**Original Research Article**

**Correlation of TIRADS Classification and Nodule Size With Serum TSH in Adults With Thyroid Incidentalomas**

**ABSTRACT**

**Background**

A thyroid incidentaloma (TI) is an unexpected, asymptomatic thyroid lesion inadvertently discovered during an investigation of an unrelated condition. Although most TIs are benign, there is a significant potential for malignancy. The prevalence of TI is increasing due to the increased detection using increasingly available high resolution modern ultrasound machines. This study aims to address the need for increased precision in separating benign from malignant lesions by using serum TSH estimation as an adjunct to standardized ultrasound categorization of these lesions for more accurate prediction of their benignity or malignancy, hence reducing the frequency of the need for invasive FNAC.

**Material and method**

This was a prospective cross-sectional study of 400 adult subjects, carried out over a period of six (6) months (January 2023 - June 2023)**.** Each was first scanned, and then blood sample taken from those with incidental thyroid nodules for estimation of serum thyroid-stimulating hormone. The data obtained from the study was analyzed using the Statistical Package for Social Sciences (SPSS), Version 25.0 (IBM Corp. Released 2017, IBM SPSS Statistics for Windows, Armonk, NY: IBM Corp.). Sociodemographic characteristics (e.g. gender) of patients were presented in frequency tables and charts where necessary and age was represented as mean ± SD and also displayed in charts. Chi-square analysis was used to determine the relationship between serum TSH levels and the TIRADS classification of the detected TIs. Pearson correlation analysis was used to determine the level of linear correlation between the size of the TIs and serum TSH levels. All *P-*values **≤** 0.05 were considered statistically significant.

**Result**

The prevalence of incidentalomas in this study was higher than values from older studies. Raised TSH levels were noted in very few subjects and were seen with the; higher TIRADS categories, nodule sizes above 1.5cm, and patients with malignant thyroid nodules. TSH was proportionally increased in more aggressive tumors. Chi Square showed statistically significant association between; the TSH levels and ACR-TIRADS categories (p-value = 0.003), and between TSH levels and the sizes of the TIs (p-value ˂0.001). Pearson’s correlation test showed statistically significant linear correlation between serum TSH levels and the size of the TIs (p-value ˂0.001).

**Conclusion**

The use of high-frequency ultrasound has led to an increase in the detection of incidental thyroid nodules during imaging of the neck. Establishing the use of TSH measurements with ultrasound algorithms in identifying high-risk thyroid nodules in routine clinical practice represents an exciting, cost-efficient and non-invasive approach to optimize thyroid cancer diagnosis.

**Key words:** association, correlation, FNAC, size, thyroid nodules, TSH, ultrasound, malignancy

**INTRODUCTION**

# One of the known lesions of the thyroid gland is thyroid nodule. The overall prevalence of thyroid nodules globally is approximately 24.83 - 29.8%1,2. Recently there has been an increase in the frequency of detection of incidental thyroid nodules also called thyroid incidentalomas3,4. Though most of the nodules are benign about 10-15% of these incidental nodules are malignant5. The possibility of malignancy among these patients raise concern among clinicians and subjects that over time lead to overdiagnosis, unnecessary interventions and inappropriate application of scarce resources6.

Management of an incidental thyroid nodule remains controversial. There is a dilemma between the need to avoid burdening the health care system with over-investigation of benign nodules and the need to avoid the adverse effects that follow a delayed cancer diagnosis7.

Ultrasound (US) is the most sensitive imaging test for the thyroid gland8. High-frequency transducers provide both low ultrasound penetration and high-resolution images9. Thus, the availability of high-resolution US with its improved sensitivity has led to an increase in the frequency of detection of incidental thyroid nodules10,11,12,13. Ultrasound is also non-invasive, readily available and non-ionizing, making it an ideal screening tool for nodular and diffuse thyroid disease14,15,16.

US-guided fine-needle aspiration cytology (FNAC) is often performed to determine the nature of suspicious nodules16,17,18. The FNAC is reported using the Bethesda system for reporting thyroid Cytopathology19. Where possible, it is imperative to reduce the number of unnecessary FNACs while identifying clinically significant malignant nodules.

This concern has been largely addressed by US. This is because its features of TI have been harnessed to create several risk stratification systems to identify nodules that warrant either biopsy or follow-up, thus reducing the number of unnecessary FNACs or surgical inteventions13,20. Many professional organizations have proposed ways to identify nodules that require active surveillance. For instance, in 2012, the American college of Radiology convened committees to investigate incidental thyroid nodules. By 2015, these committees published a white paper that presented an approach to TIs. Two years later (2017), the American College of Radiology (ACR) Thyroid Imaging Reporting and Data System (TIRADS) was created11.

The ACR TIRADS is an ultrasound-based risk stratification system (RSS) for classifying thyroid nodules11. Research has shown that it has a higher specificity than other RSSs and reduces unnecessary biopsies of benign nodules compared with other RSSs by 19.9-46.5%21.

Ultrasonography is affordable and the TIRADS classification, which is a reliable risk stratification tool is ultrasound-based, making it an ideal and cost-effective addition to risk stratification effort22,23.

In the ACR TIRADS, there are 5 ultrasound features assessed: namely; composition, echogenicity, shape, margin and echogenic foci. Points are given for all the ultrasound features in a nodule, with the more suspicious features being awarded additional points. One feature is selected from each of the first four feature categories and all the features that apply from the final feature category; the accrued points are then summed up. The total points determine the TIRADS category (Table 1).

**Table 1: ACR TIRADS Categories, risk level and recommendations11**

|  |  |  |
| --- | --- | --- |
| **ACR TIRADS CATEGORY (RISK OF CANCER IN PERCENTAGE)**  | **TOTAL POINTS** | **RECOMMENDATION** |
| TR1 – Benign (0.3%) | 0 | No FNAC |
| TR2 – Not Suspicious (1.5%) | 2\*\* | No FNAC |
| TR3 – Mildly Suspicious (4.8%) | 3 | FNAC if ≥2.5cmFollow up if ≥1.5cm |
| TR4 – Moderately Suspicious (9.1%) | 4-6 | FNAC if ≥1.5cmFollow up if ≥1cm  |
| TR5 – Highly Suspicious (35%) | ≥7 | FNAC if ≥1cmFollow up if ≥0.5cm  |

\*\* Although a nodule can be assigned zero points and be categorized TR1, all other nodules merit at least two points because a nodule that has a mixed cystic and solid appearance (one point) will also gain at least one more point for the echogenicity of its solid component. When there are multiple nodules, there should be no more than four (4) nodules classified. FNA is not recommended of more than two (2) nodules.

Serum thyroid-stimulating hormone (TSH) levels can be measured to investigate the nodule18. A hyperfunctioning nodule would produce high levels of thyroid hormones, resulting in low levels of TSH, while a hypo-functioning nodule would produce low levels of thyroid hormones, leading to high levels of TSH. Hyperfunctioning nodules are rarely malignant24. The 2009 revised American Thyroid Association Management Guidelines for Patients with Thyroid Nodules and Differentiated Thyroid Cancer states that “since hyperfunctioning nodules rarely harbor malignancy, if one is found that corresponds to the nodule in question, no cytologic evaluation is necessary”23,25.

The risk of malignancy tends to increase with serum TSH levels even within the normal range26. The serum level of the hormone is an independent predictor of malignancy and can serve as an adjunct to FNAC in predicting the risk of malignancy14,24.

Taking into cognizance the fact that there is a paucity of data on TI in developing nations like ours, and that patients with incidentally discovered thyroid nodules undergo or otherwise forgo FNAC without a standardized basis, this study in embarked upon to determine the Ultrasound characteristics of TIs in our environment, stratify them according to the ACR TIRADS standard and correlate the thyroid-stimulating hormone (TSH) levels with the size of TIs and their ACR TIRADS. This will offer patients with TIs in our environment and beyond, a standardized basis to undergo or forgo FNAC, thus paving way for the establishment of local protocols for approaching TIs, which can in turn aid early detection of cancer.

**MATERIALS AND METHODS**

This was a prospective cross-sectional study of 400 consenting adults and was conducted over a period of six (6) months (January 2023 - June 2023).The study was a hospital-based study carried out in Nnamdi Azikiwe University Teaching Hospital (NAUTH), Nnewi, Anambra State, Nigeria. The subjects were consenting adult subjects (18 years or above) who were either volunteers or patients referred for imaging to the Department of Radiology, NAUTH, for reasons other than thyroid disease. The following were excluded from the study: pregnant women, subjects who did not give consent for the study, those less than 18 years, those with evidence of current thyroid disease like a visible or palpable thyroid mass, those with previous history of thyroid disease, previous history of thyroid surgery or Radioiodine therapy or family history of thyroid disease in a first-degree relative.

The subjects were scanned using a Mindray ultrasound machine (model: DC-32 SN: 9Q-98000221; manufactured 18-08-2019) fitted with a 5-12MHz linear array transducer and Doppler capabilities. Both lobes and the isthmus of the thyroid gland were scanned in the axial and longitudinal planes. The number, size and other ultrasound characteristics of thyroid nodules were recorded in the study datasheet.

The TIs were also classified according to their risk of malignancy using the ACR TIRADS. If a subject had multiple incidentalomas with different TIRADS classifications, the higher classification was assigned to the subject.

Finally, a blood sample was obtained aseptically for serum Thyroid Stimulating Hormone (TSH) estimation.The cost of the study was borne by the researchers.

The data obtained from the study was analyzed using the Statistical Package for Social Sciences (SPSS), Version 25.0 (IBM Corp. Released 2017, IBM SPSS Statistics for Windows, Armonk, NY: IBM Corp.).

 Sociodemographic characteristics (e.g. gender) of patients were presented in frequency tables and charts where necessary and age was represented as mean ± SD and also displayed in charts.

The frequency of altered serum TSH levels among subjects with TI was presented in simple frequency and percentage tables. Chi-square analysis was used to determine the relationship between serum TSH levels and the TIRADS classification of the detected TIs. It was also used to determine the relationship between serum TSH levels and the sizes (grouped) of the TIs. Pearson correlation analysis was used to determine the level of linear correlation between the size of the TIs and serum TSH levels. All *P-*values **≤** 0.05 were considered statistically significant.

**RESULTS**

A total of 400 adults were recruited in this study and all were used in the analysis as there was no case of missing data or outlier. The age range of the subjects was 18-87 years and the mean age was 41.30±14.62 years. As can be seen from fig.1, subjects with the age range of 29-39 years were the highest in number, followed by the following age ranges in decreasing order; 40-50 years, 18-28 years, 51-61 years, 62-72 years, 73-83 years; and finally 84 and above (being the least in number). Male subjects were 151 (37.75%) in number while females were 249 (62.25%). See fig 2.

****

 **Fig. 1: Bar chart showing the age distribution of the subjects**



37.75%

62.25%

**Fig2. Pie chart showing sex distribution**

Incidental thyroid nodules (thyroid incidentalomas, TIs) were seen in 146 subject, which constituted 36.5% of the study population. Among the subpopulation with TIs, 8 subjects (5.48%) had high serum TSH while the vast majority of subjects 138 (94.52%) had normal TSH levels and none had low TSH levels. Subjects with TIs classified as TIRADS 1 and 2, all had normal TSH values.

 The ACR-TIRADS categories involved in the 8 subjects with high TSH levels were TIRADS categories 3-5. Two of these subjects were of TIRADS 3 while four of them were of TIRADS 4 and the remaining two were of TIRADS 5. See table 2

 **Table 2: Frequency of TIRAD classes among the subjects with TI**

|  |  |  |
| --- | --- | --- |
| **ACR-TIRADS** |  **Total(%)** |  **Serum TSH Level** |
|  **High (%)** | **Normal (%)** |
| Class 1 74(50.7) 0 74(50.7)Class 2 14(9.6) 0 14(9.6) Class 3 24(16.4) 2(1.4) 22(15.1)Class 4 26(17.8) 4(2.7) 22( 15.1)Class 5 8(5.48) 2(1.4) 6(4.1 ) **Total 146(100.0) 8(5.48) 138(94.52)** |

As seen in table 3, in the vast majority of the subjects with TIs (up to 80.8%), the size (maximum diameter) of the detected nodule was less than 1cm, and they were all noted to have normal TSH values. Subjects with nodule sizes ranging from 1-1.49cm were 16 in number and they all had normal TSH levels also. Total of 8 subjects had nodular size of 1.5-2.49cm and 4 of them (50%) had high TSH; while the other 4 subjects had nodular size of ≥2.5 cm and all had high TSH.

**Table 3: Frequency of TI sizes (grouped) among the subjects**

|  |  |  |
| --- | --- | --- |
| Sizes in (grouped) |  Total(%) |  Serum TSH Level |
|  High (%) | Normal (%) |
| ˂1.0 cm 118(80.8) 0 118(80.8)1.0-4.9 cm 16(11.0) 0 16(11.0) 1.5-2.49cm 8(5.5) 4(2.7) 4(2.7)≥2.5 cm 4(2.7) 4(2.7) 0**Total 146(100.0) 8(5.5) 138(94.5)** |

In the various tests carried out for the relevant statistical significance (see table 4), Chi Square showed statistically significant association between the TSH levels and ACR-TIRADS categories of the subjects (p-value = 0.003). Chi Square test also showed statistically significant relationship between the TSH levels and the sizes of the TIs (p-value ˂0.001). Pearson’s correlation test showed statistically significant linear correlation between serum TSH levels and the size of the TIs (p-value ˂0.001).

**Table 4: Tests for statistical significance**

|  |  |  |  |
| --- | --- | --- | --- |
| **Variables** | **Name of test** | **Test statistic /****Coefficient** | **p-value** |
| ACR-TIRADS TIRAD VS Serum TSH | Chi Square test for association | X2 = 16.290 | 0.003\* |
| TI size (grouped) vs Serum TSH  | Chi Square test for association | X2 = 107.384 | ˂0.001\* |
| TI size vs Serum TSH | Pearson’s correlation test | r = 0.681 | ˂0.001\* |

X2 = x2 statistic, ‘r’ = the correlation coefficient *\*(significant p-value<0.05)*

In determining the TIRADS categories and the size of the TIs in patient with multiple nodules, the nodule with the highest TIRADS category and the nodule with the largest diameter was used respectively.

**DISCUSSION**

In this study, since the only TSH derangement seen was high value, and constituted 5.48% of all the subjects with TIs, the frequency of altered TSH among subjects with TIs was 5.48%. The frequency obtained in our study varied with that in other studies, where the frequency was as high as 9.5%27-29. The explanation for this may most likely be in the differences in the population studied. For instance, the population studied by Canaris et al27.was higher than ours and was from the western world.

All the subjects with altered TSH in our study all had high TSH values, and considering the fact that a hypo-functioning nodule would produce low levels of thyroid hormones, leading to high levels of TSH and that hyperfunctioning nodules are rarely malignant and would require no cytologic evaluation10,25,26 ; and that increased TSH levels are statistically associated with an increased risk of cancer in thyroid nodular disease11,30-32, all the subjects with altered TSH in our study can be said to have increased risk of cancer and will therefore require cytologic evaluation.

Again, the high TSH levels were detected only with subjects of TIRADS 3-5 (those of TIRADS 1-2 had normal TSH), corresponding to risk levels of mildly suspicious lesions to highly suspicious lesions; and these are indications for FNAC. This shows that using ultrasound characteristics, namely TIRADS classification as used in our study is of much diagnostic value and useful in sorting out patients that would need FNAC and those that would not.

Significant statistical relationship between the TIRADS classification and TSH levels (0.003), shown by Chi-square analysis in the study further buttresses the fact that TIRADS classification can be reliably used to predict TIs with malignant potentials warranting FNAC.

Furthermore, with regards to the sizes of the TI nodules, the subjects with high TSH had TIs with sizes > 1.5cm. At this size, the chance of malignancy of TI is increased (table 1). Chi-square analysis also showed a significant relationship between TI size and serum TSH levels (˂0.001) and Pearson’s correlation showed a strong positive linear correlation between TSH levels and the sizes of the TIs (˂0.001). All these show that the size of a TI as measured by ultrasound, can be a good pointer to TIs requiring FNAC even in the absence of serum TSH.

As a corollary, the results show that the serum TSH can be used to predict TIs with likelihood for malignancy. This is in agreement with the observation by other authors putting serum TSH as an independent predictor of malignancy that can serve as an adjunct to FNAC in predicting the risk of malignancy24,26.

One of the limitations of our study is non-inclusion of FNAC results in the study. Since we did not see a similar study in our environment for comparing with ours, and our study did not include the FNAC findings for correlations, further studies that will include ultrasound characteristics, TSH, and FNAC results are recommended to compare with our results as well as to better understand the relationship between FNAC findings, serum TSH levels and the ultrasound characteristics of incidental thyroid nodules.

**CONCLUSION**

The advent and widespread use of high-frequency and high-sensitivity ultrasound has led to an increase in the detection of incidental thyroid nodules during imaging of the neck. Since most of them are small, non-palpable and clinically innocuous, they pose a clinical problem, especially when malignant. In this study, raised TSH levels when present are seen with the higher TIRADS categories and increased nodule sizes above 1.5cm, and these two parameters are considered as contributing to the likelihood of increased malignancy. Thus the study offers a practical, noninvasive method for improving the triage of patients who may require further cytologic evaluation. However, further studies that will include ultrasound characteristics, TSH, and FNAC results are recommended to better understand the relationship between FNAC findings, serum TSH levels and the ultrasound characteristics of incidental thyroid nodules.

**Disclaimer (Artificial intelligence):**

Authors hereby declare that NO generative AI technologies such as Large Language Models (ChatGPT, COPILOT, etc.) and text-to-image generators have been used during the writing or editing of this manuscript.

 Ethical Approval

Approval for this study was obtained from the Ethical Committee of NAUTH. The data collected was treated with utmost confidentiality.

Consent

As per international standards or university standards, patient(s) written consent has been collected and preserved by the author(s).

**REFERENCES**

1. Mu C, Ming X, Tian Y, Liu Y, Yao M, Ni Y, Liu Y, Li Z. Mapping global epidemiology of thyroid nodules among general population: A systematic review and meta-analysis. Front Oncol. 2022 Nov 10;12:1029926. doi: 10.3389/fonc.2022.1029926. PMID: 36439513; PMCID: PMC9685339.
2. Liang Y, Li X, Wang F, Yan Z, Sang Y, Yuan Y, Qin Y, Zhang X, Ju M. Detection of Thyroid Nodule Prevalence and Associated Risk Factors in Southwest China: A Study of 45,023 Individuals Undergoing Physical Examinations. Diabetes Metab Syndr Obes. 2023 Jun 8;16:1697-1707. doi: 10.2147/DMSO.S412567. PMID: 37312898; PMCID:
3. Ross DS. Nonpalpable thyroid nodules – managing an epidemic. J Clin Endoc Metab. 2002;87:1938–1940. doi: 10.1210/jcem.87.5.8552
4. Nguyen XV, Job J, Fiorillo LE, Sipos J. Thyroid Incidentalomas: Practice Considerations for Radiologists in the Age of Incidental Findings. Radiol Clin North Am. 2020 Nov;58(6):1019-1031. doi: 10.1016/j.rcl.2020.06.005. Epub 2020 Sep 14. PMID: 33040845.
5. Moifo, B., Moulion Tapouh, J.R., Dongmo Fomekong, S. et al. Ultrasonographic prevalence and characteristics of non-palpable thyroid incidentalomas in a hospital-based population in a sub-Saharan country. BMC Med Imaging 17, 21 (2017). <https://doi.org/10.1186/s12880-017-0194-8>
6. Singh S, Singh A, Khanna AK. Thyroid incidentaloma. Indian J Surg Oncol. 2012;3(3):173-181. doi:10.1007/s13193-011-0098-y(same with reference 7).
7. Hoang JK, Wai KL, Lee M, Johnson D, Farrell S. US features of thyroid malignancy: Pearls and pitfalls. Radiographics. 2007;27:847–60.
8. Dean DS, Gharib H. Epidemiology of thyroid nodules. Best Pract Res Clin Endocrinol Metab. 2008;22:901–11.
9. Chandramohan A, Khurana A, Pushpa B, Manipadam M, Naik D, Thomas N, et al. Is TIRADS a practical and accurate system for use in daily clinical practice? Indian J Radiol Imaging. 2016;26:145–52.
10. Ferrinho C, Cunha CV, Silva E, Saraiva C, Ferreira RC, Roque C, et al. MON-497 Evaluation and Comparison of Ultrasonographic Features According to Histology of Thyroid Nodules. J Endocr Soc. 2020;4:MON-497/5833958.
11. Tessler FN, Middleton WD, Grant EG, Hoang JK, Berland LL, Teefey SA, et al. ACR Thyroid Imaging, Reporting and Data System (TI-RADS): White Paper of the ACR TI-RADS Committee. J Am Coll Radiol. 2017;14:587–95.
12. Rossi ED, Vielh P. Thyroid and Molecular Testing. Advances in Thyroid Molecular Cytopathology. J. Mol. Pathol. 2021, 2, 77–92. https://doi.org/10.3390/jmp2020008
13. Branko K, Ivana VK, Ana K, Roberta P. Ultrasound guided fine needle aspiration cytology (FNAC): an Assessment of the Diagnostic Potential in Histologically Proven Thyroid Nodules. Med Glas (Zenica) 2022; 19(2): 184-188
14. Olusola-Bello MA, Agunloye AM, Adeyinka AO. Ultrasound prevalence and characteristics of incidental thyroid lesions in Nigerian adults. Afr J Med Med Sci. 2013;42:125–30. 13. Hoang JK, Middleton WD, Tessler FN. Update on ACR TI-RADS: Successes, challenges, and future directions, from the AJR special series on radiology reporting and data systems. Am J Roentgenol. 2020;216:570–8.
15. Dighe M, Barr R, Bojunga J, Cantisani V, Cristina Chammas M, Cosgrove D, et al. Thyroid Ultrasound: State of the Art Part 1-Thyroid Ultrasound reporting and Diffuse Thyroid Diseases. Med Ultrason. 2017;19:79–93.
16. Bonjoc KJ, Young H, Warner S, Gernon T, Maghami E, Chaudhry A. Thyroid cancer diagnosis in the era of Precision Imaging. J Thorac Dis 2020;12(9):5128-5139. doi: 10.21037/jtd.2019.08.37
17. Boudina M, Katsamakas M, Chorti A, Panousis P, Tzitzili E, Tzikos G, Chrisoulidou A, Valeri R, Ioannidis A, Papavramidis T. Diagnostic Accuracy of Ultrasound and Fine-Needle Aspiration Cytology in Thyroid Malignancy. Medicina 2024, 60, 722. <https://doi.org/10.3390/medicina60050722>
18. Aydogdu YF, Emreol U, Emre G, Buyukkasap C, Akin M. Determination of Diagnostic Features of Serum Thyroid Hormones and Thyroglobulin Ratios in Normothyroid Differentiated Thyroid Carcinoma Cases. Sisli Etfal Hastan Tıp Bul. 2023 Jun 20;57(2):257-262. doi: 10.14744/SEMB.2023.77012. PMID: 37899801; PMCID: PMC10600635.
19. Han M, Fan F. Bethesda System for Reporting Thyroid Cytopathology–An Updated Review. *J Clin Transl Pathol*. 2023;3(2):84-98. doi: 10.14218/JCTP.2023.00005.
20. Mirfakhraee S, Mathews D, Peng L, Woodruff S, Zigman JM. A solitary hyperfunctioning thyroid nodule harboring thyroid carcinoma: review of the literature. Thyroid Res. 2013;6:1–15.
21. Cooper DS, Doherty GM, Haugen BR, Kloos RT, Lee SL, Mandel SJ, et al. Revised American Thyroid Association Management Guidelines for Patients with Thyroid Nodules and Differentiated Thyroid Cancer. Mary Ann Liebert, Inc. 2009;19:1167–214.
22. Moifo B, Moulion Tapouh JR, Dongmo Fomekong S, Djomou F, Manka’a Wankie E. Ultrasonographic prevalence and characteristics of non-palpable thyroid incidentalomas in a hospital-based population in a sub-Saharan country. BMC Med Imaging. 2017;17:21.
23. Cooper DS, Doherty GM, Haugen BR, Kloos RT, Lee SL, Mandel SJ, et al. Revised American Thyroid Association Management Guidelines for Patients with Thyroid Nodules and Differentiated Thyroid Cancer. Mary Ann Liebert, Inc. 2009;19:1167–214.
24. Singh S, Singh A, Khanna AK. Thyroid Incidentaloma. Indian J Surg Oncol. 2012;3:173–81.
25. Boelaert K, Horacek J, Holder RL, Watkinson JC, Sheppard MC, Franklyn JA. Serum thyrotropin concentration as a novel predictor of malignancy in thyroid nodules investigated by fine-needle aspiration. J Clin Endocrinol Metab. 2006;91:4295–301.
26. Rumack CM, Levine D. Diagnostic Ultrasound. 5th ed. Elsevier, Philadelphia; 2018. 691–694.
27. Canaris GJ, Manowitz NR, Mayor G, Ridgway EC. The Colorado Thyroid Disease Prevalence Study. *Arch Intern Med.* 2000;160(4):526–534. doi:10.1001/archinte.160.4.526
28. Tunbridge W, Evered D, Smith P. The Spectrum Of Thyroid Disease In A Community: The Whickham Survey Clinical Endocrinology (1977) 7(6) 481-493
29. Parle JV, Franklyn JA, Cross KW, Jones SC, Sheppard MC Prevalence and follow-up of abnormal thyrotrophin (TSH) concentrations in the elderly in the United Kingdom. Clin Endocrinol (Oxf). 1991;3477- 83
30. Tamhane S, Gharib H. Thyroid nodule update on diagnosis and management. Clinical Diabetes and Endocrinology 2016 2:1 (2016) 2(1) 1-10
31. Boelaert K, Horacek J, Holder RL, Watkinson JC, Sheppard MC, Franklyn JA. Serum thyrotropin concentration as a novel predictor of malignancy in thyroid nodules investigated by fine-needle aspiration. J Clin Endocrinol Metab. 2006;91(11):4295–301.
32. Haymart MR, Repplinger DJ, Leverson GE, et al. Higher serum thyroid stimulating hormone level in thyroid nodule patients is associated with greater risks of differentiated thyroid cancer and advanced tumor stage. J Clin Endocrinol Metab. 2008;93(3):809–14.