immunohistochemistry was applied on formalin-fixed, paraffin-embeded tissue blocks using *IMP3*. clinicopathological data were reviewed from patients' pathological reports and correlated with *IMP3* expression. **Results:** IMP3 positivity was seen in 1/7 cases (14.3%) of HT, 2/10 cases (20%) of HN, 4/15 cases (26.7%) of FTA, 12/13 cases of PTC, and in all (100%) FV-PTC & FTC cases. IMP3 staining was significantly increased from normal thyroid tissue up to malignant tumors ($P<0.01$). *IMP3* showed 96% sensitivity and 78.1% specificity for malignant tumors. IMP3 expression was positively correlated with grade and tumor size in malignant cases ($P<0.05$). No significant correlation was found in *IMP3* expression with patient age, sex, capsular invasion, lymphatic/vascular invasion, lymph node metastasis, distant metastasis and TNM stage. **Conclusions:** *IMP3* is a potential diagnostic marker for thyroid cancer and can be a promising marker for distinguishing benign from malignant follicular patterned thyroid lesions.

Keyword: Thyroid lesions, insulin-like growth factor, IMP3.

Introduction:

Thyroid nodules, the most common presenting symptom of thyroid cancer, affect 3-4% of normal population, most thyroid nodules are benign and only 5% to 15% is thyroid cancer [1].

One of greatest challenges in thyroid pathology is differentiation between benign and malignant follicular-patterned neoplasms. When confronted by a follicular patterned tumour, the pathologist relies on capsular and/or vascular invasion to determine biological behaviour of a thyroid tumour. Multiple studies have demonstrated great inter-observer and intra-observer variability in histopathological diagnosis of follicular pattern thyroid lesions. This variability is because agreement about minimal criteria required for changes in nuclear features of PTC, as well as exact criteria for capsular invasion, not universally accepted. Therefore, the search for objective markers of thyroid malignancy is of great importance [2,3].

A growing number of some promising immunohisto-chemical markers for the differential diagnosis of thyroid lesions have emerged, including *CD56, HBME-1, galectin-3* and *CK19* but till now none of them are conclusive [4,5].Insulin-like growth factor II mRNA-binding protein 3 (*IMP3*) is a member of the *IMP* family, consisting of IMP1-3, that plays an important role in RNA traffking, stabilization and translation during embryogenesis. *IMP3* promote tumor cell proliferation, migration, invasion, and aggressiveness [6]. *IMP3* has been showed as an important cancer-specific gene associated with several types of cancers including lung cancer [7], germ cell cancer [8], colon cancer [9], pancreatic cancer [10], gastric cancer [11], liver cancer [12], and kidney cancer [13]. In several organ systems, *IMP3* expression has been shown to correlate with a higher grade of tumor, increased risk of metastases, and poorer prognosis [14]. Depending on the fact that *IMP3* is detected in different cancer types at high levels, we conducted this study to evaluate the diagnostic utility of *IMP3* in differentiating benign and malignant thyroid lesions, its role in thyroid carcinogenesis and its potential prognostic role.

Material and Methods: This study was conducted retrospectively on 63 selected thyroid cases including 6 cases of apparently normal thyroid tissue (as a control group) and 57 cases of different thyroid lesions as a

study group, with available formalin-fixed, paraffin-embedded tissue blocks, collected from Archives of Pathology Department and early cancer detection unit of Faculty of Medicine, Benha university during the period from April 2013 to July 2017. The study was approved by the Ethical committee of faculty of Medicine, Benha University. Hematoxylin and eosin-stained slides on all cases were reviewed by two observers simultaneously to confirm the diagnosis and to classify the lesions into one of the study categories. Thyroid tumors were classified as stated in the WHO classification.[16] The studied 57 thyroid lesions were classified as 7 cases of HT, 10 cases of HN, 15 cases of FTA, 13 cases of PTC, 6 cases of FV-PTC, and 6 cases of FTC. 6 cases of apparently normal thyroid tissue as a control group were also evaluated. At this review, blocks were selected for immunohistochemistry (IHC). The remarkable microscopic features such as presence or absence of capsular Invasion (CI), presence or absence of lymphatic/ vascular invasion (LVI), and lymph node status were noted. The patients' demographic and macroscopic data were obtained from their original files, including patient's age, sex, primary lesion site, primary lesion size and distant metastasis status. TNM staging was performed for malignant in accordance to AJCC staging system [16].We categorized cases into 3 groups; non-neoplastic group (HT and HN), benign follicular neoplasms (FTA) and malignant follicular neoplasm (PTC, FV-PTC, and FTC), and were classified according to age into two groups<55 years and ≥55 years, and according to size into three groups <2 cm, 2-4 cm and >4 cm, as shown in (Table 1).

Table 1: Patients' demographic and clinicopathological data in studied groups**:**

	Non-neoplastic lesions N. (%)	Benign neoplasm N. (%)	Malignant neoplasm N. (%)	P value
Age				
<55years	16 (94.1%)	15 (100%)	21 (84%)	>0.05
≥55years	1 (5.9%)	0	4 (16%)	
Sex				
Female	15 (88.2%)	15 (100%)	21 (84%)	>0.05
Male	2 (11.8%)	0	4 (16%)	
Site				
Right	6 (35.3%)	11 (73.3%)	14 (56%)	
Left	4 (23.5%)	4 (26.7%)	5 (20%)	>0.05
Bilateral	7 (41.2%)	0	6 (24%)	
Size				
<2 cm	2 (11.8%)	0	4 (16%)	
2-4 cm	9 (52.9%)	11 (73.3%)	16 (64%)	>0.05
>4 cm	6 (35.3%)	4 (26.7%)	5 (20%)	
Total	17 (100%)	15 (100%)	25 (100%)	

Immunohistochemical study: Three micron tissue sections were obtained from formalin-fixed, paraffin-embedded tissue blocks on coated slides. After xylene deparaffinization, the sections were rehydrated in descending grades of alcohol then in water. Antigen retrieval was performed by using 10 mmol/L citrate monohydrate buffer (PH 6.0) and heated for 15 minutes in the microwave.

The sections were then incubated in a blocking medium (3% H2O2) for 15 minutes followed by washing with distilled water. The slides then were immunostained for IMP3 Rabbit polyclonal antibody (0.1mg/ml concentration, Biospes, Chongqing, China) at a dilution of 1:100, at room temperature overnight.

Immunodetection was executed using a standard labeled streptavidin-biotin system (DakoCytomation A/S, Glostrup, Denmark). Immune staining was performed based on manufacturer's instructions. Immunoreaction was visualized by adding DAB as a chromagen. Counterstaining of slides was performed with the Mayer hematoxylin. Normal thyroid tissue present on nearly every slide served as an internal negative control. Fetal liver obtained from aborted fetus (16 weaks), was used as positive control.

Immunostaining evaluation: The slides were evaluated for the presence or absence of IHC staining in lesional and normal thyroid tissue; *IMP3* expression was detected as cytoplasmic or membranous brownish coloration. Immunoreactivity was assessed by evaluating extent of stained follicular cells and was considered positive if more than 10% of follicular epithelial cells showed cytoplasmic/ or membranous staining. The IHC staining was graded as follow; negative (up to 10% stained cells), focally positive (+: 11-25%), moderately positive (+ +: 26–50%), or diffusely positive (+++: >50%). Expression of *IMP3* was then correlated with age, sex, size, CI, LVI, lymph node status, distant metastasis status and TNM stage.

Statistical analysis: Results were analyzed using SPSS (version 16) statistical package for Microsoft windows (SPSS Inc., Chicago, Illinois, USA).The Pearson correlation coefficient was used for statistical analysis, P value <0.05 was considered statistically significant, and highly statistically significant when it was <0.01. Sensitivity, specificity, positive predictive value and negative predictive value were calculated for

benign versus malignant lesions. Receiver operating characteristic (ROC) curves were then drawn. The area under the curve (AUC) in ROC analysis was used to compare the ability of a marker to discriminate between benign and malignant lesions.

Results:

Clinico-pathological features in malignant groups:

In malignant cases, 5 cases (38.5%) of PTC were grade I (GI), 7 cases (53.8%) were grade II (GII), and 1 case (7.7%) was grade III (GIII). 2 cases (33.3%) of FV-PTC were GI and 4 cases (66.7%) were GII. Of FTC cases, 2 cases (33.3%) were GI, 2 cases (33.3%) were GII, and 2 cases (33.3%) were GIII. This was not statistically significant (P>0.05).

When CI was compared between the sub-types of malignant cases, CI was observed in 3 cases (23.1%) of PTC,1case (16.7%) of FV-PTC, and in 100% of FTC. This was statistically highly significant (P<0.01). LVI was found in 8 cases (61.5%) of PTC, 3 cases (50%) of FV-PTC and 4 cases (66.7%) of FTC, but was statistically non significant (P>0.05).

Lymph node metastasis was found in 8 cases (61.5%) of PTC and 3 cases (50%) of FV-PTC, but was absent in all cases (100%) of FTC, and this was statistically significant (P<0.05). The majority of cases (84%) were stage I; 10 cases (76.9%) of PTC, all cases (100%) of FV-PTC, and 5 cases (83.3%) of FTC were stage I, but this was not statistically significant (P>0.05)

Insulin-like growth factor II mRNA-binding protein 3 staining results:

All the control group cases were negative for *IMP3* staining (Table 2, Fig. 1)

In non-neoplastic group, 6 cases (85.7%) of HT were negative for *IMP3* staining and 1 case (14.3%) which showed Hurthle cell metaplasia was positive (++). 8 cases (80%) of HN were negative and 2 cases (20%) were positive [one of 2 cases was formed of oncocytic "Hurthle" cells and showed diffuse cytoplasmic staining for *IMP3* (+++)].

Presence of Hurthle cells in HT & HN was statistically highly significant (P<0.01).In FTA, 11 cases (73.3%) were negative, 2 cases (13.3%) were positive (++), and 2 cases (13.3%) which showed high atypical features were diffusely positive (+++), and this was statistically highly significant (P<0.01).

In malignant cases, 12 cases (92.3%) of PTC cases were positive with 7 cases (53.8%) showed diffuse positive staining (+++). All the 6 cases (100%) of FV-PTC and FTC were positive for *IMP3*.

We found statistically highly significant difference in IMP3 expression between studied cases (P<0.01) as *IMP3* expression was the highest in malignant cases and lowest in non-neoplastic cases and was completely absent in normal thyroid tissue.

IMP3 expression was compared between benign lesions (HT, HN, &FTA) and malignant lesions (PTC, FV-PTC, & FTC), and a statistically highly significant difference was found between 2 groups (P<0.01). We found nonstatistically significant difference between non-neoplastic lesions and FTA (P>0.05). When malignant tumors were compared with each others, we found nonstatistically significant difference (P>0.05).

Correlation of *IMP3* staining with clinicopathological characteristics of studied cases is presented in Table 2. We found statistically significant difference in *IMP3* expression in relation to tumor grade and size (P<0.05). There was no statistically significant difference in *IMP3* expression in relation to age, sex, CI, LVI, lymph node status, distant metastasis and stage (P>0.05).

Receiver operating characteristic curve and area under the curve analysis for insulin-like growth factor II mRNA-binding protein 3 expression in benign versus malignant thyroid lesions:

The ability of *IMP3* to distinguish benign from malignant thyroid lesions was thereafter determined by means of ROC analysis. The values of the area under the ROC curve (AUC) are shown in Table 3 and the actual curves are shown in Fig. 2.

For malignant tumors, the sensitivity of IMP3 was 96%, and specificity was 78.1%. Comparison of FTA with FTC and FTA with FV-PTC revealed 100% sensitivity and 73.3% specificity when IMP3 is used to differentiate between these lesions. Comparison of HN with FV-PTC revealed 100% sensitivity and 80% specificity. Finally, comparison of HN with PTC revealed 92.3% sensitivity and 80% specificity (Table 3).

Table 2 : *IMP3* expression and correlation with clinico/histopathological features in studied cases:

	Total	**Expression of IMP3**				**PV**
		Negative (0) N. (%)	**Focal (+) N. (%)**	**Moderate (++) N. (%)**	**Diffuse (+++) N. (%)**	
Non-neoplastic lesions						
HT	7	6 (85.7%)	0	1 (14.3%)	0	
HN	10	8 (80%)	1 (10%)	0	1 (10%)	
Benign neoplasms						<0.01**
FTA	15	11 (73.3%)	0	2 (13.3%)	2 (13.3%)	
Malignant neoplasms						
PTC	13	1 (7.7%)	2 (15.4%)	3 (23.1%)	7 (53.8%)	
FV-PTC	6	0	1 (16.7%)	2 (33.3%)	3 (50%)	
FTC	6	0	0	2 (33.3%)	4 (66.7%)	
Age (years)						
<55	52	25 (48.1%)	4 (7.7%)	9 (17.3%)	14 (26.9%)	>0.05
≥55	5	1 (20%)	0	2 (40%)	2 (40%)	
Sex						
Female	51	25 (49%)	2 (3.9%)	8 (15.7%)	16 (31.4%)	>0.05
Male	6	1 (16.7%)	2 (33.3%)	3 (50%)	0	
Grade						
GI	9	1 (11.1%)	3 (33.3%)	2 (22.2%)	3 (33.3%)	<0.05*
GII	13	0	0	4 (30.8%)	9 (69.2%)	
GIII	3	0	0	1 (33.3%)	2 (66.7%)	
LVI						
Absent	10	0	3 (30%)	1 (10%)	6 (60%)	>0.05
Present	15	1 (6.7%)	0	6 (40%)	8 (53.3%)	
CI						
Absent	15	1 (6.7%)	2 (13.3%)	5 (33.3%)	7 (46.7%)	>0.05
Present	10	0	1 (10%)	2 (20%)	7 (70%)	
Tumor size						
T1	6	1 (16.7%)	2 (33.3%)	1 (16.7%)	2 (33.3%)	<0.05*
T2	14	0	1 (7.1%)	6 (42.9%)	7 (50%)	
T3	5	0	0	0	5 (100%)	
Nodal metastasis						
N0	14	0	3 (21.4%)	3 (21.4%)	8 (57.2%)	>0.05
N1	11	1 (9.1%)	0	4 (36.4%)	6 (54.5%)	
Distant metastasis						
M0	24	1 (4.2%)	3 (12.5%)	6 (25%)	14 (58.3%)	>0.05
M1	1	0	0	1 (100%)	0	
Tumor stage (TNM)						
Stage I	21	1 (4.8%)	3 (14.3%)	5 (23.8%)	12 (57.1%)	
Stage II	3	0	0	1 (33.3%)	2 (66.7%)	>0.05
Stage III	0	0	0	0	0	
Stage IV	1	0	0	1 (100%)	0	

N.B: *HT* Hashimoto thyroiditis; *HN* Hyperplastic nodules; *FTA* Follicular thyroid adenoma*; CPC* classic papillary carcinoma; *FVPC* follicular variant of papillary carcinoma; *FC* follicular carcinoma; *LVI* lymphatic/vascular invasion; *CI* capsular invasion; *T* tumor size; *N* nodal metastasis*; M* distant metastasis;
* Significant; ** Highly Significant.

Table 3: Statistical analysis of *IMP3* as a marker for malignancy for follicular patterned thyroid lesions:

	Sensitivity	Specificity	PPV	NPV	AUC
Benign lesions* *vs.* malignant tumors	96%	78.1%	77.4%	96.2%	0.886
FTA *vs.* FTC	100%	73.3%	60%	100%	0.889
FTA *vs.* FV-PTC	100%	73.3%	60%	100%	0.856
HN *vs.* FV-PTC	100%	80%	75%	100%	0.917
HN *vs.* PTC	92.3%	80%	85.7%	88.9%	0.881

N.B: Benign lesions (includes non-neoplastic lesions and follicular thyroid adenoma)
PPV Positive predictive value, *NPV* Negative predictive value, *AUC* Area under the curve, *FTA* Follicular thyroid adenoma, *FTC* Follicular thyroid carcinoma, *FV-PTC* follicular variant of papillary thyroid carcinoma, *HN* Hyperplastic nodules, *PTC* Papillary thyroid carcinoma.

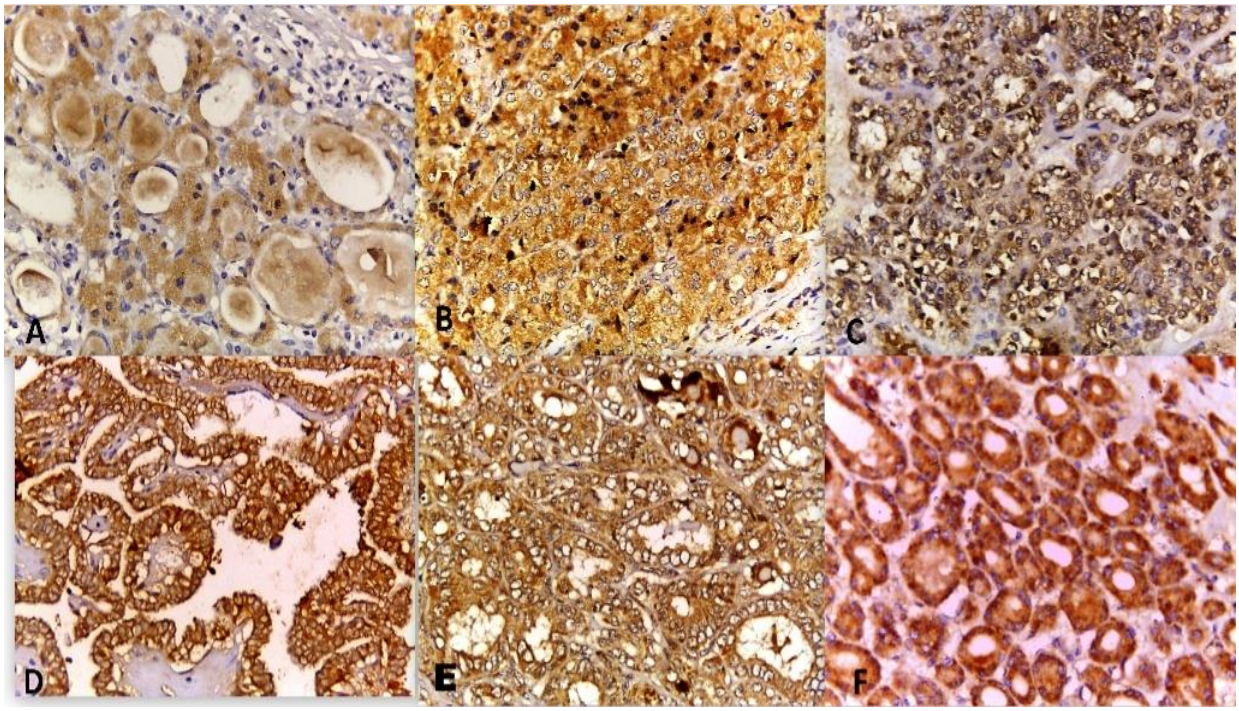

Fig. 1: Representative micrographs of immunohistochemical staining for IMP3 in different thyroid lesions. Positive staining for IMP3 in Hashimoto thyroiditis with Hurthle cells ++ (A), diffuse positive cytoplasmic staining in Hurthle cell hyperplastic nodule +++ (B), positive cytoplasmic staining in Follicular thyroid adenoma ++ (C), diffuse positive cytoplasmic and membranous staining in conventional papillary thyroid carcinoma +++ (D), diffuse positive staining in follicular variant-papillary thyroid carcinoma +++ (E), and Follicular thyroid carcinoma +++ (F), X400

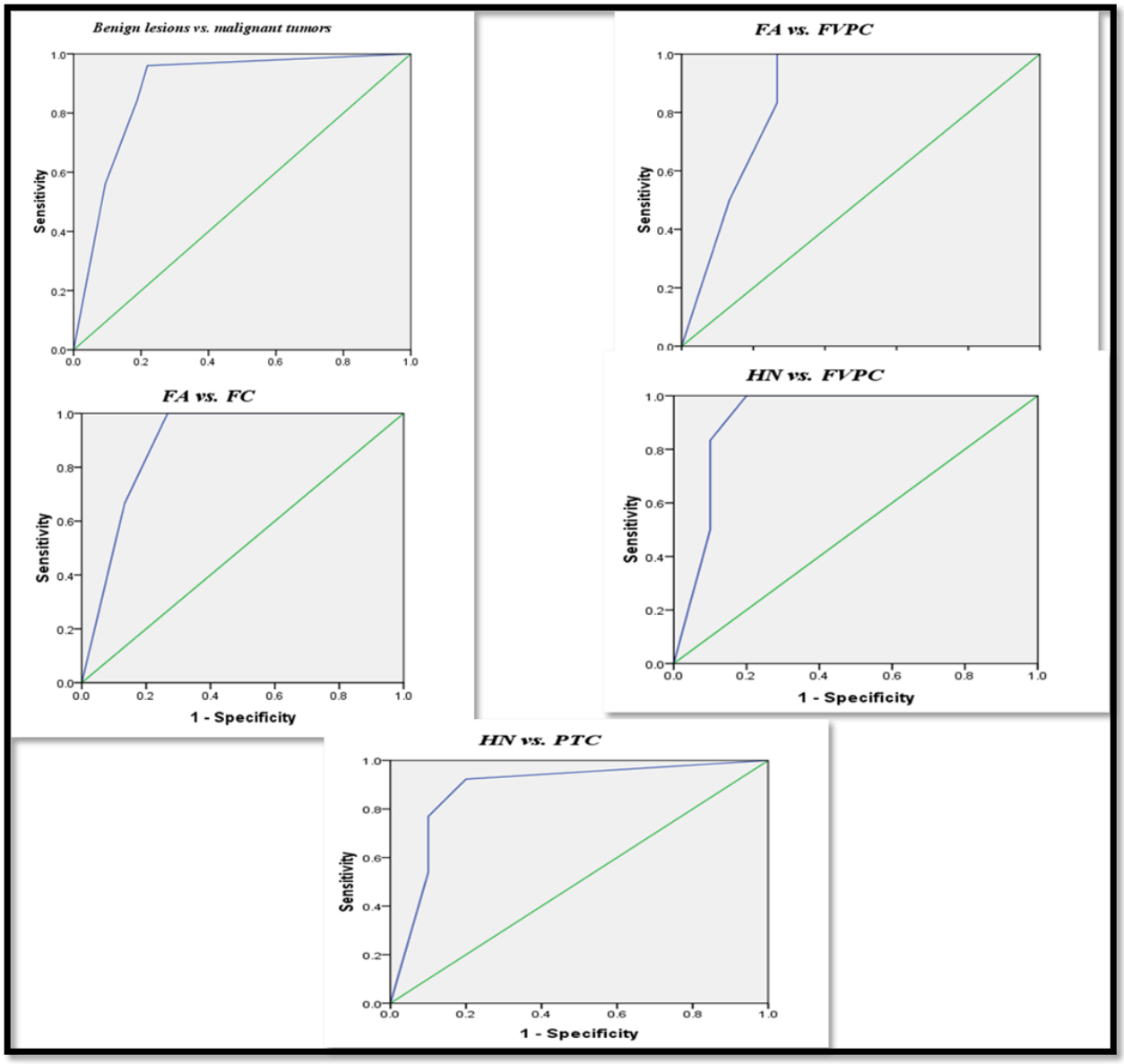

Fig. 2: Receiver operating characteristic analysis for IMP3. The area under the curve represents an optimal statistic for comparing the sensitivity and specivicity of IMP3 for differentiating between benign and malignant thyroid lesions.

N.B: *FA* Follicular adenoma, *FVPC* Follicular variant of papillary carcinoma, *FC* Follicular carcinoma, *HN* Hyperplastic nodules, *PTC* Papillary thyroid carcinoma.

Discussion:

IMP3 promotes tumor cell growth, proliferation, survival and tumor cell invasiveness in vitro, through the control of the translation or turnover of various candidate target genes, including *IGF2*, *CD44*, *HMGA2*, and *MMP9* [17,19]. In our study we aimed to evaluate the expression of *IMP3* in different thyroid lesions and to evaluate its usefulness as a diagnostic marker in differentiating benign and malignant thyroid lesions and its possible prognostic role in malignant thyroid lesions.

In present study *IMP3* expression significantly increased gradually from apparently normal thyroid tissue (100% negative expression) to non-neoplastic lesions (17.6% positivity), to benign neoplasms (26.7% positivity) to be the highest in malignant neoplasms (94% positivity) (*P<0.01*). Our finding were compatible with the results of other series in literature evaluating the expression of *IMP3* in thyroid lesions [20, 23]. This indicates that *IMP3* may be implicated in thyroid carcinogensis by initiating malignant transformation and proliferation of transformed cells. Also, we demonsrated that *IMP3* is a useful marker for differenting benign from malignant thyroid lesions, with 96% sensitivity and 78.1% specificity for malignant lesions.

In the studied 7 cases of hashimoto thyroiditis, 6 cases (85.7%) were negative for IMP3 expression and only 1 case (14.3%) was positive (++). This is consistent with the work of Jin *et al*. [24], who observed positive expression for *IMP3* in 50% of HT cases.

In hyperplastic nodules, 8 cases (80%) were negative for *IMP3* expression and only 2 cases (20%) were positive (+ & +++). This is in agreement with the results of El-Shorbagy *et al.* [22] and Kulaçoğlu and Erkılınç [23], who demonstrated positive staining for IMP3 in 25% and 50% of their studied HN, respectively.

In contrast, Slosar *et al.* [20] found complete negative *IMP3* staining in HT and HN cases. This can be explained by technical variation and different antibodies clones used. From these results, it was demonstrated that pre-existing benign thyroid disease is one of the risk factors for development of thyroid malignancy. In line with this statement, Resende de Paiva *et al.* [25] studied association between HT and thyroid cancer in 64,628 patients, and demonstrated a high association between HT and thyroid cancer, mostly PTC. Also it can be demonstrated that thyroid is a site for

hyperplasia-neoplasia sequence as it is now evident that clonal proliferations occur in some HN and can express various markers of malignant follicular derived thyroid tumours such as *PPAR, RET19* and activating *RAS* mutations [26,27].

In studied 15 cases of FTA, 11 cases (73.3%) were negative and 4 cases (26.7%) were positive for *IMP3*. Close to our results Jin *et al*. [21] and El-Shorbagy *et al.* [22], also observed positive staining in 11.1% and 25% of FTA cases, respectively, while Slosar *et al*. [20], found complete negativity for *IMP3* staining in FTAs, which disagree with our findings. Positive expression for *IMP3* in FTA confirms the biological relationship between FTA and FTC as FTA shares FTC in the same genetic alteration (e.g. chromosomal abnormalities, activating *RAS* mutations, and *PAX8/PPARG* rearrangements) [28].

In studied malignant group, we found a positive expression for *IMP3* in 12/13 cases (92.3%) of PTC, and in all cases (100%) of FV-PTC and FTC, with the highest and strongest expression was seen in FTC cases. Our results were parallel to results of other studies evaluating IMP3 expression in differentiated thyroid carcinomas [22,23,29]. Slosar *et al*. [20], found a rare and weak staining for *IMP3* in PTC group, only 4 out of 37 cases (11%) were positive, which was incompatible with our results, and on the other hand, they found a strong expression for *IMP3* in follicular variant of papillary carcinoma and follicular carcinoma (38% & 69%, respectively), which is compatible with our findings.

In this work, we studied the diagnostic performance of *IMP3* in thyroid lesions by comparing its expression between different studied groups and performing its sensitivity and specificity. We found a statistically highly significant difference in *IMP3* expression between benign lesions (HT, HN and FTA) and malignant lesions ($P<0.01$), and between benign neoplasms (FTA) and malignant neoplasms ($P<0.01$). on the other hand there was nonsignificant difference in IMP3 expression between non-neoplastic lesions and FTA (P >0.05), and between malignant tumors when compared with each other (P>0.05) in terms of positive staining.

In this study, IMP3 showed; 100% sensitivity and 73.3% specificity in differentiating FTC from FTA, 100% sensitivity and specificity (73.3 and 80%) in distinguishing FV-PTC from FTA and HN, respectively, and in distinguishing HN from PTC, *IMP3* showed 92.3% sensitivity and 80% specificity. Collectively *IMP3* has 96%

sensitivity and 78.1% specificity for malignant lesions.

Parallel to our finding, Slosar *et al*. [20]**,** found that *IMP3* had 100% specificity for FTC and FV-PTC as compared with FTA and 69% sensitivity for FTC also compared with FTA. Similarly, Jin *et al*. [21], on performing *IMP3 qRT-PCR* analysis, they documented a 91.4% specificity and 86.7% sensitivity for diagnosis of well-differentiated thyroid carcinomas.

In contrast, though Kulaçoğlu and Erkılınç [23], observed 82.1% positivity for *IMP3* in malignant cases, they found no significant difference between benign lesions and malignant tumors. Also they found a higher frequency of positivity in benign lesions (66.7%) both in HN (50%) and FTA (92.9%) with a statistically significant difference between them (*P<0.05*), which is incompatible with our results.

Our results suggest that *IMP3* could be a magic marker for differentiation of benign and malignant thyroid lesions especially follicular patterned lesions which can represent a diagnostic challenge, and it can be a complementary marker between a panel used to improve the sensitivity and specificity of an individual marker in differentiating benign and malignant follicular lesions of thyroid.

In current work, we found a significantly increased *IMP3* expression in malignant tumors with higher grade and larger size (*P<0.05*). This was in agreement with results of Gao *et al.* [21], who reported a significant correlation between *IMP3* expression and intrahepatic cholangiocarcinoma with larger tumor size and higher grade, so it can be reported that *IMP3* expression not associated only with initiation of malignancy but also with its progression and poor prognosis. In contrast, Kulaçoğlu and Erkılınç [23] and Yorukoglu *et al*. [29], reported no significant correlation between *IMP3* expression and tumor size and grade in thyroid malignancy.

Correlation of *IMP3* expression with other clinicopathological parameters including age, sex, LVI, CI, lymph node status and TNM stage, we found no clear cut correlation between these parameters and IMP3 positivity *(P>0.05),* this was in accordance with studies by Kulaçoğlu and Erkılınç [23] and Yorukoglu *et al*. [29]. In study by Asioli *et al*. [30], *IMP3* expression was compared with the clinicopathologic parameters in poorly differentiated carcinomas, and they found that *IMP3* expreassion was related to increased death

risk, lymph node metastasis, and distant metastasis, this can be explained by their study was only on poorly differentiated carcinomas and their use of different methods for *IMP3* detection.

Slosar *et al.* [20], stated that *IMP3* expression increased in differentiated thyroid carcinoma with larger tumor size, higher frequency of LVI, and lymph node metastases, but their results did not reach a stastistical significant difference. Also they found higher expression for *IMP3* in PTC with nodal metastasis, but owing to small number of positive cases in this group they couldn't draw any definite conclusions.

Given the contradictory findings in different studies, further studies with larger number of cases and long-term follow-up may be useful to establish prognostic significance of *IMP3* in thyroid carcinoma.

Conclusion:

IMP3 may be involved in thyroid carcinogenesis, the initiation, proliferation and progression of tumor cells. *IMP3* is a potential diagnostic marker for thyroid cancer, and can be a promising marker for differentiating follicular patterened thyroid lesions.IMP3 expression increases with increase size and grade of malignant thyroid tumors, which indicates a possible prognostic role for *IMP3* in thyroid cancer.

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Conflicts of interest
There are no conflicts of interest.

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