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Immunohistochemical Evaluation of Ki-67 and Galectin-3 as a diagnostic marker for Thyroid carcinoma in Wasit Province

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ABSTRACT:

Thyroid Cancer is a malignant tumor that develops from the cells of the thyroid gland. Biomarkers can assist to detect thyroid cancer before evident clinical symptoms appear, improving early diagnosis. Thus, the object of this study was to evaluate the role of Ki-67 and Galactin-3 (Gal-3) proteins as a biomarker for thyroid cancer diagnosis and to ascertain how these proteins relate to the type and stage of the tumor. This study includes forty formalin-fixed, paraffin-embedded thyroid carcinoma tissue samples were collected from the archives of Histopathology Department at Al-Karama Teaching Hospital in Wasit Governorate, Iraq which diagnosed by a specialist physician. The streptavidin-peroxidase method was used for immunohistochemical staining. "Gal-3 expression was evaluated based on staining intensity and the distribution of positive cells, whereas K-67 expression was evaluated based on the proportion of positively stained nuclei". The mean age of the patients was 44.85 ± 10.3 years, with ages ranging from 24 to 72. Males made about 15% of cases, with women making up the bulk (85%). The most prevalent histological pattern was papillary thyroid carcinoma (85%), which was followed by multifocal papillary thyroid cancer (15%). Stage I diagnoses accounted for 80% of cases, whilst stage II diagnoses made up 20%. 65% of cases had elevated Ki-67 protein levels, which were strongly correlated with the type and stage of the tumor. In 70% of cases, especially papillary thyroid carcinoma, galectin-3 protein levels were substantially positive. They also demonstrated a statistically significant link with the type and stage of the tumor. The findings suggest that Gal-3 and Ki-67 are useful markers for thyroid cancer diagnosis. While Gal-3 may be a crucial diagnostic marker for distinguishing malignant thyroid cancers, Ki-67 shows tumor growth activity and may suggest its aggressiveness.

Keywords: Thyroid Carcinoma, IHC, Ki-67, Gal-3, Tissues, Scoring.

1. INTRODUCTION

The rate of thyroid carcinoma has elevated constantly and dramatically since the 1990s [1]. Presently, thyroid carcinoma is the 5th most common cancer among women; Nevertheless, it was ranked in the 14th position two decades ago. The epidemiological studies showed that the increase thyroid carcinoma incidence was largely due to papillary thyroid carcinoma (PTC). "PTC is the most common type of thyroid carcinoma, accounting for 80–85% of all thyroid carcinomas" [2]. Although most PTCs present indolent features, some patients with aggressive tumors still have poor prognoses [3].

The diagnosis of PTC relies on nuclear features which include optical clearing, elongation, micronuclei and pseudoinclusions [4]. However, morphological overlaps between follicular adenoma, papillary carcinoma and multinodular goiter showing features of papillary budding cause a diagnostic dilemma. In view of these inconsistencies, several immunohistochemical markers have been studied to assess their use in aiding diagnoses [5]. Some useful markers for differentiated thyroid cancer which have already been studied, are Galectin-3 (Gal-3), Ki67, Hector-Battifora mesothelium antigen-1 (HBME-1), cytokeratin-19 (CK-19) and RET/PTC. The roles of Ki67 and Gal-3 in PTC and thyroid disease still remain unclear [5,6].

"Ki67 is a DNA-binding protein that is mainly distributed in the nucleus and is related to cell proliferation. Ki67 is a large protein of 395 kDa, encoded by nearly 30,000 base pairs". As one of the most important markers in cell proliferation, Ki67 has been widely used in the treatment and research of various types of tumors [7]. Ki-67 reliable marker of cellular proliferation used in cancer to indicate tumor aggressiveness, with higher expression (labeling index, LI) generally correlating with increased malignancy, poor disease-free survival, higher recurrence, and advanced clinical stage. While often used for follicular thyroid cancer to predict prognosis, its value in papillary thyroid cancer remains an area of research, with studies showing elevated levels in more aggressive tumors [8,9].

"Gal-3 is a member of the beta-galactoside-binding protein family and has an important role in biological processes such as: cell–cell adhesion and cell–matrix interactions associated with tumor spread [10]. Galectins have been extensively investigated regarding their role in cancer especially metastasis". Galectins are a large family of proteins that recognize and bind β-galactosides on cell glycoproteins and glycolipids.7 Gal-3 is a structurally unique 31-kDa member of the galectin family [11]. Although other members exist as oligomers, Gal-3 is the only member that exhibits a pentameric structure and thus is capable of crosslinking glycoproteins at the cell surface to form new lattices that are involved in cellular signaling and receptor endocytosis [12]. In the present study, we additionally investigated the effect of Ki67 and Gal-3 in diagnosis and prognostic values in PTC and thyroid disease.

2. PATIENTS AND METHODS

Tissue specimens:

"Formalin-fixed, paraffin embedded tissue blocks from forty surgically resected thyroid tissue were obtained from the pathology archives" of tissues for Thyroid cancer were collected from January-2025 to May-2025 from the Department of Pathology in Al-Karama Teaching Hospital in Wasit Province, Iraq.

Immunohistochemical staining:

The manufacturer's instructions for the streptavidin-peroxidase immunohistochemistry procedure were followed. Gal-3 and Ki67, the primary polycolonal antibody Gal-3, Ki-67 was purchased from BioSb/USA. Sections were made using the normal procedure, which involves deparaffinizing them and then boiling them in a pH 6 sodium citrate solution to remove the antigen mask. The sections were incubated in 3% oxygenated water for 30 minutes at room temperature, washed with distilled water for 10 minutes, and then placed in 1% phosphate-buffered saline for 5 minutes in order to block endogenous peroxidase. Sites that were not particular were prohibited. Following that, the sections were incubated with the primary antibodies in a refrigerator at 40°C for the entire night. After 30 minutes of room temperature incubation, the secondary antibody was rinsed with 1% phosphate-buffered saline for five minutes for each of the three passes. After 30 minutes of room temperature incubation, horseradish streptavidin-peroxidase was rinsed with 1% phosphate-buffered saline. The 3,3'-diaminobenzidine was used to observe the marker. Mayer's hematoxylin stain was then applied to the tissue. A magnification microscope (100X) was used to determine the percentage of positive cells. Gal-3 and Ki67 stained brown in the nucleus, cytoplasm, or both nucleus and cytoplasm.

Immunohistochemical Scoring and Statistical Analysis:

All Specimens received a standard immunohistochemical examination to measure the Ki-67 index. Pathologists skillfully investigated the Ki-67 staining by closely examining the cell nuclei, where those stained brown were marked as positive. The patients were carefully categorized into two groups: the High Ki-67 expression group, where the index was 5% or greater, and the low Ki-67 expression group, with an index of less than 5% [13]. In interpreting the scattered and intensity of the Gal-3 cytoplasmic signals, we draw from the established guidelines provided by Weber KB et al.& Hermann ME et al. The staining intensity was thoughtfully graded on a scale from 0 to 3, with 0 indicating no staining, 1 for weak/slight staining, 2 for moderate staining, and 3 for intense staining. Additionally, the proportion of stained cells was categorized, with levels representing < 5% of cells as 1, 5% to 50% as 2, and over 50% as 3 [14,15]. For our statistics analysis, we utilized the "Social Science Statistics and the Statistical Package for Social Sciences version 17 for Windows, along with Microsoft Excel 2010". We approached the statistical tests with care, considering a P-value of less than 0.05 to signify statistical significance [16].

2. RESULT

Present study, which included 40 patients with thyroid cancer, showed that their ages ranged from 24 to 72 years, with a mean age of 44.85 ± 10.3 years. A significantly higher incidence was observed in females compared to males, with females comprising 85% of cases versus males 15%, a statistically significant difference (P=0.0023, P<0.05), as shown in Table 1. Regarding histological distribution, table 2, papillary thyroid cancer (PTC) was the most common, accounting for 85% of cases, while multifocal papillary cancer (MPTC) accounted for 15%. As for the stage of the disease, the majority of cases were in stage I (80%) compared to stage II (20%), with statistically significant differences in the distribution of types and stages (P<0.05).

Table 1: Age and gender analysis of patients with thyroid cancer

Age properties / years	Statistical analysis
Age range	**24 -72**
Age mean	**44.85**
Standard deviation	**± 10.3**
Standard error	**1.63**
Gender	**N (%)**
Males	**6 (15%)**
Females	**34 (85%)**
P value	**0.0023***
Total number	**40**

***Statistical different (P value < 0.05)**

Table 2: Distribution of patients according to thyroid cancer types and stages

Cancer types	N (%) Males (6), Females (34)	Stage I	Stage II	P value
PTC	34 (85%)	27 (67.5%)	7 (17.5%)	0.018*
MPTC	6 (15%)	5 (12.5%)	1 (2.5%)	0.092
P value	0.0021*	0.007*	0.336	
Total number	40 (100%)	32 (80%)	8 (20%)	

***Statistical different (P value < 0.05)**

Immunohistochemical expression of Ki-67 results showed that 26 cases (65%) had high expression, while 14 cases (35%) had low expression. Analyzing the relationship between cancer type and Ki-67 expression level, PTC cases showed a higher percentage of high expression (22 cases, 55%) compared to low expression (12 cases, 30%), with this relationship being statistically significant (P = 0.022) as seen in table 3. In MPTC cases, high expression was recorded in 4 cases (10%) and low expression in 2 cases (5%), with no clear statistical relationship (P = 0.582). Overall statistical analysis also showed a significant correlation between tumor type and Ki-67 expression level, with an overall P value of 0.003, indicating that cancer type significantly influences the level of proliferative activity as measured by the Ki-67 index.

Microscopic images of Ki-67 protein expression show variations in the proliferative index of cancer cells, measured by the percentage of cells with brown-stained nuclei. In Figures 1 and 2, low expression (a) shows a very limited and scattered number of positive (brown-stained) cells, indicating that the tumor is in a state of relative dormancy or very slow growth. This pattern is often associated with stable clinical cases and non-aggressive behavior.

High expression shows a dense and pronounced concentration of brown-stained nuclei (especially in Figures 1b and 2b), reflecting increased mitotic activity in cancer cells. A high proliferative index in multifocal cancers (shown in Figure 2) may indicate a higher likelihood of invasion of adjacent tissues or lymph nodes.

When examining the relationship between disease stage and Ki-67 expression in table 4 it was found that stage I comprised 32 cases (80%) while stage II comprised 8 cases (20%). In stage I, high Ki-67 expression was observed in 20 cases (50%) “compared to low Ki-67 expression” in 12 cases (30%), with a statistically significant relationship (P = 0.021). In stage II, high Ki-67 expression was recorded in 6 cases (15%) and low Ki-67 expression in 2 cases (5%), also

with a statistically significant relationship (P = 0.049). Statistical analysis also revealed a significant relationship between tumor stage and Ki-67 expression levels, with P values of 0.013 for low expression and 0.011 for high expression, confirming a clear correlation between disease stage progression and the level of cancer cell proliferation.

Table 3: Evaluation IHC expression of Ki 67 according to thyroid cancer types

Cancer types ki 67	N (%) Males (6), Females (34)	IHC expression		P value
		Low	High	
PTC	34 (85%)	12 (30%)	22 (55%))	0.022*
MPTC	6 (15%)	2 (5%)	4 (10%)	0.582
P value	0.003*	0.013*	0.0097*	
Total number (%)	40 (100%)	14 (35%)	26 (65%)	

***Statistical different (P value ≤ 0.05)**

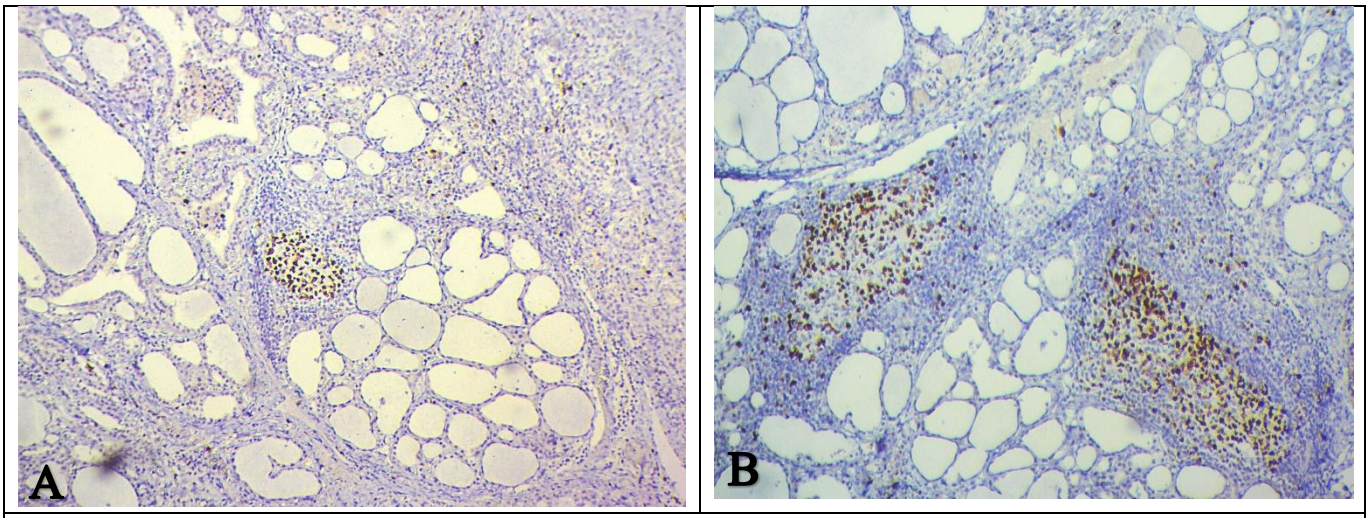

Figure (1): Microscopic sections of Ki-67 immunostaining in Papillary thyroid cancer Showed: "(a) Positive low Ki-67 expression, (b) Positive high Ki-67 expression" (100x).

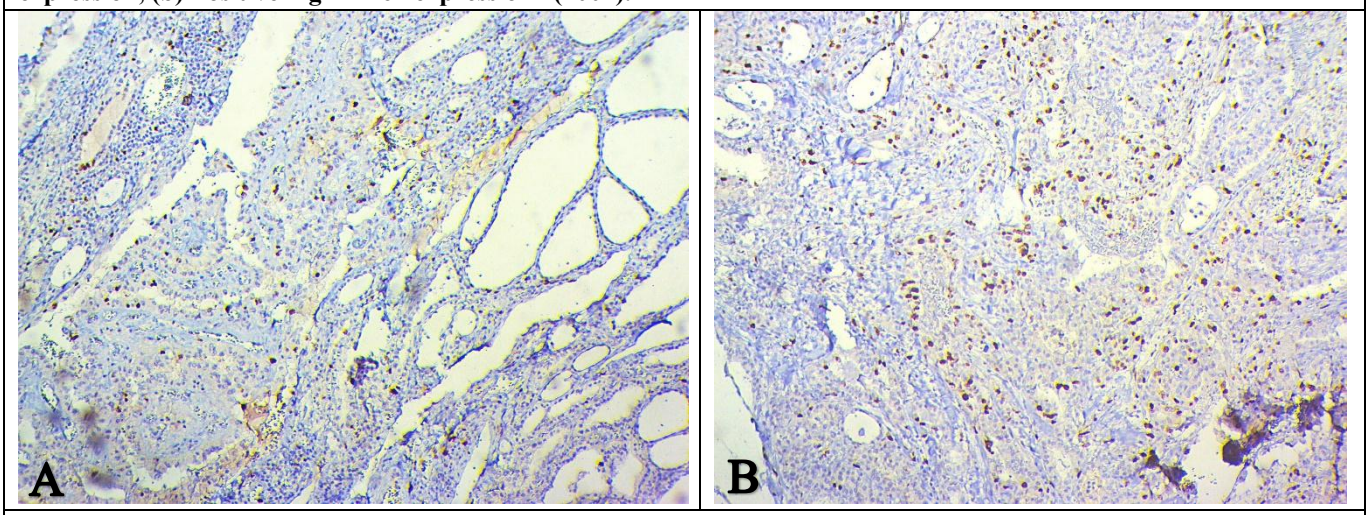

Figure (2): Microscopic sections of Ki-67 immunostaining in Multifocal papillary thyroid carcinoma Showed: "(a) Positive low Ki-67 expression, (b) Positive high Ki-67 expression" (100x).

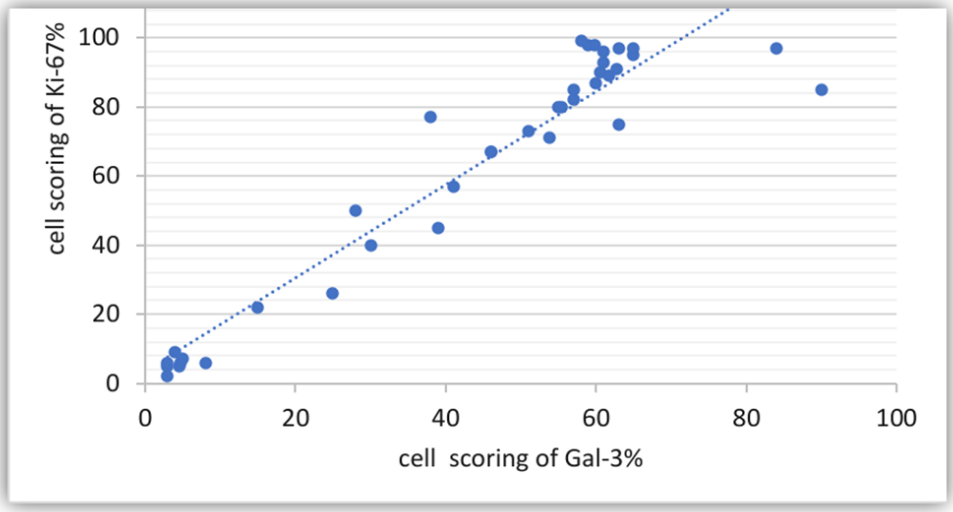

Figure (5): person confidence correlation between Ki-67 and Gal-3 (r= 0.9222, P value= 0.011)

Table 4: Evaluation IHC expression of Ki 67 according to thyroid cancer stages:

Cancer stages ki67	N (%)	IHC expression		P value
		Low	High	
Stage I	32 (80%)	12 (30%)	20 (50%)	0.021*
Stage II	8 (20%)	2 (5%)	6 (15%)	0.049*
P value		0.013*	0.011*	
Total number (%)	40 (100%)	14 (35%)	26 (65%)	

***Statistical different (P value < 0.05)**

The tables below show the results of our study evaluating Gal-3 protein expression using IHC in thyroid cancer samples. Table 5 showed that the majority of cases (70%) exhibited strong protein expression, with a statistically significant difference between cancer types (P value < 0.05). Strong expression was concentrated in PTC (65%) compared to only 5% in MPTC P=0.008). Table 6 revealed a statistically significant relationship between disease stage and protein expression (P value < 0.05). 80% of cases were in stage I, and most of these (65%) showed strong Gal-3 expression. This percentage decreased significantly in stage II, reaching only 5%, indicating a statistically significant difference ($P<0.05$) between the strength of expression of this biomarker and the type and stage of the cancer.

The microscopic sections in the figure show the results of Galectin-3 immunostaining in cases of PTC and M PTC. This protein is used as a key diagnostic marker to differentiate malignant tumors. The images in Figures 3 and 4 reveal a clear variation in the intensity of protein expression between weakly positive cases (a), showing a faint, localized brown stain, and strongly positive cases (b), showing a dark brown stain that is diffuse throughout the cytoplasm and nuclei of cancer cells. This gradient in stain intensity reflects the biological characteristics of the tumor, as strong Galectin-3 expression is typically associated with a confirmed malignant diagnosis and increased invasiveness of cancer cells, even in multifocal cases.

The results in Figure 5 indicate a positive interaction between Galectin-3 expression and the Ki-67 proliferation index, with a correlation coefficient ($r = 0.9222$), indicating a strong correlation between the two compounds. Furthermore, the statistical significance value ($P = 0.011$) indicates that this correlation is statistically significant ($P < 0.05$). Consequently, the proportion of cells expressing Galectin-3 is associated with an increased proportion of Ki-67-positive cells, with most of the Galectin-3 data concentrated in this area. Therefore, a high Galectin-3 index may be linked to the proliferative diversity of various cells, supporting its role in large-scale proliferation.

Table 5: Evaluation IHC expression of Gal-3 according to breast cancer types

IHC expression			Breast cancer types		P value
	N.	%	MPTC	PTC	
Weak focal	8	20%	2 (5%)	6 (15%)	0.049*
Moderate	4	10%	2 (5%)	2 (5%)	1.00
Strong	28	70%	2 (5%)	26 (65%)	0.008*
Total number	40	P value	1.00	0.011*	

***Statistical different (P value ≤ 0.05)**

Table 6: Evaluation IHC expression of Gal-3 according to breast cancer stages

Cancer stages	N (%)	Weak focal	Moderate	Strong	P value
Stage I	32 (80%)	2 (5%)	4 (10%)	26 (65%)	0.026*
Stage II	8 (20%)	6 (15%)	0 (0%)	2 (5%)	0.089
P value	0.0062*	0.0493*	0.0488*	0.011*	
Total number %	40 (100%)	8 (20%)	4 (10%)	28 (70%)	

***Statistical different (P value ≤ 0.05)**

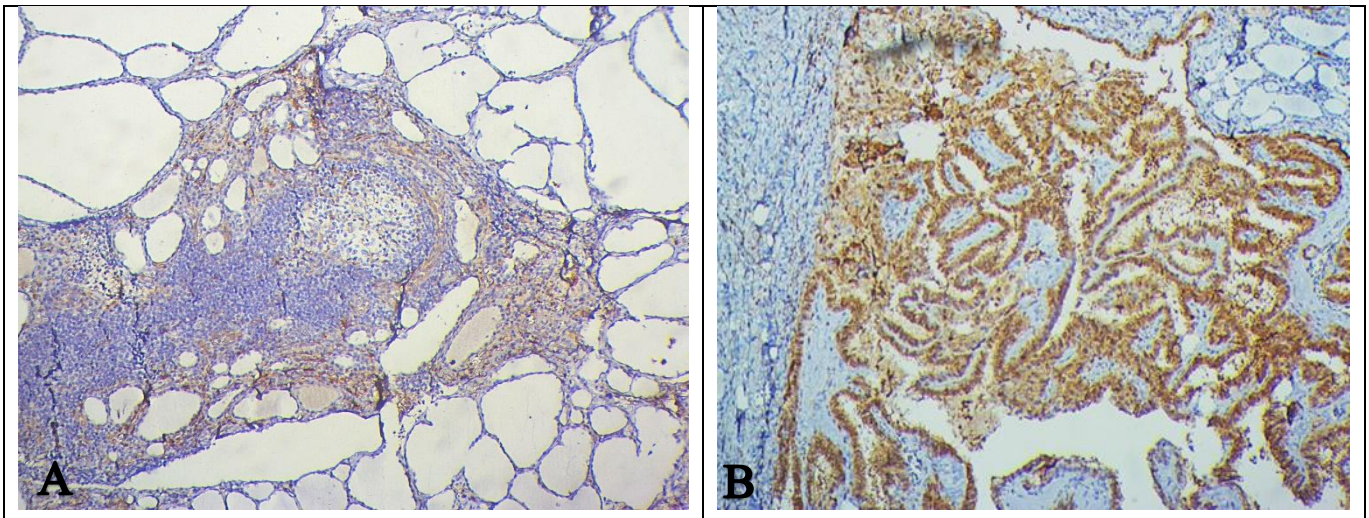

Figure (3): Microscopic sections of "Galectin-3 immunostaining in papillary thyroid carcinoma" Showed: (a) Positive weak Galectin-3 expression, (b) Positive strong Galectin-3 expression (100x).

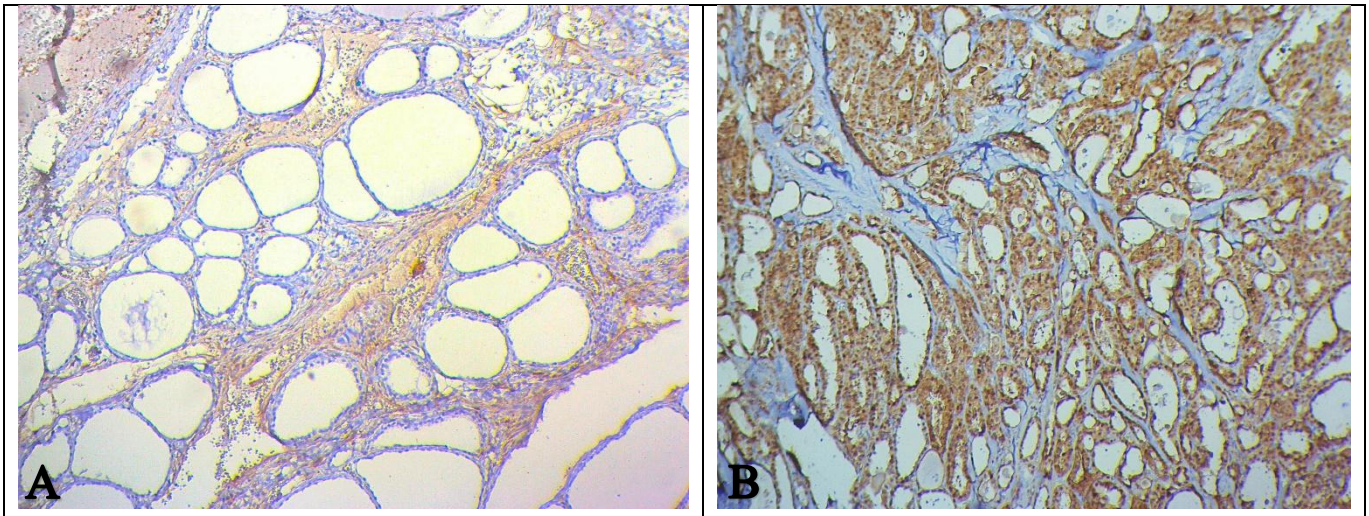

Figure (4): Microscopic sections of "Galectin-3 immunostaining in Multifocal papillary thyroid carcinoma" Showed: (a) Positive weak Galectin-3 expression, (b) Positive strong Galectin-3 expression (100x).

3. DISCUSSION

Our study results reflect a specific demographic and biological pattern, with a mean age of 44.85 years among patients. This relatively young age is often attributed by researchers to genetic and environmental factors in the region, with a clear predominance of females at 85% compared to 15% for males. Medical studies explain the higher incidence in women compared to men by citing fundamental hormonal differences. Estrogen plays a essential role in stimulating cell division, in addition to other factors such as prolonged periods of hormonal exposure (early puberty or late menopause), pregnancy, and lactation. These factors are absent in male physiology, which recorded a 15% incidence rate here—a high percentage exceeding global averages (less than 1%) [17,18]. Clinically, the histological type PTC predominates in 85%, and the majority of cases (80%) are correlated with early diagnosis in Stage 1, indicating health awareness or effectiveness in periodic screening that led to the results appearing with this statistical accuracy compared to other studies in which cases may appear in later stages [18-20].

The statistical results in Tables (3) and (4) showed a strong correlation between high Ki-67 protein expression and the clinical characteristics of thyroid cancer, with high expression in 65% of the total samples. This is a significant increase ($P < 0.05$) reflecting the high mitotic activity of the cancer cells. This 55% increase in PTC cases compared to MPTC is attributed to the fact that the conventional papillary type often exhibits gene mutations (such as the BRAF V600E mutation) that induce the cell cycle, leading to increased expression of the Ki-67 protein, which is only expressed in the active mitotic phases (S, G1, G2, M) and absent In the resting phase (G0) [21-23]. Pervious study on the molecular mechanisms of Ki67 showed that Ki67 plays an essential role in the early steps of ribosomal RNA synthesis and that the Ki67 protein may be related to various signal pathways. which may partially answer the question of why Ki67 is associated with inflammation [24]. Moving on to the histological analysis in Figures (1) and (2), we find that the contrast between images (a) with low expression and images (b) with high expression represents a visual interpretation of these figures. The dense brown staining of nuclei in images (b) indicates a high tumor growth fraction. This microscopic density explains the results in Table (4), where high expression in Stage II reached 15% with a significant probability value, suggesting that cancer stage progression requires accelerated cell division to facilitate tissue invasion and metastasis [22-24]. These findings are consistent with previous studies, such as those by Tang *et al.* and Zhu *et al.,* which confirmed that an elevated Ki-67 index (as shown in images b) is a poor prognostic factor associated with an increased likelihood of recurrence and vascular invasion. This makes the combination of digital table readings and microscopic image observation crucial for determining tumor aggressiveness and guiding patient treatment planning [25,26]. Study of Peseta *et al*. showed that the ki67 proliferation index is a diagnostic/prognostic tool of interest in differentiated thyroid carcinoma and a good predictor of disease-free survival, disease recurrence and metastatic development. Prospective studies on large cohorts may add value for ki67 as a specific tool in the management strategy of differentiated thyroid carcinoma [27].

The results of this study showed a significant superiority in the strong expression of the Gal-3 protein, with an overall percentage of 70%, and a very high concentration in the PTC type (65%) compared to only 5% in the MPTC type, with strong statistical significance (P=0.008). This is biologically attributed to the fact that Gal-3 plays a pivotal role in regulating cell-interstitial interactions, stimulating cancer cell proliferation and inhibiting apoptosis, making it a key marker of cancerous transformation in thyroid papillary cells [28]. These observations are consistent with the microscopic images in Figures (3) and (4), where image (b) shows a dense and regular cytoplasmic and nuclear brown stain, reflecting strong expression, while image (a) shows a pale and dispersed stain representing weak focal expression. According to statical analysis the strong expression was primarly associated with Stage I (65%) (P=0.026), while it decrease to 5% in stage II. This may be clarified by the fact that Gal-3 represents an early oncogenic event that helps stabilize the tumor in its early stages [29]. The result of this study come in agreement with the results of Bartolazzi *et al*. and Saggiorato *et al*., who confirmed that Gal-3 is the most accurate immunohistochemical marker for distinguishing papillary thyroid carcinoma from benign tumors [30,31]. They also conform to research indicating that the intensity of microscopic staining (figure b) increases proportionally with the cells' ability to invade locally. This makes the correlation between the expressive power in the tables and the color intensity in the images conclusive evidence of the high diagnostic value of this protein in identifying active cancer cells. A study achieved by Tang *et al.,* showed that Gal-3 is play important role in differentiate between the two types of thyroid cancers non-papillary and papillary thyroid carcinoma. Additionally, it was also recorded more commonly in patients with lymph node metastasis [32]. Gal-3 was positive expressed in 100% of papillary carcinomas, 62.5% of follicular carcinomas, 18.8% of follicular adenomas and negative in nodular goiters in research conducted by Miskad *et al.,* Galectin's sensitivity was noted to be 81.25% and at a specificity of 90.62%. This study also showed that sensitivity was increased by 10% when both Gal-3 and HBME-1 expression was combined [33].

On the other hand, our findings are consistent with several previous studies that have indicated a relationship between elevated Galectin-3 expression and increased cell proliferative activity, as measured by the Ki-67 index, in various tumors [34-36]. These studies demonstrated that increased Galectin-3 expression is associated with a higher rate of cell division and increased intensity of tumor cell proliferation, suggesting that this protein may contribute to tumor progression and increased aggressiveness [36]. This association can be explained by several potential biological mechanisms. Gal-3 is a protein involved in regulating cell growth and cell adhesion, and it also plays a role in activating cell signaling pathways associated with proliferation. Furthermore, Gal-3 has the ability to inhibit apoptosis (programmed cell death), allowing tumor cells to survive longer and continue dividing. It may also contribute to enhancing the interaction of tumor cells with the tumor microenvironment, leading to increased rates of cell growth and proliferation, which is reflected in an elevated Ki-67 index [35,37].

4. CONCLUSIONS

The conclusion of this study was that Ki-67 and Galectin-3 play important role as biomarker in the diagnosis and evaluation of thyroid cancer. The results demonstrated a strong correlation between elevated levels of these proteins and tumor type and stage, particularly in papillary thyroid cancer (PTC). While Galectin-3 stands out as a key diagnostic marker for differentiating malignant tumors, Ki-67 reflects mitotic activity and tumor aggressiveness. The strong statistical correlation between them further confirms their complementary role in predicting disease course and accurately developing treatment plans.

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