RESEARCH ARTICLE

INDONESIAN JOURNAL OF CANCER

Differences in Pre-Operative Mean Serum Concentration of Thyroid Stimulating Hormone (TSH) and Free Thyroxin (FT4) in Patients with Benign Thyroid Nodules and Thyroid Carcinoma at Sanglah General Hospital Denpasar

I Gusti Ayu Sri Mahendra Dewi [1*], Desak Putu Gayatri Saraswati Seputra [2]

[1] Anatomical Pathology Department, Faculty of Medicine, Udayana University - Sanglah Hospital, Denpasar, Bali, Indonesia
[2] Internal Medicine Department, Faculty of Medicine, Udayana University - Sanglah Hospital, Denpasar, Bali, Indonesia

ARTICLE INFO

Received : 07 December 2020
Reviewed : 21 May 2021
Accepted : 14 September 2021

Keywords:
free thyroxin, thyroid carcinoma, thyroid nodule, thyroid-stimulating hormone

*Corresponding author:
I Gusti Ayu Sri Mahendra Dewi
Anatomical Pathology Department, Faculty of Medicine, Udayana University - Sanglah Hospital, Denpasar, Bali, Indonesia
mahendradewi@rocketmail.com

ABSTRACT

Background: Thyroid Stimulating Hormone (TSH) and Free Thyroxin (FT4) concentration are currently highlighted in their relation to thyroid carcinoma development in thyroid nodule patients. This study aimed to identify the difference in the pre-operative mean serum concentration of TSH and FT4 in patients with benign thyroid nodules and thyroid carcinoma at Sanglah General Hospital Denpasar.

Methods: This study was a case-control study that involved 110 patients with thyroid nodules who underwent thyroidectomy at Sanglah General Hospital from January until December 2019, whose specimens were examined histopathologically at the Anatomical Pathology Laboratory of Sanglah General Hospital. Cases were patients with thyroid carcinoma. Controls were patients with benign thyroid nodules. The data were collected from medical records.

Results: Most subjects in the thyroid carcinoma group were female (72.7%). The thyroid carcinoma group had a higher mean age at the time of thyroidectomy (47.33 ± 13.4) compared to the benign thyroid nodule group (46.07 ± 12.5) ($p = 0.61$). Significant difference was found regarding the nodule size between the two groups ($p < 0.001$). There were no significant differences in terms of nodule lateralization ($p = 0.56$) and the number of nodules ($p = 0.58$). Papillary thyroid carcinoma was the most common type of thyroid carcinoma (89.1%). A significantly higher pre-operative mean serum TSH concentration was found in cases (1.0 ± 0.23 IU/mL) compared to controls (0.8 ± 0.23 IU/mL) ($p < 0.001$). The pre-operative mean serum FT4 concentration was significantly lower in cases (1.1 ± 0.25 IU/mL) compared to controls (1.2 ± 0.22 IU/mL) ($p = 0.006$). The optimal TSH and FT4 cut-off values for thyroid carcinoma were > 1.0 IU/mL (61% sensitivity, 71% specificity) and < 1.1 IU/mL (61% sensitivity, 51% specificity), respectively.

Conclusions: Higher pre-operative mean TSH concentration and lower mean FT4 concentration were found in patients with thyroid carcinoma. There were statistically significant differences between patients with thyroid carcinoma and benign thyroid nodules in terms of these two laboratory parameters.

INTRODUCTION

Thyroid nodules are a fairly common condition in clinical practice. Thyroid nodules are growths of cells or lumps in the thyroid gland, which differ in radiological appearances from the surrounding thyroid parenchyma [1,2]. Approximately 3% – 7% of the world's population has palpable thyroid nodules, and its prevalence may exceed 70% if screened via ultrasound [2,3,4].

Thyroid nodules are mostly benign, only 5% of the detected thyroid nodules are malignant [2,5]. However, it is very substantial in individuals with thyroid nodules to rule out the possibility of thyroid carcinoma [5]. The annual incidence of thyroid carcinoma is estimated to be 12.9 per 100,000 populations with a mortality rate of 0.5 per 100,000 populations per year [2]. Data on the prevalence of thyroid carcinoma in Indonesia is still not widely available.

Various factors including clinical factors, laboratory parameters, or other diagnostic workup features are known to be beneficial in predicting thyroid carcinoma. Laboratory assessment of thyroid function which comprises Thyroid Stimulating Hormone (TSH) and Free Thyroxin (FT4) concentration is currently highlighted in their application to stratify the risk of malignancy in patients with thyroid nodules. TSH has been shown to act as a growth factor for thyroid cells, which stimulates growth in both normal and neoplasm cells [3]. The role of TSH as a predictor of thyroid nodule malignancy has been evaluated by various studies in recent years. Since one research reported an increased risk of malignancy parallel to the elevation of serum TSH concentration, several authors have conducted similar studies investigating the difference between serum TSH concentration in benign thyroid nodules and thyroid carcinoma with conflicting results [6]. Previous studies have also shown inconsistent results regarding differences in FT4 concentration among patients with malignant and benign thyroid nodules [3,7,8].

Previous studies investigating the differences in TSH and FT4 concentration on the occurrence of thyroid carcinoma which showed contradictory results emphasized the need for additional evidence. The utilization of thyroid function laboratory parameters in predicting the malignant potential of thyroid nodules has not been fully explored and examined in Indonesian patients as limited previous literature can be found. Therefore, this study aimed to identify the difference in pre-operative mean serum concentration of TSH and FT4 in patients with benign thyroid nodules and thyroid carcinoma at Sanglah General Hospital Denpasar.

METHODS

This study was a case-control study to determine the difference in pre-operative mean serum concentration of TSH and FT4 in patients with benign thyroid nodules and thyroid carcinoma who underwent thyroidectomy at Sanglah General Hospital Denpasar. The study samples were patients with thyroid nodules who underwent thyroidectomy at Sanglah General Hospital from January 1 until December 31, 2019, whose specimens were examined histopathologically at the Anatomical Pathology Laboratory of Sanglah General Hospital.

The sample size was calculated using sample size formulation for case-control study or hypothesis testing for a difference in two population means, with type I error (α) of 5% (two-tailed hypothesis) and type II error (β) of 20%. The minimum sample size was 10 samples for each group. This study was initiated by identifying the patients with thyroid carcinoma as the case group and selecting patients with benign thyroid nodules as a control group afterward. Identification was made according to the histopathology result. Cases were selected by the total sampling method while controls were selected by randomization. The number of control randomization was in multiples of two and was obtained from the total number of patients with benign thyroid nodules (n = 121) divided by the number of samples needed. The ratio of case and control in this study was 1:1; each group consisted of 55 samples. The exclusion criteria were incomplete medical record data; histopathology results that could not determine the malignancy status of thyroid nodules or stated as unknown malignant potential; and patients receiving thyroid hormone replacement or suppressant therapy prior to thyroidectomy. The flow chart of sample selection is shown in **Figure 1**.

The data of histopathology results and preoperative serum concentration of TSH and FT4 were collected from medical records. Serum concentrations of TSH and FT4 were measured prior to thyroidectomy. Measurements were made using the Cobas 6000 Roche with Electrochemiluminescence Immunoassay Analyzer (ECLIA) method. TSH and FT4 concentrations were expressed in IU/mL. Additional data including gender, age, the number of nodules, nodule size, nodule

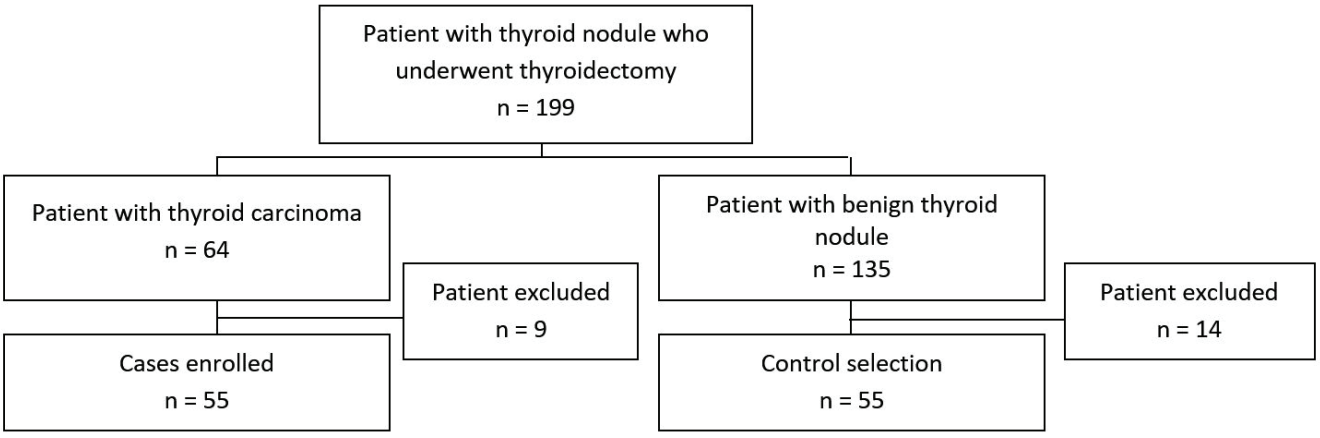

Figure 1. Flow chart of sample selection

P-ISSN: 1978-3744 E-ISSN: 2355-6811

lateralization, and histopathology type of thyroid carcinoma were also obtained. The number of nodules was later categorized into uninodular and multinodular. Nodule size was categorized into < 2 cm, 2–4 cm, and > 4 cm. Nodule lateralization was categorized into unilateral and bilateral. It was unilateral if it involved only the right lobe, left lobe, or isthmus and bilateral if it involved more than one of the previously mentioned.

Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) software for Windows version 21. Descriptive statistics were expressed in frequency and percentage. Determination of data normality was done by the Kolmogorov-Smirnov test. A homogeneity test was carried out with Levene's test. Unpaired t-test was used to determine the difference in the pre-operative mean serum concentration of TSH and FT4 between case and control groups. A Chi-square test was performed to assess differences in gender and characteristics of thyroid pathology (the number of nodules, nodule size, and nodule lateralization) between cases and controls. The age difference between case and control groups was evaluated using unpaired t-test. TSH and FT4 cut-off values for thyroid carcinoma prediction were determined by receiver operating characteristic (ROC) curve analysis. Statistical significance was defined as $p < 0.05$.

RESULTS

A total of nine patients from the case group were excluded. Thyroid carcinoma patients with incomplete medical record data and patients receiving thyroid hormone replacement or suppressant therapy prior to thyroidectomy were not included in the study. **Table 1** shows gender, age, and the characteristics of thyroid pathology of the study population. Most subjects in both the thyroid carcinoma group and the benign thyroid nodule group were female. There was no significant difference in gender between the two groups ($p = 0.36$). Patients with thyroid carcinoma had a higher mean age at the time of thyroidectomy (47.33 ± 13.4) compared to patients with benign thyroid nodules (46.07 ± 12.5); however, this difference was not statistically significant ($p = 0.61$).

Patients with thyroid carcinoma had a higher proportion of nodules sized less than 2 cm (43.6%) while the lesions of the benign thyroid nodule group were mostly larger than 4 cm (96.4%). A significant difference was found between the two groups ($p < 0.001$). There were no significant differences in terms of nodule lateralization and the number of nodules.

Papillary thyroid carcinoma was the most common type of thyroid carcinoma in the study population (89.1%). Medullary thyroid carcinoma was not found in this study. Histopathology types of thyroid carcinoma are shown in **Table 2**.

This study found a higher pre-operative mean serum TSH concentration in thyroid carcinoma patients (1.0 ± 0.23 IU/mL) compared to benign thyroid nodule patients (0.8 ± 0.23 IU/mL) with a significant result ($p < 0.001$). A significant difference in the pre-operative mean serum FT4 concentration between cases and controls was also noted ($p = 0.006$). The mean FT4 concentration was lower in the thyroid carcinoma group (1.1 ± 0.25 IU/mL) compared to that in the benign thyroid nodule group (1.2 ± 0.22 IU/mL) (**Figure 2**).

ROC curve analyses were performed to determine the optimal TSH and FT4 concentration for thyroid carcinoma prediction. Areas under the curve (AUC) were 72% (95% CI 0.63–0.82, $p < 0.001$) and 62% (95% CI 0.51–0.72, $p = 0.02$) for TSH and FT4, respectively. It was found that 1.0 IU/mL was the optimal TSH cut-off value for thyroid carcinoma with a sensitivity of 61% and specificity of 71%. A level of less than 1.1 IU/mL for FT4 showed a sensitivity of 61% and specificity of 51% for predicting thyroid carcinoma (**Figure 3**).

Table 1. Characteristics of thyroid patients in case and control group

Variable	Case	Control	p
Gender [n (%)]			
Male	15 (27.3)	11 (20)	0.36
Female	40 (72.7)	44 (80)	
Mean age (mean ± SD)	47.33 ± 13.4	46.07 ± 12.5	0.61
Nodule size			<0.01
< 2 cm	24 (43.6%)	0 (0.0%)	
2–4 cm	10 (18.2%)	2 (3.6%)	
> 4 cm	21 (38.2%)	53 (96.4%)	
Nodule lateralization			0.56
Unilateral	24 (43.6%)	21 (38.2)	
Bilateral	31 (56.4%)	34 (61.8)	
Number of nodule			0.58
Uninodular	9 (16.4)	7 (12.7)	
Multinodular	46 (83.6)	48 (87.3)	

Table 2. Histopathology types of thyroid carcinoma

Histopathology types	N	%
Papillary thyroid carcinoma	49	89.1
Follicular thyroid carcinoma	4	7.3
Anaplastic thyroid carcinoma	2	3.6

P-ISSN: 1978-3744 E-ISSN: 2355-6811

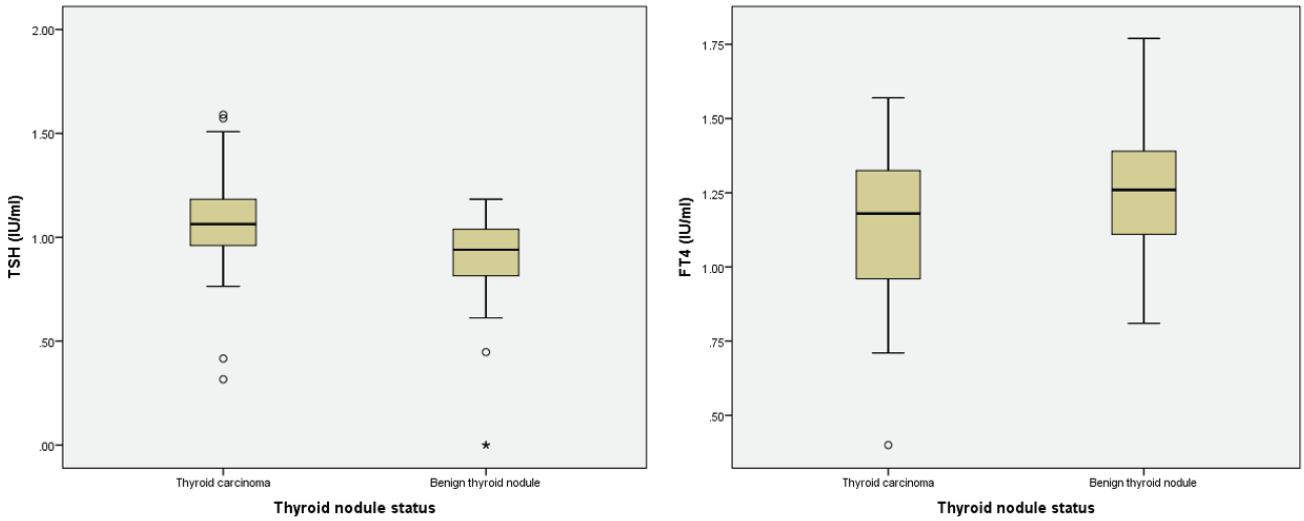

Figure 2. Level of pre-operative TSH and FT4 in subjects with thyroid carcinoma compared to benign thyroid nodules.

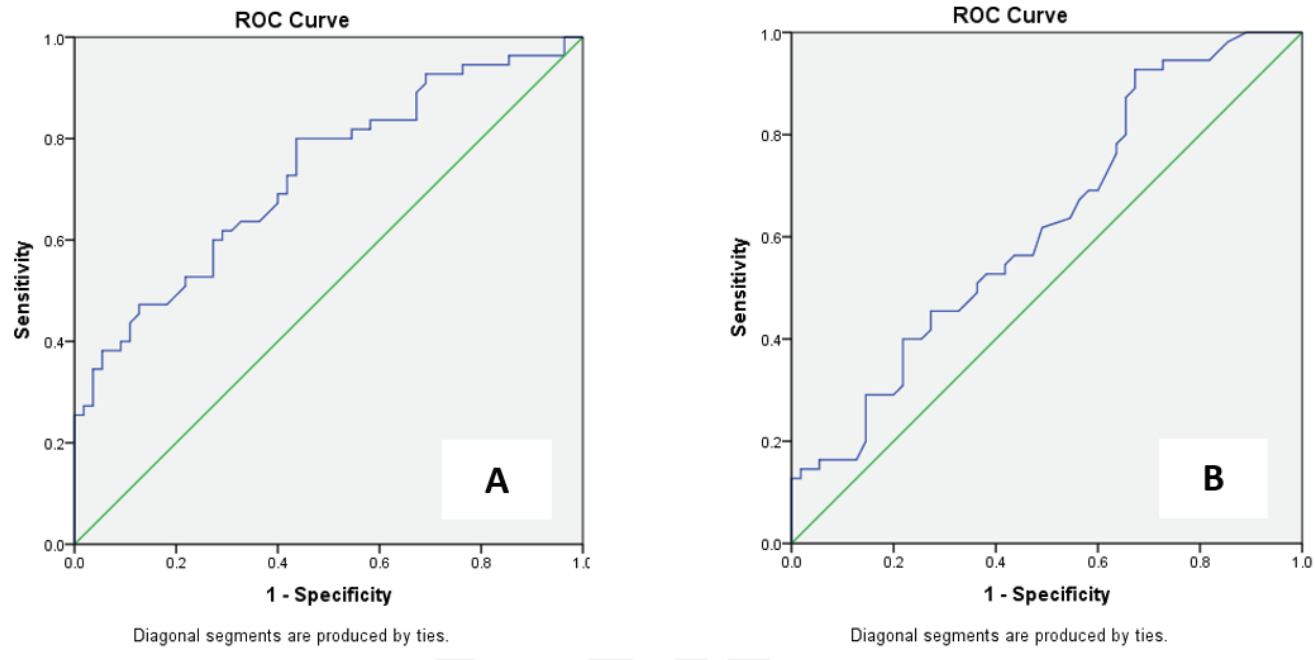

Figure 3. ROC curve for thyroid carcinoma prediction based on pre-operative TSH level (A) and FT4 level (B).

DISCUSSION

Serum TSH concentration has been stated in various studies as an independent predictor for thyroid carcinoma [7]. Epidemiological studies have shown a strong association between serum TSH levels and the risk of malignancy in thyroid nodules. Elevated TSH levels in previous clinical studies were said to be associated with a higher incidence of thyroid cancer in patients with nodular thyroid disease [9]. The risk for developing advanced thyroid carcinoma is also increased in patients with higher TSH levels [10].

This study found a higher pre-operative mean serum concentration of TSH in patients with thyroid carcinoma (1.0 ± 0.23 IU/mL) compared to patients with benign thyroid nodules (0.8 ± 0.23 IU/mL). This difference was found to be significant ($p < 0.001$). A statistically significant difference in TSH concentration between patients with malignant and benign nodules was also found in other studies [7,8]. TSH concentrations were found to be significantly higher in patients with well-differentiated thyroid carcinoma (2.08 ± 2.1 mIU/L) compared to patients with benign thyroid disease (1.36 ± 1.62 mIU/L) [11]. Another study found that the mean

pre-operative TSH concentration was significantly higher in patients with well-differentiated thyroid carcinoma (2.10 ± 0.07 mIU/L) compared to patients with benign nodules (1.86 ± 0.04 mIU/L) [3].

The thyroid gland, anterior pituitary gland, and hypothalamus form a complex regulated system, known as the hypothalamus-pituitary-thyroid axis. Thyrotropin-releasing hormone (TRH) from the hypothalamus activates the pituitary gland to synthesize and secrete thyroid-stimulating hormone (TSH) and subsequently stimulates the thyroid gland to produce thyroid hormones. Tetraiodothyronine (T4) is the main hormone synthesized in the thyroid gland, which will then be catalyzed into Triiodothyronine (T3) by specific iodothyronine deiodinase [12].

TSH, which acts via the TSH receptor, is the main stimulator of thyroid cell growth and function post-differentiation [6]. TSH has been shown to stimulate the growth of both normal and neoplasm cells [3]. Stimulation by TSH in the thyroid can cause glandular hypertrophy, which in turn may lead to the development of malignancy. However, the mechanism of thyroid carcinoma as a result of excess TSH is not clearly established yet [13]. There is strong evidence that TSH regulates thyroid cells to undergo cell cycle progression in response to growth factors, especially Insulin-like Growth Factor I (IGF-I) or insulin. This can be seen from the high expressions of TSH receptors in well-differentiated thyroid carcinomas [14].

Another study reported that lower FT4 and higher TSH even within a normal range were correlated with thyroid cancer. A small alteration in FT4 concentration can lead to consequential changes in serum TSH because of their inverse logarithmic relationship [15]. This study found a significant difference in pre-operative serum concentration of FT4 between cases and controls (p = 0.006). Mean FT4 concentration was lower in the thyroid carcinoma group (1.1 ± 0.25 IU/mL) than in the benign thyroid nodule group (1.2 ± 0.22 IU/mL). This finding is similar to the results of a previous study highlighting a significant difference in FT4 levels between patients with thyroid nodules that are malignant and benign in nature [7,8]. A study conducted in 2020 also found a significantly lower level of FT4 in malignant thyroid nodule patients [8]. However, these results contradict other studies which compared FT4 levels of patients with well-differentiated thyroid carcinoma and patients with benign thyroid enlargement, where there was no significant difference found between the two groups (p = 0.91) [3].

TSH showed a sensitivity of 61% and specificity of 71% at a cut-off of 1.0 IU/mL determined with the ROC curve analysis in this study, which showed an AUC of 0.72 (95% CI 0.63–0.82, p < 0.001). Meanwhile, the ROC curve analysis of FT4 found that a level of less than 1.1 IU/mL showed a sensitivity of 61% and specificity of 51% for predicting thyroid carcinoma, with an AUC of 0.62 (95% CI 0.51–0.72, p = 0.02).

This study also noted female predominance in thyroid carcinoma patients and higher mean age at the time of thyroidectomy (47.33 ± 13.4) compared to benign thyroid nodule patients although this difference was not statistically significant. Thyroid carcinoma has been known to be more common in women than men with a ratio of 3:1 and occurs in all age groups, but it is more frequently found in adults aged 45 to 54 years with a mean age of 50 years at diagnosis [2]. Papillary thyroid carcinoma was the most common type of thyroid carcinoma found in the sample population. This finding is consistent with previous literature. Papillary thyroid carcinoma is the most prevalent type of thyroid carcinoma, accounting for 70–80% of all thyroid carcinomas [2].

In summary, a consistent association and higher TSH levels in thyroid carcinoma have been found in most studies. However, the lack of studies intended to determine the optimal TSH cut-off value has limited the use of serum TSH levels as a predictor of thyroid malignancy. Currently, there is no optimal TSH threshold value to predict the risk of thyroid carcinoma [6]. The findings of this study may have a notable clinical impact since they indicate that thyroid function laboratory assessment of TSH and FT4 may assist the diagnosis strategy and risk stratification of thyroid carcinoma. The concentration of T3, another parameter of thyroid function, however, cannot be included in this study as it is not regularly checked pre-operatively in patients with thyroid nodules, and no report was available in the medical records of Sanglah General Hospital. It is important to note that serum TSH and FT4 concentration could not be used solely and should be combined with other patient characteristics for decision-making purposes. Given the paucity of evidence, further research is required to establish the role of TSH and FT4 in the development and progression of thyroid carcinoma.

CONCLUSIONS

Thyroid carcinoma is a potentially fatal condition with an increasing incidence. We found a higher pre-operative mean serum TSH concentration as well as a lower pre-operative mean serum FT4 concentration in patients with thyroid carcinoma compared to those with benign thyroid nodules. There were significant differences between patients with thyroid carcinoma and benign thyroid nodules in terms of these two laboratory parameters. Further research is needed to determine the role of TSH and FT4 in thyroid carcinoma, the underlying mechanism, and the optimal TSH and FT4 cut-off values for the utilization of their concentration as an acceptable predictor of thyroid malignancy.

P-ISSN: 1978-3744 E-ISSN: 2355-6811

DECLARATIONS

Ethics Approval

This study has been approved by the Health Research Ethics Commission of Medical Faculty Udayana University/Sanglah General Hospital under reference number 2195/UN14.2.2.VII.14/LT/2020.

Competing of Interest

The authors declare no competing interest in this study.

Acknowledgment

The authors wish to thank the Head of Anatomical Pathology Laboratory of Sanglah Hospital Denpasar and all staff that contribute to the completion of this research article.

REFERENCES

1. Haugen BR, Alexander EK, Bible KC, et al. 2015 2015 American Thyroid Association Management Guidelines for Adult Patients with Thyroid Nodules and Differentiated Thyroid Cancer: The American Thyroid Association Guidelines Task Force on Thyroid Nodules and Differentiated Thyroid Cancer. Thyroid. 2016;26(1):1–133.
2. Nguyen QT, Lee EJ, Huang MG, et al. Diagnosis and treatment of patients with thyroid cancer. Am Health Drug Benefits. 2015;8(1):30–40.
3. He L, Zeng T, Pu L, et al. Thyroid hormones, autoantibodies, ultrasonography, and clinical parameters for predicting thyroid cancer. Int J Endocrinol. 2016:1–12.
4. Popoveniuc G, Jonklaas J. Thyroid nodule. Med Clin North Am. 2012;96(2):329–49.
5. Rosario PW, Ward LS, Carvalho GA, et al. Thyroid nodules and differentiated thyroid cancer: update on the Brazilian consensus. Arq Bras Endocrinol Metab. 2013;57(4):240–64.
6. Golbert L, Cristo AP, Faccin CS, et al. Serum TSH levels as a predictor of malignancy in thyroid nodules: A prospective study. PLoS ONE. 2017;12(11):1–12.
7. Rageh TM, Abdou AG, Elkhouly EA, et al. Preoperative significance of thyroglobulin, thyroid stimulating hormone and thyroglobulin antibody in differentiated papillary thyroid carcinoma. Int Surg J. 2019;6(12):4229–37.
8. Rianto BU, Wibowo AS, Herdini C. The difference in thyroid stimulating hormone levels between differentiated carcinoma and benign enlargement. Int Arch Otorhinolaryngol. 2020;24(1):74–9.
9. Ariannia A, Mehrjerdian M, Jalali M. Higher TSH level is associated with increased risk of malignancy in thyroid nodules. J Pioneer Med Sci.2020;9(1):8–10.
10. Fiore E, Rago T, Provenzale MA, et al. Lower levels of TSH are associated with a lower risk of papillary thyroid cancer in patients with thyroid nodular disease: thyroid autonomy may play a protective role. Endocr Relat Cancer. 2009;16:1251–60.
11. Fiore E, Vitti P. Serum TSH and risk of papillary thyroid cancer in nodular thyroid disease. J Clin Endocrinol Metab. 2012;97(4):1134–45.
12. Krashin E, Piekiełko-Witkowska A, Ellis M, Ashur-Fabian O. Thyroid hormones and cancer: a comprehensive review of preclinical and clinical studies. Front Endocrinol. 2019;10(59):1–23.
13. Nayci AE, Arikan S, Akkus O, et al. Incidence of thyroid carcinoma among patients with hyper and hypothyroidism. Int Surg. 2017;102:328–333.
14. Bonnefond S, Davies TF. Thyroid cancer—risks and causes. Oncology & Hematology Review. 2014;10(2):144–51.
15. Gul K, Ozdemir D, Dirikoc A, et al. Are endogenously lower serum thyroid hormones, new predictors, for thyroid malignancy in addition to higher serum thyrotropin?. Endocr. 2010;37:253–60.