

Sociodemographic and Clinical Pattern of Thyroid Nodules in Sindh, Pakistan: A Prospective Analysis from a Tertiary Care Centre

Abstract

Objectives: To study the sociodemographic and clinical patterns of thyroid lesions in Sindh, Pakistan

Methodology: A prospective observational study was conducted at the department of Surgery, Ward - 26, Jinnah Postgraduate Medical Centre, Karachi between March 2018 to 2020. All patients presenting with complaints of thyroid nodule as diagnosed clinically and by ultrasound imaging were included in the study. Patients with deranged thyroid hormone levels were excluded. Sociodemographic, clinical, and pathological parameters were recorded in a predefined pro forma. Statistical Package of Social Sciences v.26 (SPSS) was used for data analysis.

Results: A total of 330 patients were evaluated for thyroid lesions. Out of these, only 81 patients were diagnosed with thyroid nodules. Mean age was 35.14 ± 12.28 years. We had 37 patients (11.2%) with a diagnosis of thyroid carcinoma. This included papillary and follicular carcinoma majorly. Among patients diagnosed with carcinoma, 31 (83.8%) were females.

Conclusion: We presented a significantly higher rate of thyroid carcinoma on histopathology in our centre as compared to previous studies. The majority of the lesions were diagnosed among females. This highlights the increasing incidence of thyroid carcinoma in our population.

Keywords: grave's disease, hashimoto's, follicular carcinoma, FNAC, thyroiditis, papillary carcinoma

Introduction

Thyroid gland is located in front of the neck just below the larynx. It is an endocrine gland and is responsible for several bodily functions. Enlargement of the thyroid gland is a common problem resulting in inability to maintain normal physiological functions of the body.^{1,2} Thyroid nodules can be a manifestation of a wide array of disorders and require thorough investigations. Thyroid nodules are one of the common endocrine disorders, 2-6% of which are discovered on palpation.¹ While among randomly selected individuals 19%-67% of TNs are detected on high-resolution ultrasonography.^{1,2} The prevalence of TNs is increasing globally per annum. Moreover, thyroid carcinoma, which has become the fastest growing cancer, constitutes 5%-15% of the TNs.³ In numerous parts of the world endemic goiter, which is hypothesized as a precursor lesion to thyroid carcinoma, is a serious concern.⁴ Additionally, iodine deficiency has a well-understood causal association with increased incidence of thyroid lesions.⁵ If left untreated, thyroid disease may develop some serious life-threatening complications including Graves' disease, Hashimoto's thyroiditis or even carcinoma.^{6,7} Previous literature has highlighted the association between geographical location, age, and sex with the increasing incidence of thyroid lesions.^{4,6-8} In a study conducted in the year 2018, Laci et al., found that out of the 212 patients diagnosed with thyroid lesions, the majority (84.9%) were women, and many of these patients had a positive family history.⁸

Furthermore, exposure to radiation is among the major predisposing factors. It is estimated that one in every eight women will eventually suffer from thyroid related issues during her life.⁹ Thyroid lesions can present as solitary nodules, multinodular, or diffuse goiter and are diagnosed on clinical examination and non-invasive investigations such as ultrasonographic imaging.^{10,11} The prevalence of thyroid lesions differs in various reports both locally and globally. In Pakistan, the incidence of thyroid lesions is on the rise. A recent study by Samad et al., reported that out of a total of 1465 cases of thyroid nodules presented in their center, 1169 cases were established as simple goiter, ten percent were diagnosed as adenoma while 6 percent were diagnosed as thyroid carcinoma.¹⁰ It is alarming to observe such a high percentage of thyroid carcinoma arising from only one city of the country. Therefore, the present study aimed to find out the sociodemographic and clinicopathological pattern of thyroid lesions detected on ultrasonography and histopathological examinations in Sindh, Pakistan.

Methodology

A prospective observational study was conducted at the Department of Surgery, Jinnah Postgraduate Medical Centre, Karachi between March 2018 to March 2020. Ethical approval was obtained prior to the data collection. All patients above the age of 18 years, irrespective of gender, presenting to the outpatient's department with thyroid nodules were eligible to partake in the study. Patients with deranged levels of thyroid profile i.e., thyroid stimulating hormone (TSH), free thyroxine (FT₄), and free triiodothyronine (FT₃) were first referred to endocrinology department for a consult before enrollment in the study. Patients with abnormally high or low levels of thyroid profile tests were referred to the Endocrinology Department for pharmacological intervention. Thyroid nodule was described as an abnormal overgrowth of tissue in the thyroid gland categorized into benign and malignant.¹¹

A thorough clinical examination was done in the outpatient's department in the examination room by the consultant while the ultrasound imaging of the thyroid lesion was performed by radiologists with an experience of over five years.

The final diagnosis was established on the findings of ultrasound imaging, followed by the FNAC of the nodule correlated with clinical and histopathological analysis. The Bethesda System for Reporting Thyroid Cytopathology (TBSRTC) was used in all the cases.¹²

For data analysis, Statistical Package for Social Sciences (SPSS) version 26 was used. The continuous variables including the age of the patient were presented as mean and standard deviation while for the categorical variables, frequency and percentages were determined. Chi square tests were applied to explore the associations between age groups and type of lesions. A p value of < 0.05 was set as the cut-off value for significance.

Results

A total of 330 patients were evaluated for thyroid lesions. Out of these, only 81 patients were diagnosed with thyroid nodules. A mean age of 35.14 ± 12.28 years was observed with a minimum age of 14 years and maximum age of 75 years. The mean age with standard deviation for men was 33.18 ± 8.43 years and for female patients, 35.63 ± 13.07 years. The majority of the patients were female i.e., 65 (80.2%). We had 37 patients (11.2%) with a diagnosis of thyroid carcinoma. Figure 1 demonstrates the distribution of the patients in the study.

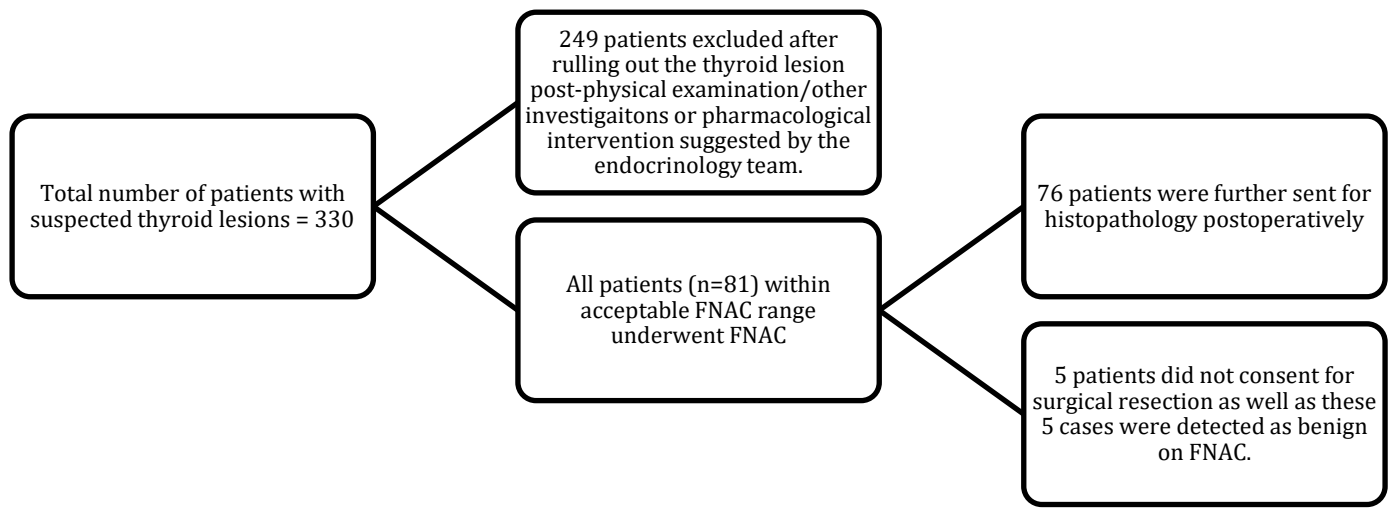


Figure 1. Flow diagram illustrating the patient distribution

Table 1 demonstrates the distribution of patients according to the age groups and location of the thyroid nodules.

Table 1. Distribution of Patients according to their age groups and Location of the Thyroid Nodule

| | Bilateral | Isthmus | Left | Midline | Diffuse | Only LN | Right | P-value |
|-------|------------|-------------|------------|-------------|------------|-------------|-------------|---------|
| <18 | 0 (0.00%) | 0 (0.00%) | 1 (4.50%) | 0 (0.00%) | 1 (7.70%) | 0 (0.00%) | 0 (0.00%) | 0.985 |
| 18-25 | 1 (16.70%) | 0 (0.00%) | 6 (27.30%) | 0 (0.00%) | 3 (23.10%) | 0 (0.00%) | 7 (18.90%) | |
| 26-35 | 4 (66.70%) | 1 (100.00%) | 6 (27.30%) | 1 (100.00%) | 3 (23.10%) | 1 (100.00%) | 15 (40.50%) | |
| 36-45 | 0 (0.00%) | 0 (0.00%) | 6 (27.30%) | 0 (0.00%) | 3 (23.10%) | 0 (0.00%) | 6 (16.20%) | |
| 46-55 | 1 (16.70%) | 0 (0.00%) | 3 (13.60%) | 0 (0.00%) | 2 (15.40%) | 0 (0.00%) | 6 (16.20%) | |
| >55 | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 1 (7.70%) | 0 (0.00%) | 3 (8.10%) | |

There was no significant association between the age groups and the location of the thyroid nodule as detected by ultrasound imaging ($P = 0.985$) (Table 1). However, 31 (37.8%) were in the age group between 26 and 35 years. 13 (16%) patients were diagnosed as multi nodular goiter on ultrasonography.

Furthermore, the site of thyroid lesion was not significantly associated with the gender (Table 2).

Table 2. Distribution of Patients according to the gender and Location of the Thyroid Nodule

| Gender | Bilateral | Isthmus | Left | Midline | Diffuse | LN Only | Right | P-value |
|--------|------------|-------------|-------------|-------------|-------------|-------------|-------------|---------|
| Male | 2 (33.30%) | 0 (0.00%) | 5 (22.70%) | 1 (100.00%) | 2 (15.40%) | 1 (100.00%) | 5 (13.50%) | 0.114 |
| Female | 4 (66.70%) | 1 (100.00%) | 17 (77.30%) | 0 (0.00%) | 11 (84.60%) | 0 (0.00%) | 32 (86.50%) | |

Table 3. Distribution of Thyroid nodules according to fine needle aspirate cytology (n=81)

| FNAC Report | Frequency | Percent |
|---|-----------|---------|
| Atypia of undetermined significance | 5 | 6.2 |
| Benign colloid nodule | 17 | 21 |
| Benign follicular nodule | 15 | 18.5 |
| Benign peripheral nerve sheath tumor | 1 | 1.2 |
| Chronic granulomatous inflammation | 2 | 2.5 |
| Cystic lesion | 7 | 8.6 |
| Follicular carcinoma | 9 | 11.1 |
| Hurthle cell adenoma | 2 | 2.5 |
| Hurthle cell carcinoma | 1 | 1.2 |
| Hyperplasia | 6 | 7.4 |
| Medullary carcinoma | 2 | 2.5 |
| Metastatic papillary | 1 | 1.2 |
| Non-diagnostic | 4 | 4.9 |
| Papillary carcinoma | 5 | 6.2 |
| Poorly differentiated thyroid carcinoma | 1 | 1.2 |
| Suspicion of Malignancy | 3 | 3.7 |
| Total | 81 | 100 |

Table 4 shows the frequency and percentages of patients who presented with thyroid nodules. The most common of thyroid nodules were Benign Nodular Hyperplasia with a frequency of 27 (33.3%), followed by Papillary Carcinoma 19 (23.5%), and Follicular Carcinoma 15 (18.5%).

Table 4. Frequency and Percentage of Diagnosis of Thyroid Disease on Histopathology

| Diagnosis | Frequency | Percent |
|----------------------------|-----------|---------|
| Benign Cyst | 1 | 1.20% |
| Benign Nodular Hyperplasia | 27 | 33.30% |
| Follicular Adenoma | 9 | 11.10% |
| Follicular Carcinoma | 15 | 18.50% |
| Hashimoto's Thyroiditis | 1 | 1.20% |
| Medullary Carcinoma | 3 | 3.70% |
| Non-diagnostic | 4 | 4.90% |

| | | |
|--------------------------------|----|--------|
| Papillary Carcinoma | 19 | 23.50% |
| Suspicious of Malignancy (SOM) | 1 | 1.20% |
| Thyroglossal Cyst | 1 | 1.20% |
| Total | 81 | 100% |

Table 5 shows the distribution of patients according to the gender and diagnosis as established by histopathology.

Table 5. Distribution of Patients according to the Gender and Diagnosis

| Diagnosis | Male | Female | Total | P-value |
|--------------------------------|------------|-------------|--------------|---------|
| Adenoma | 3 (33.30%) | 6 (66.70%) | 9 (100.00%) | 0.861 |
| Benign | 6 (20.70%) | 23 (79.30%) | 29 (100.00%) | |
| Lymphocytic (Hashimotos) | 0 (0.00%) | 1 (100.00%) | 1 (100.00%) | |
| Malignant | 6 (16.20%) | 31 (83.80%) | 37 (100.00%) | |
| Non-diagnostic | 1 (25.00%) | 3 (75.00%) | 4 (100.00%) | |
| Suspicious of Malignancy (SOM) | 0 (0.00%) | 1 (100.00%) | 1 (100.00%) | |

We had 37 patients (11.2%) with a diagnosis of thyroid carcinoma. This included papillary and follicular carcinoma majorly. Out of these, 31 (83.8%) malignant cases were found among female patients while around 16.2 percent of patients were male (Table 6).

Table 6. Distribution of Patients according to the Age Groups and Diagnosis

| Age Groups | Adenoma | Benign | Lymphocytic (Hashimotos) | Malignant | Non-diagnostic | Suspicion of Malignancy (SOM) | P-value |
|------------|------------|-------------|--------------------------|-------------|----------------|-------------------------------|---------|
| <18 | 0 (0.00%) | 1 (50.00%) | 0 (0.00%) | 1 (50.00%) | 0 (0.00%) | 0 (0.00%) | 0.658 |
| 18-25 | 2 (11.80%) | 4 (23.50%) | 0 (0.00%) | 11 (64.70%) | 0 (0.00%) | 0 (0.00%) | |
| 26-35 | 4 (12.90%) | 13 (41.90%) | 0 (0.00%) | 11 (35.50%) | 3 (9.70%) | 0 (0.00%) | |
| 36-45 | 3 (20.00%) | 6 (40.00%) | 0 (0.00%) | 5 (33.30%) | 0 (0.00%) | 1 (6.70%) | |
| 46-55 | 0 (0.00%) | 4 (33.30%) | 1 (8.30%) | 6 (50.00%) | 1 (8.30%) | 0 (0.00%) | |
| >55 | 0 (0.00%) | 1 (25.00%) | 0 (0.00%) | 3 (75.00%) | 0 (0.00%) | 0 (0.00%) | |

Table 5 presents the distribution of patients according to the final diagnosis in different age groups. It was found that 75% of the patients in the age group > 55 years were malignant lesions while 64.7% cases in the age group between 18-25 years were malignant lesions. The majority of the lesions in the age group between 26 and 35 years and 36 to 45 years were benign with a frequency of 13 (41.90%) and 6 (40.00%), respectively (Table 5).

Discussion

The prevalence of TNs in the general population is heavily dependent upon the screening modality used. The incidence of TNs discovered rose from a mere 4-7% on routine clinical examination to a staggering 20-76% on Ultrasonography.¹³⁻¹⁵ **Due to incidence of thyroid cancer on the rise, it's pertinent to evaluate the clinical pattern of the TNs.**

The patterns of TNs noticed in our current study are in concordance with the available world literature. Our study observes that the majority of patient's who presented with TNs were younger (age group of 26-35 years) and had a mean age of 35.14 ± 12.28 years, which is lesser than Handa et al. where the patient's mean age was found to be 37.69 ± 14.93 years.¹⁶ Some studies conducted in Pakistan and India, reveal the highest incidence in the age group 30-40 years, while those in Saudi Arabia report an even older population (age group 41-50).¹⁶⁻²⁰ Moreover, our investigation found a higher prevalence of TNs in women (80.2%) and a female to male ratio of 4:1. This finding is comparable with various researches worldwide that reveal a gender disparity and the female to male ratio between 2-9: 1.^{14,16, 24-26} Conditions like menstruation, pregnancy and breastfeeding where the demand of thyroid hormones is increased or the effects of estrogen could account for the female predisposition found in our study.²⁷

Furthermore, the nodules were predominantly located in the right lobe of the thyroid gland in both the genders, which could be due to the large size of the right lobe and its increased vascularity.²⁸ The most common of the TNs observed in our study were Benign Nodular Hyperplasia (33.3%), followed by papillary carcinoma (23.5%), and follicular carcinoma (18.50%). This finding is unlike a study conducted in western Algeria, where most of the cases were benign dystrophic lesions (25.93%), followed by benign nodular hyperplasia (22.56%) and suspicion of malignancy (14.14%).²⁹

Even though more than half of the TNs were benign lesions, an alarmingly high incidence of thyroid carcinoma (45.1%) was observed with papillary carcinoma constituting the majority of the cases. These results are slightly higher than the study conducted in China where 44.7% of the cases were found to be malignant.³⁰ Other retrospective studies conducted in India, Pakistan and Saudi Arabia report a lower prevalence in the range 4.63%-12.65%.^{17,20,21}

Similarly, papillary carcinoma was reported to be the most common subtype in Sengupta et al.¹⁷

The gender stratification of TNs based on histopathology in our study revealed that women (83.8%) presented with five times more malignant lesions than men (16.2%) which is higher than the female to male ratio of 3:1 for thyroid cancer.³¹ Moreover, majorly the malignancies (75%) were found in the older participants in the age group >55 years followed by the younger participants in the age group 18-25 years (64.7%). However, a study conducted by Kwong et al. reported a decreasing trend in the likelihood of thyroid malignancy with advancing age.³²

There are certain limitations of the study. The study only included patients who presented with thyroid nodules at our center therefore, the data was limited by demographics and also the sample size was also small, refraining us to generalize the current findings to a larger population. However, this study still holds quite useful information in terms of association of location and type of thyroid nodules with age and gender.

Thyroid disease is a major problem in our country especially in low socioeconomic regions. Due to inaccessibility of healthcare facility in rural areas of Pakistan, many women and men tend to ignore the symptoms of thyroid disease until the disease is so severe that it becomes life threatening. We recommend that future studies should be directed towards a comprehensive mixed method approach to study the spectrum of thyroid disease in Pakistan as well as qualitatively explore the multifaceted factors leading to delay in treatment.

Conclusion

We presented a significantly higher rate of thyroid carcinoma on histopathology in our centre as compared to previous studies. The majority of the lesions were diagnosed among females. This highlights the increasing incidence of thyroid carcinoma. Further epidemiological studies are required to explore the various risk factors and socio-demographic patterns associated with thyroid nodules in our population.

Ethical Approval:

As per international standard or university standard written ethical approval has been collected and preserved by the author(s).

Consent

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

References

1. Dean DS, Gharib H. Epidemiology of thyroid nodules. *Best practice & research Clinical endocrinology & metabolism*. 2008 Dec 1;22(6):901-11.
2. Forkin KT, Huffmyer JL, Nemergut EC. *Endocrine Physiology. Pharmacology and Physiology for Anesthesia*. 2019 Jan 1:6693-707.
3. DeLellis RA, Williams ED. Pathology of the thyroid and parathyroid. In: DeLellis RA, Lloyd RV, Heitz PU, Eng C (eds), *Pathology and genetics of tumours of endocrine organs, World Health Organization Classification of Tumours*, IARC Press, Lyon, 2004; p. 57-66.
4. Lawal O, Agbakwuru A, Olayinka OS, Adelusola K. Thyroid malignancy in endemic nodular goitres: prevalence, pattern and treatment. *European Journal of Surgical Oncology (EJSO)*. 2001 Mar 1;27(2):157-61.
5. Aghini-Lombardi F, Antonangeli L, Martino E, Vitti P, Maccherini D, Leoli F, Rago T, Grasso L, Valeriano R, Balestrieri A, Pinchera A. The spectrum of thyroid disorders in an iodine-deficient community: the Pescopagano survey. *The Journal of Clinical Endocrinology & Metabolism*. 1999 Feb 1;84(2):561-6.

6. Regalbuto C, Le Moli R, Muscia V, Russo M, Vigneri R, Pezzino V. Severe graves' ophthalmopathy after percutaneous ethanol injection in a nontoxic thyroid nodule. *Thyroid*. 2012 Feb 1;22(2):210-3.
7. Caturegli P, De Remigis A, Rose NR. Hashimoto thyroiditis: clinical and diagnostic criteria. *Autoimmunity reviews*. 2014 Apr 1;13(4-5):391-7.
8. LAÇI I, SPAHIU A, FICO A. EPIDEMIOLOGY OF THE NODULES OF THE THYROID GLAND IN ALBANIA. *Management in Health*. 2018 Jan 18;21(4).
9. Sanabria A, Kowalski LP, Shah JP, Nixon IJ, Angelos P, Williams MD, Rinaldo A, Ferlito A. Growing incidence of thyroid carcinoma in recent years: factors underlying overdiagnosis. *Head & neck*. 2018 Apr;40(4):855-66.
10. Samad A, Ali KS, Fayyaz N, Akhtar N, Mahmood N, Kashif M. Histopathological audit of thyroid lesions: A retrospective study in a Tertiary Care Hospital. *International Journal of Medical Research & Health Sciences*. 2019;8(5):173-6.
11. Gharib H, Papini E, Paschke R, Duick DS, Valcavi R, Hegedus L. Medical guidelines for clinical practice for the diagnosis and management of thyroid nodules. *Endocr Pract*. 2006;12(1):63-102.
12. Cibas ES, Ali SZ. The 2017 Bethesda system for reporting thyroid cytopathology. *Thyroid*. 2017 Nov 1;27(11):1341-6.
13. Mazzaferri EL. Management of a solitary thyroid nodule. *New England Journal of Medicine*. 1993 Feb 25;328(8):553-9.
14. Ezzat S, Sarti DA, Cain DR, Braunstein GD. Thyroid incidentalomas: prevalence by palpation and ultrasonography. *Archives of internal medicine*. 1994 Aug .
15. Tan GH, Gharib H. Thyroid incidentalomas: management approaches to nonpalpable nodules discovered incidentally on thyroid imaging. *Annals of internal medicine*. 1997 Feb 1;126(3):226-31.
16. Handa U, Garg S, Mohan H, Nagarkar N. Role of fine needle aspiration cytology in diagnosis and management of thyroid lesions: A study on 434 patients. *Journal of cytology*. 2008 Jan 1;25(1):13.
17. Sengupta S, Tuli I, Baruah B, Kesari S, Ilapakurty B, Gupta A. Spectrum of goitrous lesions in patients at a tertiary care center of Sikkim. *Sahel Medical Journal*. 2014 Jul 1;17(3):112-.
18. Qureshi IA, Khabaz MN, Baig M, Begum B, Abdelrehman AS, Hussain MB. Histopathological findings in goiter: A review of 624 thyroidectomies. *Neuroendocrinology Letters*. 2015 Jan 1;36(1):48-52
19. Refeidi A, Al Shehri G, Al Ahmary A, Tahtouh M, AlSetei S, Al Ghamdi A, Mahfouz A, Abu Eshy S. Patterns of thyroid cancer in Southwestern Saudi Arabia. *Saudi Med J*. 2010 Nov 20;31(11):1238-41.
20. Saeed MI, Hassan AA, Butt ME, Baniyaseen KA, Siddiqui MI, Bogari NM, Al-Allaf FA, Taher MM. Pattern of thyroid lesions in western region of Saudi Arabia: A retrospective analysis and literature review. *Journal of clinical medicine research*. 2018 Feb;10(2):106.
21. Musani AM, Khan AF, Ashrafi KS, Jawaid I, Muger N, Malik S. Spectrum of thyroid disease presenting in ENT dept. Evaluation by FNAC *Pak J Otolaryngol*. 2010;26:74-5.

22. Hurtado-López LM, Basurto-Kuba E, de Oca-Durán ER, Pulido-Cejudo A, Vázquez-Ortega R, Athié-Gutiérrez C. Prevalence of thyroid nodules in the Valley of Mexico. *Cirugia y cirujanos*. 2011;79(2):114-7.
23. Ogbera AO, Kuku SF. Epidemiology of thyroid diseases in Africa. *Indian journal of endocrinology and metabolism*. 2011 Jul;15(Suppl2):S82.
24. Mansoor R, Rizvi SR, Huda ST, Khan C. Spectrum of thyroid diseases, an experience in the tertiary care and teaching hospital. *Ann Pak Inst Med Sci*. 2010;6:101-6.
25. Gamboa-Domínguez A, Lino-Silva S, Candanedo-González F, Medina-López E, Acuña-González D, Jacinto-Cortés I, González-Treviño O. Trends of thyroid pathology in a referral center: Steady prevalence of papillary thyroid carcinoma but goiter increase in thyroidectomies. *Revista de Investigación Clínica*. 2011;63(2):148-54.
26. Htwe TT, Hamdi MM, Swethadri GK, Wong JO, Soe MM, Abdullah MS. Incidence of thyroid malignancy among goitrous thyroid lesions from the Sarawak General Hospital 2000-2004
27. Wang K, Yang Y, Wu Y, Chen J, Zhang D, Liu C. The association of menstrual and reproductive factors with thyroid nodules in Chinese women older than 40 years of age. *Endocrine*. 2015 Mar;48(2):603-14
28. Larsen PR. , Thyroid physiology and diagnostic evaluation of patients with thyroid disorders. *Williams textbook of endocrinology*. 2003.
29. Bendoudia AF, Harir N, Diaf M, Belhandouze L, Sellam F, Moulessehoul S, Rih A. Clinical cytohistopathological study of benign thyroid disease in Sidi Bel Abbes region, Western Algeria. *The Egyptian Journal of Internal Medicine*. 2016 Mar;28(1):5-8.
30. Yan HX, Pang P, Wang FL, Tian W, Luo YK, Huang W, Yang GQ, Jin N, Zang L, Du J, Ba JM. Dynamic profile of differentiated thyroid cancer in male and female patients with thyroidectomy during 2000–2013 in China: a retrospective study. *Scientific reports*. 2017 Nov 20;7(1):1-8.
31. Ortega J, Sala C, Flor B, Lledo S. Efficacy and cost-effectiveness of the UltraCision® harmonic scalpel in thyroid surgery: an analysis of 200 cases in a randomized trial. *Journal of Laparoendoscopic & Advanced Surgical Techniques*. 2004 Feb 1;14(1):9-12
32. Kwong N, Medici M, Angell TE, Liu X, Marqusee E, Cibas ES, Krane JF, Barletta JA, Kim MI, Larsen PR, Alexander EK. The influence of patient age on thyroid nodule formation, multinodularity, and thyroid cancer risk. *The Journal of Clinical Endocrinology & Metabolism*. 2015 Dec 1;100(12):4434-40.