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The prevalence and associated predictors for Bethesda III–VI for reporting thyroid cytopathology in Royal Commission Hospital, Kingdom of Saudi Arabia

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Hussain Alyousif, Ishag Adam, Naser A. Alamin, Mona A. Sid Ahmed, Ayat Al Saeed, Abdulmuhsen Hussein Hassoni and Imad R. Musa

Abstract

Background: Thyroid cancer is increasing globally and is currently the most prevalent endocrine malignancy. Recent data show an increase in the incidence of thyroid cancer in the Kingdom of Saudi Arabia (KSA). Thyroid ultrasound and fine-needle aspiration cytology (FNAC) are the cornerstones in managing thyroid nodules. We conducted this study to evaluate the prevalence and the associated predictors for thyroid nodule Bethesda III–VI in eastern KSA.

Methods: A retrospective study was conducted between January 2015 and 31 August 2021. The participants were recruited patients who received a thyroid ultrasound and ultrasound-guided thyroid FNAC, using the thyroid imaging reporting and data system (TI-RADS) and the Bethesda Classification, respectively.

Result: Three hundred and ten patients who underwent thyroid FNAC were enrolled in the study. The median (interquartile, IQR) age was 47.0 (20.0) years, and 266 (85.8%) of them were females. The median (IQR) body mass index was 30.2 (7.6) kg/m^2. Out of these participants, 64.8% were euthyroid, 27.4% had hypothyroidism and 7.7% had hyperthyroidism. The ACR TI-RADS-3, 4 and 5 were 51.3%, 46.1% and 2.6%, respectively. The Bethesda outcome of thyroid FNAC I–VI was 5.2%, 63.9%, 15.5%, 5.8%, 3.5% and 6.1%, respectively. The risk for malignancy (Bethesda III–VI) was documented in 31.0% and atypia of undetermined significance was most prevalent (15.5%). A higher ACR TI-RADS score was associated with a higher risk of malignancy: ACR TI-RADS-3 (20.8%), ACR TI-RADS-4 (39.2%) and ACR TI-RADS-5 (87.5%). In a multivariate analysis, only the ACR TI-RADS score was significantly associated with the outcome of thyroid FNAC: ACR TI-RADS-4 [OR = 2.59 (95% CI = 1.54–4.36)] and ACR TI-RADS-5 [OR = 29.03 (95% CI = 3.44–245.07)].

Conclusion: There was a high prevalence of Bethesda III–VI and atypia of undetermined significance was most prevalent. A thyroid ultrasound report for TI-RADS was significantly associated with the outcome of thyroid FNAC and is a reliable tool in the absence of molecular testing for thyroid cancer.

Keywords: Bethesda, fine-needle aspiration cytology, predictors, prevalence

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Correspondence to:
Imad R. Musa
Royal Commission Hospital at AL Jubail Industrial City, Al Lulu Road, Al Fanateer, Al Jubail 31961, Kingdom of Saudi Arabia.
irthesudanese@hotmail.com

Hussain Alyousif
Mona A. Sid Ahmed
Ayat Al Saeed
Abdulmuhsen Hussein Hassoni
Royal Commission Hospital at AL Jubail Industrial City, Al Jubail, Kingdom of Saudi Arabia

Ishag Adam
Department of Obstetrics and Gynecology, Unaizah College of Medicine and Medical Sciences, Qassim University, Unaizah, Kingdom of Saudi Arabia

Naser A. Alamin
King Fahad Medical City, Riyadh, Kingdom of Saudi Arabia

Introduction

The incidence of thyroid cancer continues to increase globally.[1] Thyroid cancer is considered the most prevalent endocrine cancer worldwide.[2] A marked increase in thyroid cancer was reported in gulf countries, including the Kingdom of Saudi Arabia (KSA).[3–5] A thyroid nodule is defined as an abnormal lesion within the thyroid gland

Table 1. TI-RADS and category definitions.

TI-RADS-1	Benign
TI-RADS-2	Not suspicion
TI-RADS-3	Mildly suspicion
TI-RADS-4	Moderately suspicion
TI-RADS-5	Highly suspicion

TI-RADS, thyroid imaging reporting and data system.

tissue.[6] Thyroid fine-needle aspiration cytology (FNAC) is the cornerstone for assessing thyroid nodules.[7] A thyroid ultrasound enhances the ability to manage thyroid nodule disorders by diagnosing nonpalpable thyroid nodules.[8] Besides offering reliable classification of thyroid nodules that assists in the decision-making regarding the need for biopsy and directing the fine needle to target the most suspicious area of the nodule.[9] Sonography-guided FNAC improves the accuracy and safety of the technique for diagnosing thyroid nodules.[10,11] The Bethesda System for Reporting Thyroid Cytology (TBSRTC) is a very important tool for evaluating thyroid nodules with reliable diagnostic accuracy.[12] Previous studies have recommended the TBSRTC as an effective tool for pre-operative diagnosis of thyroid nodules.[9,13–15] Thyroid FNAC management was cost-effective compared with watchful management.[16] Several factors – such as age,[17] female sex,[18] thyroid status, thyroid hormone level,[19] thyroid autoantibodies,[20] metabolic syndrome components,[21,22] smoking and alcohol consumption,[23] environmental factors,[18,24] diet and nutritional pattern,[25] and genetic factors[26] – have been reported as risk factors associated with thyroid nodular diseases and cancers.

Studies conducted in KSA reported an increase in the thyroid cancer rate (9–11.7%)[5,27] with a significant geographical variation in the different regions of KSA.[5,18,28] Despite the wide use and importance of such essential diagnostic tools, along with improvement in reporting system globally, there are few published data on the topic in the region. Hence, this study aimed to investigate the prevalence of thyroid FNAC based on Bethesda reporting and its associated predictors among adult patients in the Royal Commission Hospital in eastern KSA.

Materials and methods

Study area

Jubail Industrial City, the World's Largest Industrial City, was established in 1975 and situated on the Arabian Gulf, north of Dhahran, in the eastern Province of KSA.[29] It has an area of 1016 square kilometres and includes industrial complexes and port facilities.[29] Moreover, it contributes to about 7% of Saudi Arabia's gross domestic product.[29]

Methods

A retrospective study was conducted at the Royal Commission Hospital during 1 January 2015 through 31 August 2021. Royal Commission Hospital has a capacity of 217 beds and 200 physicians in all major specialties and most subspecialties. The records were retrieved of patients aged 18 years and above (males and females) with documented thyroid nodules based on ultrasound findings, who underwent ultrasound-guided FNAC in the hospital. Records of those with incomplete data, patients who underwent partial thyroid surgery without prior thyroid FNAC, patients diagnosed with thyroid cancer from lymph node biopsy, patients with known thyroid malignancy and reports from other hospitals were excluded. The sociodemographic data were gathered using a data collection sheet, including age, sex, body mass index (BMI), thyroid status, comorbidities, family history of thyroid cancer, smoking and exposure to radiation. Moreover, laboratory tests were performed for thyroid function, complete white blood count, lipid profile and vitamin D levels. A specialist conducted the thyroid ultrasound in the radiology department and a consultant radiologist revised and approved the report. Thyroid ultrasound reports based on the thyroid imaging reporting and data system [American College of Radiology thyroid imaging reporting and data system (ACR TI-RADS)] were adopted to assess the thyroid nodule (Table 1).[30]

An expert radiologist conducted the thyroid FNAC under ultrasound guidance. Consent for the procedure was obtained after proper explanation. After the application of a local anaesthetic and under aseptic conditions, a 22-gauge needle was used with a 10-ml syringe. The tip of the needle-targeted areas presumed to contain the most cellular material of the thyroid nodule, under

Table 2. Bethesda's system for reporting thyroid cytopathology.

I. Nondiagnostic or Unsatisfactory	Cyst fluid only, virtually acellular specimen and other (obscuring blood, clotting artefact, etc.)
II. Benign	Consistent with a benign follicular nodule (includes adenomatoid nodule, colloid nodule, etc.), consistent with lymphocytic (Hashimoto) thyroiditis in the proper clinical context or consistent with granulomatous (subacute) thyroiditis.
III. Atypia of Undetermined Significance	Follicular Lesion of Undetermined Significance.
IV. Follicular Neoplasm	Suspicious for a Follicular Neoplasm or specify if Hürthle cell (oncocytic) type.
V. Suspicious for Malignancy	Suspicious for one of these cancers; papillary carcinoma or medullary carcinoma or metastatic carcinoma or lymphoma or other cancer.
VI. Malignant	Diagnostic for one of these: papillary thyroid carcinoma, poorly differentiated carcinoma, medullary thyroid carcinoma, undifferentiated (anaplastic) carcinoma, squamous cell carcinoma, carcinoma with mixed features (specify), metastatic carcinoma, nonHodgkin lymphoma or other.

ultrasound guidance. Continuous low negative pressure was then applied simultaneously with a to-and-fro movement of the needle within the lesion to obtain the material in the needle hub. Mild pressure was applied to the site of the needle in order to prevent bleeding, and the patient was kept for 15 min before being reassured and discharged. One drop of aspirated material was forced onto each of several glass slides, and smears were prepared using a second glass slide similar to that adopted for the blood smears. Labelled slides were immediately wet fixed by placing them in an alcohol bottle before transferring them to the histopathology department in the hospital. A final cytopathology report was released after an expert pathologist studied each cell block. The ultrasound-guided thyroid FNAC and outcome were reported using TBSRTC,[31] as shown in Table 2. The results of the thyroid ultrasound scan and outcome of thyroid FNAC were grouped in two categories according to diagnostic ability of the ACR TI-RADS/TBSRTC systems in distinguishing thyroid nodules that did or did not require the FNAC and the potential risk of malignancy as a reference standard (<ACR TI-RADS-3/TBSRTC III *versus* ⩾ACR TI-RADS-3/TBSRTC III).[32] While FNAC was clearly indicated for ACR TI-RADS-4 and 5, certain indications were adopted for ACR TI-RADS-3: size more than 2.5 cm, significant increase in size, young patients and strong family history of thyroid cancer. Then, the nondiagnostic or unsatisfactory I and Benign II were grouped as low risk for malignancy and III–VI were classified as high risk for malignancy, in order to assess the outcome and its predictors.

Statistical analysis

Data were analysed with a computer using SPSS for Windows (version 22.0). Continuous data were checked for normality by the Shapiro–Wilk test, and all were not normally distributed. Data were expressed as proportions, median [interquartile range (IQR)] or number (proportion), as applicable. Moreover, the prevalence of the Bethesda categories was calculated. Univariate analysis was performed with the outcome of thyroid FNAC as the dependent variable. Independent variables were age, sex, thyroid status, exposure to radiation, thyroid function test, 25-hydroxyvitamin D (25[OH]D) levels, haemoglobin, white blood count, platelets, lipid profile, smoking and thyroid ultrasound report. Variables were shifted to the logistic regression analyses if their univariate p was <0.20 and backward-stepwise likelihood ratio regression was used for adjustment. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated, and a p value of <0.05 was considered significant.

Result

General characteristics

Three hundred and ten patients who underwent thyroid FNAC were enrolled in the study. The median (IQR) age was 47.0 (20.0) years, and 266 (85.8%) of them were females. Out of the participants, 297 (95.8%) were not smokers, 8 of them were exposed to radiation and 9 had a family history of thyroid cancer. The median (IQR) BMI was 30.28 (7.6) kg/m^2, and 25[OH]D level was 14.65 (10.8) nmol/l. The median (IQR) levels for the thyroid function test were as follows: thyroid-stimulating hormone (TSH) 1.70 (2.38) mmol/l, free thyroxine (FT4) 1.12 (0.40) ng/dl and free triiodothyronine (FT3) 2.67 (0.42) nmol/l. The median (IQR) of lipid profile, total cholesterol, low-density lipoprotein (LDL), high-density lipoprotein (HDL) and triglyceride were 5.68 (3.92), 3.75 (0.80), 2.99 (1.70) and 1.73 (1.12) mmol/l, respectively. The median (IQR) of haemoglobin was 12.6 (1.9) gm/dl, platelet was 275.90 (96.6) 10^9/l and white blood cell count was 6.87 (2.4) 10^9/l, as shown in Table 3.

Most of the participants were euthyroid (201) (64.8%), 85 had hypothyroidism (27.4%) and 24 had hyperthyroidism (7.7%). The thyroid ultrasound report for TI-RADS-3, 4 and 5 was 51.3%, 46.1% and 2.6%, respectively. The outcome of the thyroid FNAC based on the Bethesda reporting system was nondiagnostic or unsatisfactory in 5.2%, benign in 63.9%, atypia of undetermined significance in 15.5%, follicular neoplasm in 5.8%, suspicious for malignancy in 3.5% and malignant in 6.1%.

The finding of high risk for malignancy (Bethesda III–VI) was 31.0% and atypia of undetermined significance was most prevalent (15.5%). The risk for malignancy was directly correlated with the increased ACR TI-RADS score: ACR TI-RADS-3 (20.8%), ACR TI-RADS-4 (39.2%) and ACR TI-RADS-5 (87.5%).

In the univariate analysis, there was no association between the age, sex, BMI, smoking, exposure to radiation, 25[OH]D levels and thyroid FNAC across the group. Similarly, there was no significant association between thyroid status, family history of thyroid cancer and the thyroid function test of TSH and FT3. There was no association between the outcome of the thyroid FNAC and comorbidities (diabetes mellitus, hypertension and bronchial asthma). There was no significant association between total cholesterol, LDL, HDL and triglyceride nor haematological indices, including haemoglobin, platelets and white blood cell count. There was, however, a significant association between the thyroid FNAC and FT4 [OR = 1.22 (95% CI = 1.01–1.46)] and the ultrasound findings based on TI-RADS: ACR TI-RADS-4 [OR = 2.45 (95% CI = 1.47–4.09)] and ACR TI-RADS-5 [OR = 26.72 (95% CI = 3.17–224.91)], as shown in Table 4.

In multivariate analysis, age, diabetes mellitus, FT4, FT3 and tobacco were not significantly associated with the outcome of the thyroid nodule FNAC. The thyroid ultrasound report based on TI-RADS was significantly associated with the outcome of the thyroid nodule FNAC: ACR TI-RADS-4 [OR = 2.60 (95% CI = 1.55–4.36)] and ACR TI-RADS-5 [OR = 29.03 (95% CI = 03.44–245.07)], as shown in Table 5.

Discussion

The prevalence of thyroid FNAC in this study based on the Bethesda reporting system was nondiagnostic or unsatisfactory (5.2%), benign (63.9%) and those with potential risk for malignancy (Bethesda III–VI) (31%): atypia of undetermined significance (15.5%), follicular neoplasm (5.8%), suspicious for malignancy (3.5%) and malignant (6.1%). The high risk of malignancy (Bethesda III–VI) was considerably higher than that obtained in Riyadh, the capital of KSA (10.2%),[33] and in Qassim (10.8%), which is in the centre of KSA.[34] It was slightly lower than the outcome of Bethesda III–VI reported in the southwestern region of KSA (36.5%), however.[35] Interestingly, a markedly higher rate of potential risk for malignancy (Bethesda III–VI) in KSA was reported in the eastern region (Johns Hopkins Aramco Healthcare) (62.6%)[36] and in Jeddah (western region) (62.1%).[37] Atypia of undetermined significance (15.5%) was the most prevalent among the group at high risk for malignancy and in the Qassim region, which is in the central part of KSA (4%).[34] Follicular neoplasm (16.1%), however, was prevalent in the southwestern[35] and eastern regions (28.2%),[36] those suspicious for malignancy (5.2%) were prevalent in Riyadh,[33] and malignant (23.5%) was prevalent in Jeddah.[37] Interestingly, our results and result of literature review study showed almost similar findings regarding the benign, Bethesda III–VI, and the

Table 3. General characteristics of patients who underwent thyroid FNAC in eastern region 2015–2021.

Variables	Median	Interquartile range
Age, years	47.00	20.0
Body mass index, kg/m^2	30.28	7.6
Haemoglobin, gm/dl	12.60	1.9
White blood cell, 10^9/l	6.87	2.4
Platelet, 10^9/l	275.90	96.6
Thyroid-stimulating hormone, mmol/l	1.70	2.38
Free triiodothyronine, nmol/l	2.67	0.4
Free thyroxine, ng/dl	1.12	0.4
Total cholesterol, mmol/l	5.68	3.9
Low-density lipoprotein, mmol/l	3.75	0.8
High-density lipoprotein, mmol/l	2.99	1.7
Triglyceride, mmol/l	1.73	1.12
25-hydroxyvitamin D (25[OH]D) levels, nmol/l	14.65	10.8
	Number	**Proportion**
Thyroid status		
Euthyroid	201	64.8
Hypothyroidism	85	27.4
Hyperthyroidism	24	7.7
Sex		
Female	266	85.8
Male	44	14.2
Tobacco		
Never	297	95.8
Current/former	13	4.2
Exposure to radiation		
No	302	97.4
Yes	8	2.6
Family history of thyroid cancer		
No	301	97.1
Yes	9	2.9

(Continued)

Table 3. (Continued)

Variables	Median	Interquartile range
Diabetes mellitus		
No	208	67.1
Yes	89	28.7
Hypertension		
No	238	76.8
Yes	72	23.2
Asthma		
No	289	93.2
Yes	21	6.8

FNAC, fine-needle aspiration cytology.

most prevalent among them (atypia of undetermined significance) which were 68.8%, 21.1% and 12.4%, respectively.[38] The high prevalence of Bethesda III–VI might be explained by the global increase of thyroid cancer,[1,2] in gulf countries[3,4] and in KSA.[5,27,39] Moreover, this could be explained by the improvement of high-quality ultrasounds and screening for thyroid nodules – enhancing detection and diagnosis of thyroid cancers – and a possible increase in exposure to risk factors.[3,28] A significant geographical variation in the incidence of thyroid cancer throughout the KSA was documented in 2013.[5] This geographical variation pointed to different risk factors contributing to thyroid cancer: nutritional patterns, together with excessive weight gain,[39] high consumption of processed chicken and fresh and processed fish products[25] and environmental carcinogens, such as pollutants and radiation exposure.[24] Furthermore, the differences in the genetic backgrounds of the study groups and the polygenetic factors – activation of oncogenes such as Rat sarcoma (RAS), human gene that encodes a protein called B-Raf (BRAF), receptor tyrosine kinase/phenylthiocarbamide (RET/PTC) and the overstimulation of the phosphatidylinositol 3-kinase/protein kinase *B* (PI3K/AKT) pathway – are involved in thyroid tumorigenesis.[26] In addition, the thyroid FNAC procedure is operator dependent,[40] and the influence of different methodology adopted for these studies.

Our results of ultrasound findings based on TI-RADS reporting were significantly associated with the ultrasound-guided thyroid FNAC and the Bethesda reporting system. This aligned with the results of many studies, demonstrating that ultrasound findings using TI-RADS reporting can predict the thyroid FNAC with reasonable specificity and sensitivity.[8,9] Ultrasonography reliably classifies thyroid nodules, and thus can assist in the decision-making of whether to proceed for a thyroid FNAC.[9] This was in concordance with the result of ARC TI-RADS obtained in this study: ACR TI-RADS-3 (20.8%), ACR TI-RADS-4 (39.2%) and ACR TI-RADS-5 (87.5%). This study showed that age was not a significant predictor for the outcome of Bethesda III–VI. This goes with the nonsignificant association obtained in recently published data.[18,41] One study identified age as an independent predictor for thyroid malignancy, however.[17] This study along with one conducted in the eastern region showed no significant association between sex and the outcome of a thyroid FNAC, despite the fact that females represented the majority of cases.[18] Likewise, most clinical data demonstrated that females were more vulnerable to thyroid cancer.[3,4] This may reflect the imbalance between the two oestrogen receptor isoforms, α and β, as triggering factors and might be responsible for cell proliferation.[42] This study showed no significant association between metabolic syndrome

Table 4. Univariate analysis of the predictors associated with Bethesda III–VI in eastern region, 2015–2021.

Variables	High risk for malignancy (*n* = 96)	Low risk for malignancy (*n* = 214)	OR (95% CI)	*p*
	Median			
Age, years	44.0 (22.5)	47.0 (18.0)	0.98 (0.96–1.01)	0.085
Body mass index, kg/m^2	29.5 (7.1)	30.57 (7.5)	0.97 (0.94–1.01)	0.206
haemoglobin, gm/dl	12.6 (1.7)	12.6 (1.9)	1.02 (0.98–1.06)	0.324
White blood cell, 10^9/l	6.99 (2.4)	6.83 (2.4)	0.97 (0.86–1.09)	0.665
Platelet, 10^3/dl	275.45 (105)	275.9 (90.5)	1.00 (0.99–1.01)	0.933
Thyroid-stimulating hormone, mmol/l	1.6 (2.47)	1.71 (2.37)	1.002 (0.949–1.05)	0.946
Free triiodothyronine, nmol/l	2.69 (0.42)	2.69 (0.4)	0.75 (0.52–1.08)	0.129
Free thyroxine, ng/dl	1.13 (0.44)	1.11 (0.39)	1.22 (1.01–1.46)	0.036
Total cholesterol, mmol/l	5.62 (4.12)	5.7 (3.8)	0.98 (0.91–1.06)	0.758
Low-density lipoprotein, mmol/l	3.75 (0.91)	3.75 (0.6)	0.99 (0.95–1.04)	0.981
High-density lipoprotein, mmol/l	2.99 (1.83)	2.99 (1.6)	0.90 (0.70–1.15)	0.410
Triglyceride, mmol/l	1.69 (1.09)	1.76 (1.1)	0.97 (0.85–1.12)	0.740
25-hydroxyvitamin D (25[OH]D) levels, nmol/l	14.45 (11.6)	14.7 (10.9)	1.01 (0.98–1.03)	0.541
	Number			
Sex				
Female	80 (83.3)	186 (86.9)	1.32 (0.68–2.59)	0.404
Male	16 (16.7)	28 (13.1)	Reference	
Thyroid status				
Euthyroid	57 (59.4)	144 (67.3)	Reference	
Hypothyroid	32 (33.3)	53 (24.8)	1.26 (0.49–3.23)	0.635
Hyperthyroid	7 (7.3)	7 (7.9)	1.57 (0.59–4.23)	0.369
Tobacco				
Never	90 (93.8)	207 (96.7)	Reference	0.156
Current/former	6 (6.2)	7 (3.3)	2.09 (0.75–5.77)	

(Continued)

Table 4. (Continued)

Variables	High risk for malignancy (*n* = 96)	Low risk for malignancy (*n* = 214)	OR (95% CI)	*p*
	Median			
Exposure to radiation				
No	93 (96.9)	209 (97.7)	Reference	0.687
Yes	3 (3.1)	5 (2.3)	1.348 (0.32–5.76)	
Family history of thyroid cancer				
No	93 (96.9)	209 (97.7)	Reference	0.691
Yes	3 (3.1)	5 (2.3)	1.342 (0.31–5.74)	
Diabetes mellitus				
No	59 (61.5)	149 (69.6)	Reference	0.158
Yes	37 (38.5)	65 (30.4)	1.438 (0.87–2.38)	
Hypertension				
No	74 (77.1)	164 (76.6)	Reference	0.931
Yes	22 (22.9)	50 (23.4)	0.98 (0.55–1.73)	
Asthma				
No	92 (95.8)	197 (92.1)	Reference	0.229
Yes	4 (4.2)	17 (7.9)	0.50 (0.16–1.54)	
Ultrasound				
ACR TI-RADS-3	33 (34.4)	126 (58.9)	Reference	
ACR TI-RADS-4	56 (58.3)	87 (40.7)	2.46 (1.48–4.09)	0.001
ACR TI-RADS-5	7 (7.3)	1 (0.5)	26.727 (3.18–224.92)	0.003

ACR TI-RADS, American College of Radiology thyroid imaging reporting and data system; CI, confidence interval; OR, odds ratio.

components (diabetes mellitus, hypertension, BMI and lipid profile) and the outcome of the Bethesda reporting system, thereby supporting similar findings of one study conducted in the eastern region.[43,44] Some studies reported metabolic syndrome was an independent risk factor for the increased prevalence of thyroid nodular disease and cancer in both sex, however.[21,22] This study demonstrated that the thyroid status and thyroid function test were not significant predictors for the thyroid FNAC outcome. A similar result was obtained in a recently published study conducted in the same region.[18] In contrast to this finding, some studies documented that both hyperthyroidism and hypothyroidism were associated with a higher risk of thyroid cancer[19] either a suppressed or elevated TSH.[45,46] Interestingly, vitamin D level was not a significant predictor for the risk of thyroid cancer in this study, because vitamin D deficiency was prevalent in the studied group (91.0%). Moreover, vitamin D levels were not significantly associated with thyroid disorders.[47] Our result was in concordance with another study, revealing that haemoglobin levels, platelet and white blood counts were not significant predictors for thyroid nodule FNAC.[48] The nonsignificant association with many risk factors, as obtained in this study, supports the concept

Table 5. Multivariate analysis of the predictors associated with Bethesda III–VI in eastern region 2015–2021.

Variables	OR (95% CI)	*p*
Age, years	0.99 (0.97–1.01)	0.139
Free thyroxine, ng/dl	1.08 (0.88–1.34)	0.463
Free triiodothyronine, nmol/l	0.74 (0.51–1.09)	0.131
Tobacco		
Never	Reference	
Current/former	2.83 (0.94–8.48)	0.063
Diabetes mellitus		
No	Reference	
Yes	1.507 (0.88–2.60)	0.139
ACR TI-RADS scoring system		
ACR TI-RADS-3	Reference	
ACR TI-RADS-4	2.60 (1.55–4.36)	0.000
ACR TI-RADS-5	29.03 (3.44–245.07)	0.002

ACR TI-RADS, American College of Radiology thyroid imaging reporting and data system; CI, confidence interval; OR, odds ratio.

that thyroid cancer is under the influence of multifactorial aetiology.

The limitations

The study was retrospective. Other factors – such as thyroid antibodies, iodine levels, nutritional pattern, genetic analysis and environmental factors – were not assessed.

Conclusion

There was a considerably high prevalence of Bethesda III–VI, atypia of undetermined significance being the most prevalent among them, and the TI-RADS reporting was the most significant predictor for thyroid FNAC in Royal Commission Hospital. ACR TI-RADS and Bethesda are reliable tools to evaluate thyroid nodules in the absence of molecular testing facilities.

Declarations

Ethics approval and consent to participate

The study was approved by the ethical committee of Royal Commission Hospital, KSA (IB-RCH-012) that waived the verbal or written consent from participants.

Consent for publication

Not applicable.

Author contributions

Hussain Alyousif: Data curation; Methodology; Writing – original draft; Writing – review & editing.

Ishag Adam: Conceptualization; Formal analysis; Writing – original draft; Writing – review & editing.

Naser A. Alamin: Conceptualization; Data curation; Investigation; Writing – original draft; Writing – review & editing.

Mona A. Sid Ahmed: Data curation; Investigation; Methodology; Writing – review & editing.

Ayat Al Saeed: Data curation; Investigation; Methodology; Writing – review & editing.

Abdulmuhsen Hussein Hassoni: Data curation; Investigation; Methodology; Writing – review & editing.

Imad R. Musa: Conceptualization; Formal analysis; Writing – original draft; Writing – review & editing.

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Availability of data and materials
Available on request.

ORCID iD
Imad R. Musa https://orcid.org/0000-0002-1138-0710

References

1. Kitahara CM and Sosa JA. The changing incidence of thyroid cancer. *Nat Rev Endocrinol* 2016; 12: 646–653.
2. Bray F, Ferlay J, Soerjomataram I, *et al*. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin* 2018; 68: 394–424.
3. Alawadhi E, Al-Madouj A and Al-Zahrani A. Trends in thyroid cancer incidence in the gulf cooperation council states: a 15-year analysis. *Gulf J Oncolog* 2020; 1: 31–38.
4. Al-Zahrani AS and Ravichandran K. Epidemiology of thyroid cancer: a review with special reference to Gulf Cooperation Council (GCC) states. *Gulf J Oncolog* 2007: 17–28.
5. Hussain F, Iqbal S, Mehmood A, *et al*. Incidence of thyroid cancer in the Kingdom of Saudi Arabia, 2000-2010. *Hematol Oncol Stem Cell Ther* 2013; 6: 58–64.
6. American Thyroid Association (ATA) Guidelines Taskforce on Thyroid Nodules and Differentiated Thyroid Cancer, Cooper DS, Doherty GM, *et al*. Revised American thyroid association management guidelines for patients with thyroid nodules and differentiated thyroid cancer. *Thyroid* 2009; 19: 1167–1214.
7. Martin HE and Ellis EB. Biopsy by needle puncture and aspiration. *Ann Surg* 1930; 92: 169–181.
8. Yang X, Zhai D, Zhang T, *et al*. Use of strain ultrasound elastography versus fine-needle aspiration cytology for the differential diagnosis of thyroid nodules: a retrospective analysis. *Clinics* 2020; 75: e1594–e1598.
9. Al-Ghanimi IA, Al-Sharydah AM, Al-Mulhim S, *et al*. Diagnostic accuracy of ultrasonography in classifying thyroid nodules compared with fine-needle aspiration. *Saudi J Med Med Sci* 2020; 8: 25–31.
10. Guo HQ, Zhao H, Cao J, *et al*. Implementation of the Bethesda system for reporting the thyroid cytopathology: study on 5 729 cases from a cancer center. *Zhonghua Er Bi Yan Hou Tou Jing Wai Ke Za Zhi* 2020; 55: 258–262.
11. Bahaj AS, Alkaff HH, Melebari BN, *et al*. Role of fine-needle aspiration cytology in evaluating thyroid nodules A retrospective study from a tertiary care center of Western Region, Saudi Arabia. *Saudi Med J* 2020; 41: 1098–1103.
12. Pandya A, Caoili EM, Jawad-Makki F, *et al*. Retrospective cohort study of 1947 thyroid nodules: a comparison of the 2017 American college of radiology TI-RADS and the 2015 American thyroid association classifications. *AJR Am J Roentgenol* 2020; 214: 900–906.
13. Zhu Y, Song Y, Xu G, *et al*. The Bethesda System for Reporting Thyroid Cytopathology (TBSRTC): a report of 2,781 cases in a Chinese population. *Chin J Cancer Res* 2020; 32: 140–148.
14. Kim E, Pudhucode R, Chen H, *et al*. Discordance between the American Thyroid Association and the American College of Radiology Guideline Systems for Thyroid Nodule Biopsy. *J Surg Res* 2020; 255: 469–474.
15. Alshoabi SA and Binnuhaid AA. Diagnostic accuracy of ultrasonography versus fine-needle-aspiration cytology for predicting benign thyroid lesions. *Pak J Med Sci* 2019; 35: 630–635.
16. Wong CKH, Liu X and Lang BHH. Cost-effectiveness of fine-needle aspiration cytology (FNAC) and watchful observation for incidental thyroid nodules. *J Endocrinol Invest* 2020; 43: 1645–1654.
17. Allen M, Sapinho I, Raposo L, *et al*. [Cyto-histological correlation of malignant thyroid nodules: clinical factors as predictors of malignancy]. *Acta Med Port* 2008; 21: 135–140.
18. Musa IR, El khatim Ahmad M, Raddady FS, *et al*. Predictors of a follicular nodule (Thy3) outcome of thyroid fine needle aspiration cytology among Saudi patients. *BMC Res Notes* 2017; 10: 612.

19. Tran TV, Kitahara CM, de Vathaire F, *et al*. Thyroid dysfunction and cancer incidence: a systematic review and meta-analysis. *Endocr Relat Cancer* 2020; 27: 245–259.
20. Jia X, Pang P, Wang L, *et al*. Clinical analysis of preoperative anti-thyroglobulin antibody in papillary thyroid cancer between 2011 and 2015 in Beijing, China: a retrospective study. *Front Endocrinol* 2020; 11: 452.
21. Youssef MR, Reisner ASC, Attia AS, *et al*. Obesity and the prevention of thyroid cancer: impact of body mass index and weight change on developing thyroid cancer – pooled results of 24 million cohorts. *Oral Oncol* 2021; 112: 105085.
22. Chen YH, Partyka KL, Dougherty R, *et al*. The importance of risk of neoplasm as an outcome in cytologic-histologic correlation studies on thyroid fine needle aspiration. *Diagn Cytopathol* 2020; 48: 1237–1243.
23. An SY, Kim SY, Oh DJ, *et al*. Obesity is positively related and tobacco smoking and alcohol consumption are negatively related to an increased risk of thyroid cancer. *Sci Rep* 2020; 10: 19279.
24. Barrea L, Gallo M, Ruggeri RM, *et al*. Nutritional status and follicular-derived thyroid cancer: an update. *Crit Rev Food Sci Nutr* 2021; 61: 25–59.
25. Memon A, Varghese A and Suresh A. Benign thyroid disease and dietary factors in thyroid cancer: a case-control study in Kuwait. *Br J Cancer* 2002; 86: 1745–1750.
26. Cortés JMR and Zerón HM. Genetics of thyroid disorders. *Folia Medica* 2019; 61: 172–179.
27. Bazarbashi S, Al Eid H and Minguet J. Cancer incidence in Saudi Arabia: 2012 data from the Saudi cancer registry. *Asian Pacific J Cancer Prev* 2017; 18: 2437–2444.
28. Saeed MI, Hassan AA, Butt ME, *et al*. Pattern of thyroid lesions in Western Region of Saudi Arabia: a retrospective analysis and literature review. *J Clin Med Res* 2018; 10: 106–116.
29. Areej HA, Ali AAH, Afaf IS, *et al*. Brown macroalgae as bio-indicators for heavy metals pollution of Al-Jubail coastal area of Saudi Arabia. *African J Biotechnol* 2012; 11: 15888–15895.
30. Tessler FN, Middleton WD, Grant EG, *et al*. ACR Thyroid Imaging, Reporting and Data System (TI-RADS): white paper of the ACR TI-RADS committee. *J Am Coll Radiol* 2017; 14: 587–595.
31. Cibas ES and Ali SZ. The 2017 Bethesda system for reporting thyroid cytopathology. *Thyroid* 2017; 27: 1341–1346.
32. Seminati D, Capitoli G, Leni D, *et al*. Use of diagnostic criteria from ACR and EU-TIRADS systems to improve the performance of cytology in thyroid nodule triage. *Cancers* 2021; 13: 5439.
33. Al-Rikabi AC, Al-Omran M, Cheema M, *et al*. Pattern of thyroid lesions and role of fine needle aspiration cytology (FNA) in the management of thyroid enlargement: a retrospective study from a teaching hospital in Riyadh. *APMIS* 1998; 106: 1069–1074.
34. Mufti ST and Molah R. The Bethesda system for reporting thyroid cytopathology: a five-year retrospective review of one center experience. *Int J Health Sci* 2012; 6: 159–173.
35. Al-Shraim MM, Kaood OM, Hussein MR, *et al*. Assessment of malignancy rate in thyroid nodules according to the Bethesda system of fine-needle aspiration: report from a tertiary center in the Southwestern region of Saudi Arabia. *Saudi Med J* 2012; 33: 167–171.
36. Alhashem MH, Alabidi A and Aly MG. The Bethesda system for reporting thyroid cytopathology: a retrospective review of its diagnostic utility at Johns Hopkins Aramco Healthcare, Saudi Arabia. *Am J Otolaryngol – Head Neck Med Surg* 2021; 42: 103088.
37. Zarif HA, Ghandurah SE, Al-Garni MA, *et al*. Thyroid nodules cytopathology applying the Bethesda system with histopathological correlation. *Saudi J Med Med Sci* 2018; 6: 143–148.
38. Alshaikh S, Harb Z, Aljufairi E, *et al*. Classification of thyroid fine-needle aspiration cytology into Bethesda categories: an institutional experience and review of the literature. *Cytojournal* 2018; 15: 4.
39. Saeed Alqahtani W, Abdulrahman Almufareh N, Mostafa Domiaty D, *et al*. Epidemiology of cancer in Saudi Arabia thru2010–2019: a systematic review with constrained meta-analysis Running title: epidemiology of cancer in Saudi Arabia thru 2010–2019. *AIMS Public Heal* 2020; 7: 679–696.
40. Le AR, Thompson GW and Hoyt BJA. Thyroid fine-needle aspiration biopsy: an evaluation of its utility in a community setting. *J Otolaryngol – Head Neck Surg* 2015; 44: 12.
41. Trimboli P, Scappaticcio L, Treglia G, *et al*. Testing for BRAF (V600E) mutation in thyroid nodules with Fine-Needle Aspiration (FNA) read

as suspicious for malignancy (Bethesda V, Thy4, TIR4): a systematic review and meta-analysis. *Endocr Pathol* 2020; 31: 57–66.

42. Yao R, Chiu CG, Strugnell SS, *et al*. Gender differences in thyroid cancer: a critical review. *Expert Rev Endocrinol Metab* 2011; 6: 215–243.
43. Balkan F, Onal ED, Usluogullari A, *et al*. Is there any association between insulin resistance and thyroid cancer? A case control study. *Endocrine* 2014; 45: 55–60.
44. Almquist M, Johansen D, Björge T, *et al*. Metabolic factors and risk of thyroid cancer in the Metabolic syndrome and Cancer project (Me-Can). *Cancer Causes Control* 2011; 22: 743–751.
45. He LZ, Zeng TS, Pu L, *et al*. Thyroid hormones, autoantibodies, ultrasonography, and clinical parameters for predicting thyroid cancer. *Int J Endocrinol* 2016; 2016: 8215834.
46. Witczak J, Taylor P, Chai J, *et al*. Predicting malignancy in thyroid nodules: feasibility of a predictive model integrating clinical, biochemical, and ultrasound characteristics. *Thyroid Res* 2016; 9: 4–7.
47. Musa IR, Gasim GI, Khan S, *et al*. No association between 25 (OH) vitamin D level and hypothyroidism among females. *Open Access Maced J Med Sci* 2017; 5: 126–130.
48. Bayhan Z, Zeren S, Ozbay I, *et al*. Mean platelet volume as a biomarker for thyroid carcinoma. *Int Surg* 2016; 101: 50–53.