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ACCURACY OF THE BETHESDA SCORING SYSTEM IN PREDICTING HISTOPATHOLOGICAL OUTCOMES

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ABSTRACT

Background: The Bethesda system for reporting thyroid cytopathology (TBSRTC) classified thyroid nodules into sex categories, each with an associated risk of malignancy. It provided an approach for evaluating fine needle aspiration cytology and guiding clinical decisions. However, its predictive accuracy varied across populations. Many studies examined how well Bethesda classifications align with final histopathological findings to assess its effectiveness in distinguishing between benign and malignant thyroid lesions. **Objective:** This study aimed to assess the accuracy of the Bethesda system in predicting the final histopathological diagnosis of thyroid nodules. **Methodology:** We conducted an observational, retrospective, single center study at the Princess Haya Military Hospital in Ajloun, Jordan between 2023/2024 on patients who underwent thyroid FNA cytology followed by surgical excision and histopathological evaluation. Data were collected for demographic information like age, gender. Clinical characteristics such as Bethesda classification results, histopathological findings, and associated medical history such as comorbidities (diabetes mellitus, hypertension, and hypothyroidism) were analyzed. Statistical analyses were performed using R studio (version 2024.09.0) Vienna, Austria. **Results:** Our study analyzed 99 cases with a mean age of 46.97 years, 89.9% of whom were female. Common comorbidities included diabetes (15.15%), hypertension (18.18%), and hypothyroidism (8.08%). Fine-needle aspiration (FNA) findings classified 27.2% of cases as benign, 27.2% as malignant, and 36.3% as indeterminate. The most frequent Bethesda category was III (37.76%), followed by II (25.51%) and IV (16.33%). Histopathology confirmed 53.5% as benign and 41.41% as malignant, with papillary carcinoma being the most common (36.36%). Surgery was performed in 81.81% of cases. Statistical analysis showed malignancy was exclusive to Bethesda categories V and VI (100%), with category IV at 75% and category III at 40.54%. Logistic regression identified lesion size as a significant predictor of malignancy (OR = 1.24, p = 0.01), while hypertension and diabetes showed possible associations but were not statistically significant. **Conclusion:** Our study demonstrated that the Bethesda system effectively predicted thyroid malignancy, with high specificity but moderate sensitivity. Malignancy was exclusive to Bethesda categories V and VI. Lesion size was an important predictor.

KEYWORDS: Bethesda Scoring System, Thyroid Cytology, Fine-Needle Aspiration, Histopathology, Malignancy Risk, Jordan.

INTRODUCTION

The thyroid gland is a small, butterfly-shaped organ in the front of the neck that plays an important role in regulating metabolism, energy levels, body temperature, heart function, digestion and reflexes. It influences growth and the overall balance of nearly all organs, ensuring their appropriate function.[1] A thyroid nodule is an abnormal growth within the thyroid tissue, while most of these nodules are benign and don't cause dangerous health problems, some may indicate an underlying thyroid disease or cancer.[2] This highlights the importance of distinguishing benign from malignant nodules to ensure appropriate diagnosis and management.

Fine needle aspiration cytology (FNAC) is a highly accurate, sensitive and specific test for initial evaluation of thyroid nodules.[3] The Bethesda system for reporting thyroid cytopathology (TBSRTC) provides a standardized classification system for reporting FNAC of thyroid nodules.[4] It categorizes thyroid cytology findings into six groups, each associated with an estimated risk of malignancy and recommended clinical management.[4] The application of TBSRTC has improved diagnosis accuracy, standard reporting among

pathologist, and better communication with clinicians. This has helped in patient care by reducing unnecessary surgeries in thyroid FNAC cases.[5] The Bethesda classification for thyroid cytology shows variations across different surgical centers and countries.[6] Factors influencing the effectiveness of TBSRTC include pathologist knowledge, sample quality and interobserver variation.[7] The system's diagnostic accuracy is enhanced by surgical follow-up which can assess the risk of malignancy.[7] Some studies have reported discrepancies between Bethesda classifications and final histopathological outcomes, especially in countries with less resource.[8]

Although the Bethesda system has been widely studied in the world, its application and accuracy in specific regions, such as those in Jordan should be considered, taking into account regional differences and healthcare practices. In Jordan, research evaluating the accuracy of the Bethesda system remains limited, making it necessary for further investigation. This study aims to assess the predictive accuracy of the Bethesda score in histopathological outcomes among patients in Ajloun, Jordan. The results could help improve patient care and diagnostic procedures.

METHODS AND MATERIALS

Study Design

This study was a retrospective, single center observational study conducted in the period between 2023-2024 at Princess Haya Military Hospital in Ajloun, Jordan, on patients who underwent thyroid FNA cytology followed by surgical excision and histopathological evaluation. Our study aimed to evaluate the accuracy of the Bethesda scoring system in predicting histopathological outcomes of thyroid nodules. Data were collected from medical records of patients managed at Princess Haya Military Hospital.

Data Collection

A total of 99 patients who had went under thyroid FNA cytology followed by surgical excision were included in the study. We recorded patient demographic information including age and gender. Clinical data were extracted including Bethesda classification results, histopathological findings, and associated medical history such as comorbodities (diabetes mellitus, hypertension, and hypothyroidism). We included other variables included previous thyroid surgery (hemithyroidectomy or total thyroidectomy). All extracted data were recorded in a structured database for statistical analysis.

Ethical Consideration

This study approval was waived by the Institutional Review Board (IRB) committee in Princess Rahma Hospital (approval no:###). This study was conducted in accordance with the declaration of Helsinki 1964. Approval was obtained before data collection.

Statistical Methods

Descriptive and inferential statistics were used in the analysis of the collected data. Categorical variables were described by frequency and percentage, while continuous variables were described using mean and standard deviation (SD). Fisher's exact test was used to assess significant differences in benign and malignant diagnoses across Bethesda categories. The sensitivity, specificity, and accuracy of the BETHESDA system in predicting malignancy or benign outcomes were assessed. Sensitivity was the proportion of correctly identified malignant cases, while specificity was the proportion of correctly identified benign cases. Accuracy represented the overall proportion of correctly classified cases (both malignant and benign).

The significance of the results was measured using a p-value of <0.05. All statistical analyses were carried out in R software version 4.4.2(Vienna).

RESULTS

A total of 99 cases were analyzed, with a mean age of 46.97 years (SD = 13.11). The majority of patients were female (89.9%). Among the recorded risk factors, diabetes mellitus (DM) was present in 15.15% of cases, hypertension (HTN) in 18.18%, hypothyroidism in 8.08%, and previous hemithyroidectomy in 7.07%. Fine-needle aspiration (FNA) findings showed that 27.2% of cases were benign, including colloid nodules (24.24%), follicular nodules (2.02%), and Hashimoto's thyroiditis (1.01%). Malignant findings accounted for another 27.2%, with papillary carcinoma (14.14%), follicular carcinoma (8.08%), Hurthle cell carcinoma (4.04%), and a combination of follicular and Hurthle cell carcinoma (1.01%). Cases of undetermined significance comprised 36.3%, including atypia (15.15%), follicular (13.13%), follicular/Hurthle cell (5.05%), and Hurthle cell (3.03%). The Bethesda classification showed category III (37.76%) as the most frequent, followed by category II (25.51%), category IV (16.33%), category V (9.18%), category I (8.16%), and category VI (2.04%). Final histopathology results confirmed benign diagnoses in 53.5% of cases, consisting of hyperplastic nodules (21.21%), Multinodular goiter (16.16%), Follicular adenoma (12.12%), Hurthle cell adenoma (2.02%), and Multinodular goiter with follicular adenoma (2.02%). Malignant cases comprised 41.41%, with papillary carcinoma (36.36%) being the most prevalent, followed by follicular carcinoma (2.02%), Hurthle cell carcinoma (2.02%), and Anaplastic neoplasm (1.01%). Surgical excision was performed in 81.81% of cases, with hemithyroidectomy accounting for 47.47% and total thyroidectomy for 34.34% **(Table 1)**.

Statistical analysis showed significant differences in benign and malignant diagnoses across Bethesda categories ($p < 0.001$) **Table 2**. Malignancy was exclusively found in categories V (100%) and VI (100%), while category IV had a malignancy rate of 75% and category III had 40.54%. Papillary carcinoma was

the most frequent malignancy (36.73%), predominantly in categories V and VI ($p < 0.001$). While benign diagnoses were most common in Bethesda category I (87.5%) and II (80%), decreasing with higher Bethesda scores. Category III had 56.76% benign cases, dropping to 31.25% in category IV, with none in categories V and VI. Multinodular goiter was most frequent in categories I (50%) and II (36%), while hyperplastic nodules were more common in category III (32.43%). Follicular adenoma appeared most in categories II (24%) and IV (12.5%). Hashimoto's thyroiditis was rare, seen in only a few cases in categories II (4%) and III (5.41%).

The diagnostic performance of the Bethesda scoring system in predicting histopathological outcomes was evaluated using key statistical metrics. The sensitivity of the system was 56.1%, indicating its moderate ability to detect malignant cases. In contrast, specificity was high at 93.1%, demonstrating strong accuracy in identifying benign cases. The positive predictive value (PPV) was 85.2%, meaning that the majority of cases identified as malignant were confirmed as such upon histopathological examination. The negative predictive value (NPV) was 75%, suggesting that three-quarters of cases classified as benign were truly benign. The overall accuracy of the Bethesda scoring system in predicting final histopathological outcomes was 77.8%, highlighting its reliability in thyroid nodule assessment **Table 3**.

Logistic regression analysis evaluates the factors predicting the final histopathology of thyroid lesions, identifying whether they are malignant or benign. Among the examined predictors, lesion size was found to be statistically significant (OR = 1.24, 95% CI: 1.05–1.52, p = 0.01, **Table 4**), indicating that larger lesion size is significantly associated with a higher likelihood of malignancy. Additionally, hypertension (HTN) approached statistical significance (OR = 0.10, 95% CI: 0.007–0.81, p = 0.052), suggesting a possible inverse association with malignancy. Diabetes mellitus (DM) also demonstrated a high odds ratio (OR = 9.63, 95% CI: 1.04–147.18, p = 0.06), indicating a potential link between diabetes and malignancy, though it did not reach the conventional significance threshold.

Other predictors, including male gender (OR = 6.17, p = 0.09), hemi-thyroidectomy (OR = 8.52, p = 0.10), and hypothyroidism (OR = 0.83, p = 0.90), did not reach statistical significance but exhibited varying odds ratios suggesting potential associations.

Table 1: Baseline Characteristics, Radiological Findings, andFinal Histopathology of Thyroid Lesions.

Characteristic	**N = 99**[1]
Age	46.97 (13.11)
Gender	
Female	89 (89.9%)
Male	10 (10.1%)
Risk Factors	
DM	15 (15.15%)
HTN	18 (18.18%)
Hypothyroidism	8 (8.08%)
Hemithyroidectomy	7 (7.07%)
FNA Finding	
Benign	27 (27.2%)
Colloid nodule	24 (24.24%)
Follicular nodule	2 (2.02%)
Hashimottos thyrodittis	1 (1.01%)
Malignant	27 (27.2%)
Papillary carcinoma	14 (14.14%)
Follicular carcinoma	8 (8.08%)
Follicular carcinoma\Hurthle cell carcinoma	1 (1.01%)
Hurthle cell carcinoma	4 (4.04%)
Undetermined Significant	36 (36.3%)
Atypia	15 (15.15%)
Follicular	13 (13.13%)
Follicular / Hurthle cell	5 (5.05%)
Hurthle cell	3 (3.03%)
BETHESDA	
I	8 (8.16%)
II	25 (25.51%)
III	37 (37.76%)
IV	16 (16.33%)
V	9 (9.18%)

VI	2 (2.04%)
Final Histopathology	
Benign	53 (53.5%)
Hyperplastic nodule	21 (21.21%)
Multinodular Goiter	16 (16.16%)
Follicular adenoma	12 (12.12%)
Hurthle cell adenoma	2 (2.02%)
Multinodular Goiter\Follicular adenoma	2 (2.02%)
Malignancy	41 (41.4%)
Papillary carcinoma	36 (36.36%)
Follicular carcinoma	2 (2.02%)
Hurthle cell carcinoma	2 (2.02%)
Anaplastic neoplasm	1 (1.01%)
Excision	
Hemithyroidectomy	47 (47.47%)
Total Thyroidectomy	34 (34.34%)
[1] Mean (SD); n (%)	

Table 2: Comparison of Final Histopathology Across Bethesda Categories.

Characteristic	**I** N = 8[1]	**II** N = 25[1]	**III** N = 37[1]	**IV** N = 16[1]	**V** N = 9[1]	**VI** N = 2[1]	**Overall** N = 98[1]	**P value**[2]
Benign	7 (87.50%)	20 (80.00%)	21 (56.76%)	5 (31.25%)	0 (0.00%)	0 (0.00%)	53 (54.08%)	**<0.001**
Multinodular Goiter	4 (50.00%)	9 (36.00%)	4 (10.81%)	1 (6.25%)	0 (0.00%)	0 (0.00%)	18 (18.37%)	**0.014**
Hyperplastic nodule	1 (12.50%)	6 (24.00%)	12 (32.43%)	2 (12.50%)	0 (0.00%)	0 (0.00%)	21 (21.43%)	0.4
Follicular adenoma	1 (12.50%)	6 (24.00%)	3 (8.11%)	2 (12.50%)	0 (0.00%)	0 (0.00%)	12 (12.24%)	0.5
Hashimottos thyroditis	0 (0.00%)	1 (4.00%)	2 (5.41%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	4 (4.08%)	0.14
Malignant	0 (0.00%)	3 (12.00%)	15 (40.54%)	12 (75.00%)	9 (100.00%)	2 (100.00%)	41 (41.84%)	**<0.001**
Papillary carcinoma	0 (0.00%)	3 (12.00%)	11 (29.73%)	11 (68.75%)	9 (100.00%)	2 (100.00%)	36 (36.73%)	**<0.001**
[1] Mean (SD); n (%)								
[2] Fisher's exact test								

Table 3: Performance Metrics of Bethesda scoring system in Predicting Thyroid Malignancy.

Metric	**Value**
Sensitivity	0.561
Specificity	0.931
PPV	0.852
NPV	0.75
Overall Accuracy	0.778
PPV: Positive Predictive Value , NPV: Negative Predictive Value	

Table 4: Logistic Regression Analysis of Factors Predicting Malignant Thyroid Lesions.

Predictor		**95% CI**		
	OR	**Lower**	**Upper**	**P-value**
Age	1.0189	0.9486	1.0957	0.6
Gender				
Female	-	-	-	-
Male	6.1718	0.8205	70.6815	0.09
Size	1.2371	1.0549	1.5166	**0.01**
DM	9.6314	1.0436	147.1814	0.06
HTN	0.1002	0.0070	0.8097	0.052

Hypothyroidism	0.8327	0.0087	128.1949	0.9
Hemi-thyroidectomy	8.5234	0.5752	170.3273	0.1
DM: Diabetes Mellitus, HTN: Hypertension				

DISCUSSION

In our study, we analyzed 99 cases of thyroid nodules and studied their clinical, cytological, histopathological characteristics in relation to the Bethesda scoring system. Our findings showed a strong association between Bethesda classification and final histopathology, with increased Bethesda scores indicating higher likelihood of malignancy. Our study showed a higher prevalence of female patients (89.9%), aligning with other studies that report a higher incidence of thyroid nodules in women due to hormonal factors.[9] The mean age of our cohort (46.97 years) aligns worldwide data indicating peak thyroid pathology occurrence in middle aged adults.[10] Our results reported that the prevalence of diabetes mellitus (15.15%), hypertension (18.18%) and hypothyroidism (8.08%) as comorbidities corresponds with existing studies that suggest the relationship between the presence of metabolic disorders as a risk factor for thyroid abnormalities.[11] Our FNA results showed that 27.2% of cases were benign, including colloid nodules (24.24%), follicular nodules (2.02%), and Hashimoto's thyroiditis (1.01%). Malignant findings in our cohort accounted for another 27.2%, with papillary carcinoma (14.14%), follicular carcinoma (8.08%), Hurthle cell carcinoma (4.04%), and a combination of follicular and Hurthle cell carcinoma (1.01%). We reported cases of undetermined significance comprised 36.3%, including atypia (15.15%), follicular (13.13%), follicular/Hurthle cell (5.05%), and Hurthle cell (3.03%).

Another study reported that among FNA results, 4% were unsatisfactory, 52% were benign, 40% were classified as atypia of undetermined significance, and only 4% were diagnosed as malignant.[12] The Bethesda classification in our study reported category III as the most frequent (37.76%) followed by category II (25.51%), category IV (16.33%), category V (9.18%), category I (8.16%), and category VI (2.04%). However, final histopathology results in our cohort confirmed benign diagnoses in 53.5% of cases, consisting of hyperplastic nodules (21.21%), Multinodular goiter (16.16%), Follicular adenoma (12.12%), Hurthle cell adenoma (2.02%), and Multinodular goiter with follicular adenoma (2.02%). Malignant cases comprised 41.41%, with papillary carcinoma (36.36%) being the most prevalent, followed by follicular carcinoma (2.02%), Hurthle cell carcinoma (2.02%), and Anaplastic neoplasm (1.01%). A 2018 study conducted in Jordan reported that out of 499 thyroid FNAs, 54.7% were benign, and 16.2% were atypia of undetermined significance, with a malignancy rate of 6.4%.[13] Additionally, a study analyzing 230 patients with thyroid nodules found that 58.3% were benign and 41.7% were malignant.[14] Our cohort reported that surgical excision was performed in 81.81% of cases with hemithyroidectomy accounting for 47.47% and total thyroidectomy for 34.34%. Another study identified that out of 1,027 patients who underwent thyroid surgery total thyroidectomy was performed in 50% of cases, hemithyroidectomy followed by completion thyroidectomy in 35%, and hemithyroidectomy alone in 14%.[15] However, the choice between total thyroidectomy and hemithyroidectomy is influenced by several factors such as tumor diameter.[16]

our results showed malignancy was exclusively found in category V (100%) and VI (100%). A study reported malignancy rates of 73.8% for category V and 98.9% for category VI.[17] Similarly, another study showed malignancy rates of 86.5% in category V and 100% in category VI.[18] These studies assure the high predictive value for malignancy in Bethesda categories V and VI. Our cohort reported papillary carcinoma was the most frequent malignancy (36.73%), predominantly in categories V and VI.

In our cohort benign diagnoses were most common in Bethesda category I (87.5%) and II (80%) which align with another study reported that 75.9% of cases in Bethesda category II were benign, with nodular goiter being the most prevalent diagnosis.[7] Our results revealed that category III had 56.76% benign cases, dropping to 31.25% in category IV, with none in categories V and VI. A study showed that among 335 cases classified as Bethesda categories III and IV, 50.8% were benign and 17.9% were malignant.[19] Multinodular goiter in our cohort was most frequent in categories I (50%) and II (36%), while hyperplastic nodules were more common in category III (32.43%). In our study, follicular adenoma appeared most in categories II (24%) and IV (12.5%). Hashimoto's thyroiditis was rare in our results, seen in only a few cases in categories II (4%) and III (5.41%).

We reported the sensitivity of the system (56.1%), indicating its moderate ability to detect malignant cases. In contrast, specificity was high at 93.1%, demonstrating strong accuracy in identifying benign cases. A study analyzing 6,226 FNA biopsies of the thyroid reported a sensitivity of 93% and specificity of 96% for detecting malignancy.[20] Our results reported the positive predictive value was 85.2%, while the negative predictive value was 75%.

Our logistic regression analysis showed that lesion size is a significant predictor of malignancy with larger lesions more likely to be malignant. Hypertension showed a possible link to a lower risk of malignancy. Other factors like male gender, hemithyroidectomy, and hypothyroidism didn't show significant results but may be possible connections that might need further studying.

CONCLUSION

This study evaluates the Bethesda system accuracy in predicting malignancy of thyroid nodules. It shows high specificity but moderate sensitivity, which means it is effective in identifying benign cases but less effective in detecting malignancy. Malignancy was most identified in in Bethesda categories V and VI (100%), while benign cases were more found in categories I and II. Lesion size was an important predictor of malignancy, with larger nodules being more likely to be malignant. Our study confirms that higher Bethesda categories correlate more with malignancy while lower categories are mostly benign.

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