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ORIGINAL ARTICLE

Ultrasonographic and Pathological Features of Surgically Excised Thyroid Nodules- A cross-sectional study

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Abstract

Introduction: Thyroid nodules are commonly encountered in clinical practice and require laboratory and radiological investigations for their evaluation. This study aimed to evaluate the correlation between ultrasonographic and pathological features of thyroid nodules and to determine the diagnostic accuracy of cytological assessment.

Methods: A retrospective cross-sectional study was conducted at a tertiary care hospital in the Kingdom of Bahrain. Ultrasound and pathology reports were retrospectively reviewed for all patients who had their nodules excised from January 2016 to December 2018. All statistical analyses were conducted using Prism 7 (Graph Pad software, version 7)

Results: A total of 287 patients had thyroid surgery during the study period but only 190 of them had an ultrasonographic assessment. Of the 190, 135 (71%) were diagnosed with benign pathologies. Multinodular goitre (n=86, 63.7%) was the most common benign pathology, whereas papillary thyroid carcinoma (n=48, 87.2%) was the most common malignant pathology. Most cases affected females (n=171), with a female-to-male ratio of 9:1. Non-cystic nodules, nodules ≥ 1cm, presence of calcification, increased vascularity and hypoechogenicity were significantly different between benign and malignant nodules.

Conclusion: Ultrasonographic features and cytological assessment are useful in evaluating thyroid nodules. However, histological analysis may be inevitable as none of these diagnostic techniques are enough to exclude thyroid cancer.

Keywords: Thyroid nodules, Ultrasound, Neck sonography, Histopathology, Fine needle aspiration

Introduction

Thyroid Nodules (TNs), defined as discrete lesions in the thyroid glands, are commonly encountered in clinical practice. Epidemiological studies showed that the prevalence of TNs, though widely variable, can be as high as 60%.[1,] This high prevalence of TNs necessitates careful evaluation and assessment to determine whether a nodule is benign or malignant.[,]

In the Gulf Cooperation Council (GCC) states, thyroid cancer ranked fifth most common cancer between January 1998 and December 2012 and the second most common cancer in women, just after

lung cancer. Among the leading malignancies in the region, thyroid cancer is one of the top five.[1]

Based on well-designed nonrandomized diagnostic accuracy studies, American Thyroid Association (ATA) strongly recommends performing thyroid sonography in all patients with TNs. Ultrasound, though operator-dependent, is extremely useful in evaluating the size, site, margins, vascularity, calcification and parenchymal features of the thyroid nodules. Other investigations such as Fine Needle Aspiration or FNA (the procedure of choice), excisional biopsy, other radiological tests and/or genetic analysis may be used to evaluate TNs, although they may not be indicated in all cases. Most of these nodules are benign, occur in females and elderly people in whom prompt surgical intervention is rarely indicated.[2]

A recent study conducted in the Kingdom of Bahrain found that around 35% of surgically treated thyroid diseases had malignant pathologies. This percentage was higher compared to an older study performed at another tertiary health centre in Bahrain (24%). Some ultrasonographic features such as border irregularity, microcalcifications and nodule hypoechogenicity have been associated with a higher risk of malignancy. These features can be used in risk stratification and clinical decision-making in the management of TNs. [3]

The primary aim of this study was to determine the ultrasonographic features of surgically excised TNs in a tertiary care hospital in Bahrain between 2016 and 2018. In addition, it aimed to highlight the ultrasonographic characteristics that could help minimize unnecessary therapeutic and other diagnostic procedures. To the best of our knowledge, this is the first study to assess the correlation between radiological and pathological findings of TNs in Bahrain.

Methods

Study design and participants

This retrospective cross-sectional study was conducted at a tertiary care hospital in Bahrain from January 2016 to December 2018. The protocol was reviewed and approved by Secondary Healthcare Research Committee, Ministry of Health, Kingdom of Bahrain. All adults (≥18 years) who underwent surgical excision of TNs were enrolled. Patients who had no thyroid ultrasonographic study prior to their thyroid surgery were excluded.

Radiological assessment

Real-time US examinations of the thyroid gland and the cervical region were performed using a 5-12 MHz linear array transducer. The final reports were approved by senior radiologists. Size of nodules (greatest dimension), site of nodule, number of nodules, presence of calcification, vascularity of nodules, type of nodule (cystic/non-cystic), presence of lymphadenopathy, heterogeneity and echogenicity of the nodules were evaluated.

Pathological assessment

Under aseptic measures, three passes using 23-25 gauge needles were taken from TNs by FNA. To ensure adequate specimens, a bedside evaluation with Diff-Quik stain was performed. Half the slides were stained with Giemsa stain and the others were stained with Pap stain. The samples were reported by senior histopathologists using the Bethesda system. The histopathological analysis involved gross examination, slicing the specimen and assessing any suspicious lesion. The descriptive reports were validated by consultant histopathologists. Cytological and histological diagnoses were determined. All patients signed an informed consent before the procedure.

Based on the histopathological and nuclear features, thyroid lesions were classified as benign or malignant lesions. For instance, follicular carcinoma was differentiated from follicular adenoma by the presence of capsular or vascular invasion whereas papillary carcinoma was mainly diagnosed based on nuclear features such as nuclear enlargement, nuclear irregularity, nuclear grooves and nuclear pseudo-inclusions. Epithelioid to spindled cells and finely speckled nuclei were used to identify medullar carcinoma.

Data collection

The outcomes of interest were ultrasound features, cytological and histological diagnoses of TNs. In addition, patient baseline characteristics (age, sex and nationality) and preoperative Thyroid

Stimulating Hormone (TSH) were retrospectively collected from electronic medical records. All the data were reviewed by one of the investigators. No differences of the collected material were found. This design was adopted to minimize potential for error.

Statistical analysis

Categorical variables were expressed as frequencies and percentages, while continuous variables were expressed as means with 95% confidence interval. All statistical analyses were conducted using Prism 7 (Graph Pad software, version7, San Diego, California) and differences with P value <0.05 were considered statistically significant. Differences, associations and interactions between categorical variables were analysed using the chi-square and Fisher's exact tests as appropriate. Additionally, T-test was used to compare between continuous data. All data were de-identified in the analysis process using serial numbers. To determine the sensitivity, specificity and predictive values, further analysis of ultrasonographic variables was performed.

Results

Baseline characteristics

A total of 287 nodules were surgically excised in the selected period but ultrasound reports were available in 190 cases only. Most of the lesions were benign (n=135; 71%), occurred predominantly in females (n=171; 90%), with a female-to-male ratio of 9:1. The mean age of patients with benign nodules was 44.56 years, as compared to those who had malignant nodules, which was 43.53 years (95% CI, 41.81 - 45.25). No significant differences in sex ratio, mean age, and TSH level (P-values 0.0620, 0.5985 and 0.7528, respectively) were observed in all the groups (Benign and Malignant). Table (1), Graph (1).

Table 1: Baseline characteristics of participants

Characteristics	n (%)	Benign Nodules	Malignant Nodules
Age (Years)			
<20	2	2	0
20-29	27	15	12
30-39	39	28	11
40-49	53	43	10
50-59	50	33	17
60-69	8	4	4
≥70	11	10	1
Sex			
Male	19	10	9
Female	171	125	46
Nationality			
Bahraini	164	115	49
Non-Bahraini	26	20	6
Number of nodule (s)			
Solitary	53	37	16
Multiple	137	98	39
Site of nodule (s)			
Right Lobe	126	93	33
Left Lobe	57	40	17
Isthmus	7	2	5
TSH level (Mean)		**2.24 (0.75 - 3.71)**	**1.86 (1.35 - 2.37)**

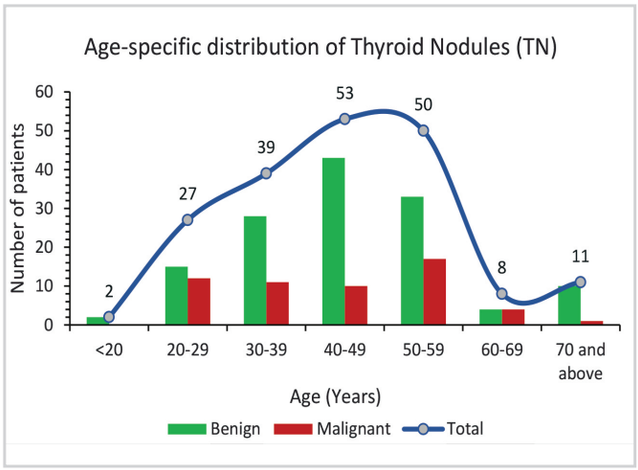

Figure 1: Distribution of TNs based on age and histology diagnoses

Histopathological diagnoses of TNs

Multinodular goitre (MNG) (n=86, 63.70 %) and thyroid adenomas (n=23; 17.04%) were the most common benign aetiologies, whereas most malignant cases (n=48; 87.2%) were due to papillary thyroid carcinoma (Table 2).

In the analysis of thyroids' background histology, the presence of underlying thyroid diseases was associated with a significant increase in the risk of malignancy compared to normal underlying thyroid parenchyma. (P=0.0001).

Association between cytological and histopathological findings

The association between cytological and histopathological diagnoses was analysed and both sensitivity and specificity of FNA were calculated. FNA tests were not performed in all cases, and as a result, the only patients included (n=119 patients) were those who underwent FNA test prior to their surgeries. The sensitivity of FNA was 69.2%, specificity 92.5% and accuracy 84.9 %. Furthermore, PPV and NPV of FNA were 81.8 % and 86 %, respectively.

Association between radiological and histological features of TNs

The number of nodules (P=0.8145), nodules' vascularity (P=0.4426) and presence of lymphadenopathy (P=0.5104) were not significantly different between benign and malignant nodules. However, the size of nodules (P= 0.0002), presence of calcification, regardless the type (P= 0.0001) and echogenicity (P=0.0413) were significantly different between the two groups. (Table 3).

Sensitivity of nodules' size (≥1 cm), number of nodules (multiple), calcification and vascularity of nodules were 72.7%, 70.9%, 47.3% and 65.5 % respectively (Table 4), (Graphs 2, 3, 4 and 5).

Table 2: Histopathological diagnoses of thyroid nodules

Histopathological findings		n (%)
Benign nodules (n= 135)		
	MNG	86 (45%)
	Thyroid Adenoma	23 (12%)
	Thyroiditis	19 (10%)
	Others; Cyst (4) Graves (2) and normal (1)	7 (4%)
Malignant nodules (n= 55)		
	Papillary thyroid carcinoma	48 (25%)
	Follicular thyroid carcinoma	6 (3%)
	Medullary thyroid carcinoma	1 (<1%)
Background histology (n=190)		
	Normal	110 (58%)
	MNG	28 (15%)
	Hashimoto's	25 (13%)
	Other pathologies *	27 (14%)

*Includes adenoma, cystic degeneration and changes. MNG: Multinodular goitre

Table 3: Association between Radiological and histological features of thyroid nodules

		Malignant	Benign	P value
Cytological diagnoses*	Malignant/Suspicious	27	6	NC **
	Benign	12	74	
Background histological diagnosis	Normal	21	89	0.0001
	MNG	10	18	
	Hashimoto's Thyroiditis	17	8	
	Other pathologies	7	20	
Size of nodules (Greatest dimension)	≥1 cm	40	125	0.0002
	< 1 cm	15	10	
Site of nodule	Right lobe	33	93	0.0364
	Left lobe	17	40	
	Isthmus	5	2	
Number of nodules	Multiple	39	98	0.8145
	Solitary	16	37	
Calcification of nodule	Yes	26	22	0.0001
	No	29	113	
Vascularity of nodules	Yes	36	96	0.4426
	No	19	39	
Cystic or has cystic component	Yes	9	56	0.0009
	No	46	79	
Presence of lymphadenopathy	Yes	8	15	0.5104
	No	47	120	
Heterogeneity	Heterogenous	34	79	0.6744
	Homogenous	21	56	
Echogenicity	Hypoechoic	23	32	0.0413
	Hyperechoic	4	21	
	Isoechoic	8	33	
	Heterogenous	20	49	

*Cytological assessment was performed for 119 patients only, ** NC: Not Calculated

Table 4: Diagnostic values of cytological and radiological features in patients with TNs

	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Cytological assessment	69.2	92.5	81.8	86.0
Size of nodules ≥1 cm	72.7	7.4	24.2	40
Number of nodules (Multiple)	70.9	27.4	28.5	69.8
Presence of calcification	47.3	83.7	54.2	79.6
Vascularity of nodules	65.5	28.9	27.3	67.2
Cystic or has cystic component	16.4	58.5	13.8	63.2
Presence of lymphadenopathy	14.5	88.9	34.8	71.9
Heterogeneity of the nodules	61.8	41.5	30.1	72.7

PPV: Positive Predictive Value; NPV: Negative Predictive Value.

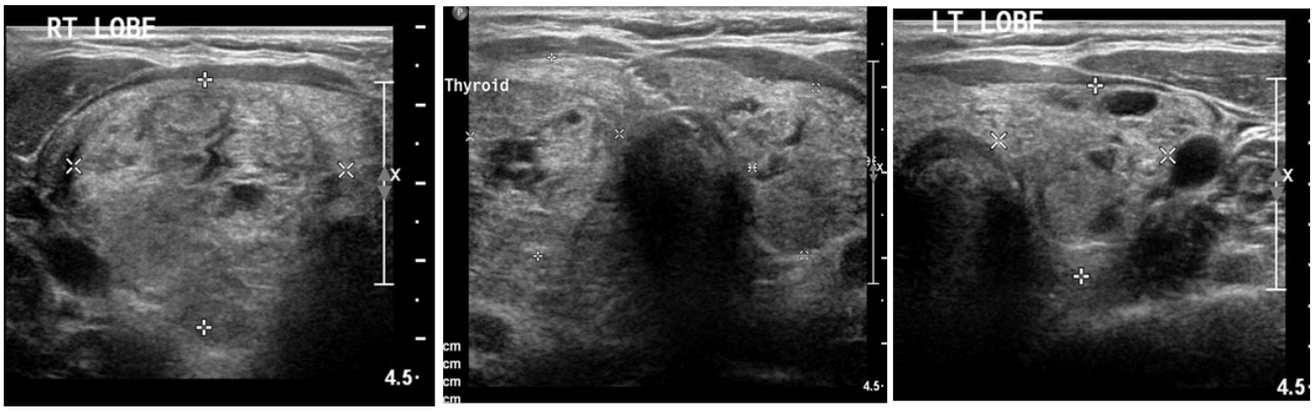

Figure 2: Diffuse enlargement of the entire thyroid gland. Coarse heterogenous echogenicity with multiple bilateral variable size nodules are seen. Diagnosis of multinodular goitre was confirmed by pathological exam

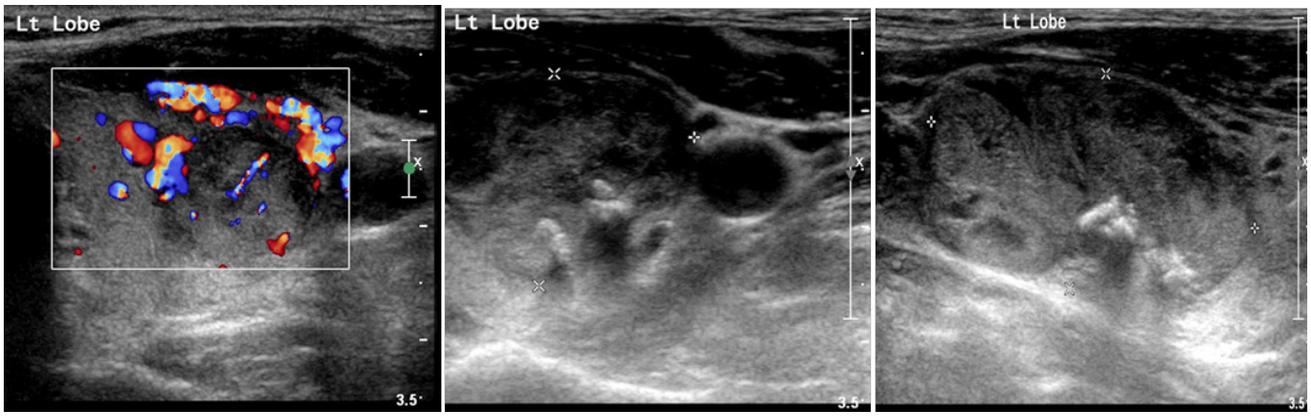

Figure 3: A well-defined heterogenous lesion within the left thyroid lobe. Cystic changes along with peripheral microcalcifications and internal vascularity are seen. Diagnosis of Papillary thyroid cancer was confirmed by pathological assessment

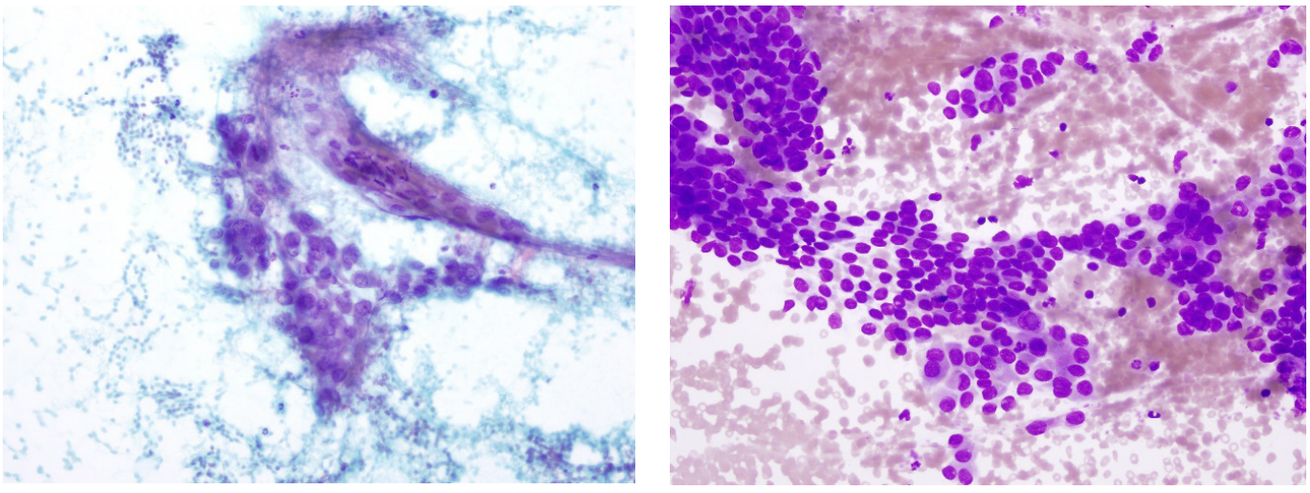

Figure 4: Pathological features of papillary thyroid cancer, Left (PAP stain), Right (Giemsa stain)

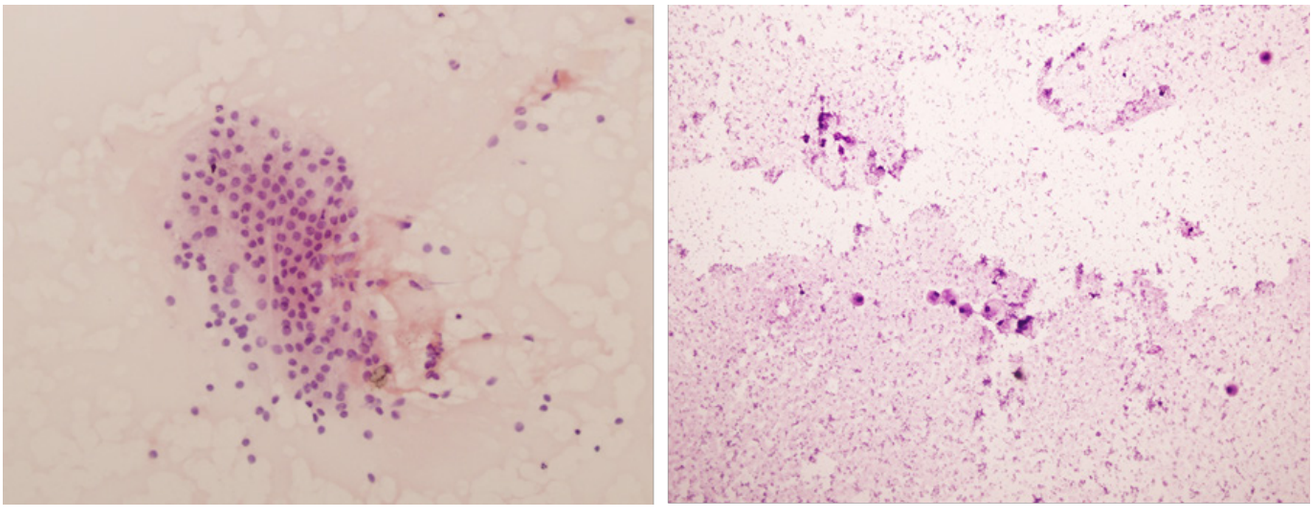

Figure 5: Pathological features of Multinodular goitre. Left (PAP stain), Right (Giemsa stain)

Discussion

This study evaluated the radiological features of TNs and the diagnostic accuracy of ultrasound in identifying malignant lesions. Our findings were generally consistent with other studies. Most patients had benign, multiple nodules and normal underlying thyroid parenchyma. As expected, these lesions were predominant among females between 30 to 60 years of age. Compared to previous local studies, this study yielded a higher female-to-male ratio (9:1 vs 5:1), but similar benign-to-malignant figures and histopathological diagnoses. Additionally, a non-linear relationship was found between patients' age and number of TNs.[6,7]

In our study, thyroid ultrasonographic features including nodule's size of more than 1 cm and presence of calcifications were found to be significantly predictive of malignant nodules. Malignant nodules were also more likely to be non-cystic, have no cystic component, hypoechoic and heterogenous. However, none of these measures were specific.

Consistent with our findings, other studies have showed that presence of calcifications, irregular margins, heterogeneity of TNs were associated with a higher risk of malignancy. For instance, a study conducted at Mayo clinic reported that almost 90% of malignant nodules were solid or minimally cystic (vs 84% in our study). Another large study noted that heterogeneity and calcification were present in around 50% and 20% of malignant TNs, respectively. Similarly, a recent systematic review of fifty-two studies found that these variables probably predict the risk of cancer although the positive likelihood ratio and sensitivity were somewhat low.[7] In contrast, this study determined higher sensitivity values. For example, the sensitivity of nodules' size (≥1 cm), number of nodules (multiple) and vascularity of nodules was around 70%. According to the literature, other features such as absence of elasticity, a taller than wide shape and irregular margins carry a high risk of malignancy as well.

Interestingly, it has been reported in the literature that nodules in the thyroid isthmus have higher potential for malignancy.[12] Our results were comparable with these studies. However, in disagreement with multiple studies, sex, age and pre-operative TSH were not associated with a higher risk of cancer in this study.[7]

It was surprising, particularly when considering the cost effectiveness and diagnostic accuracy, that as high as 30% of the patients had not had FNA cytological assessment performed before the surgical intervention. Although most guidelines recommend cytological assessment for nodules ≥1cm, almost all those who did not undergo FNA had nodules ≥1 cm in greatest dimension.[4] The sensitivity of FNA for detecting malignancy in this study was found to be around 70%, the specificity was as high as 93%, while the accuracy was around 85%.

There are conflicting conclusions on the association between Hashimoto's Thyroiditis (HT) and thyroid cancer. A large systematic review that included 36 retrospective studies (64628 subjects) reported a relative risk of malignancy in patients with HT of 1.4 (higher risk of malignancy). This study supported this finding, and revealed that almost 70% of patients with HTs had thyroid cancer. However, a prospective study of more than 900 nodules failed to find a significant association between thyroid cancer and HT. In our study, HT was found in around 30% of the malignant cases but in less than 6% of benign cases.

This study had several strengths including selection method, the analysis of pathological features by gold standard tests and consideration several possible confounders factors into account in the analysis. However, our findings may be limited by the sample size which may possibly be underpowered to detect small associations. In addition, some factors like border regularity, absence of elasticity and taller than wide shape that could potentially impact cancer risk have not been evaluated, and therefore, the diagnostic value of these features were not determined. The present findings however have important clinical implications and auditing importance.

Conclusion

Overall, thyroid sonography is an important diagnostic tool that can be utilized to make treatment decisions for patients with TNs. Radiological features like nodules size, parenchymal features, presence of calcification, increased vascularity and hypoechogenicity were significantly different between benign and malignant nodules. An integrated approach incorporating clinical, radiological and cytological assessments is vital and might limit unnecessary surgical interventions. Further studies to confirm our results and to assess the diagnostic value of other radiological features are warranted.

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Conflict of Interest

The authors of this study have no conflict of interest to declare.

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