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Role of TSHs and FT4 Levels in Thyroid Nodule Histopathology

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ABSTRACT

Thyroid nodules are a common clinical finding, although only a minority are malignant. Thyroid stimulating hormone (TSH) and free thyroxine (FT4) have been investigated as potential biomarkers for predicting thyroid malignancy, yet previous studies have shown inconsistent results. This study aimed to analyse the association between TSHs and FT4 levels and histopathological outcomes in patients with thyroid nodules undergoing surgery. This analytical observational study used a cross-sectional design with retrospective medical record data from patients who underwent thyroid surgery at Wangaya Regional General Hospital during 2021–2025. Total sampling was applied based on the inclusion criteria, resulting in 121 patients with complete histopathological, TSHs, and FT4 data. The association between histopathological findings and hormone levels was analysed using chi-square test and logistic regression. Most patients were female (84.3%), and benign lesions predominated (71.1%). Higher TSHs levels were more frequent in borderline (66.7%) and malignant (56.3%) groups than in benign lesions (46.5%), but the association was not statistically significant (p=0.535). Lower FT4 levels were also more common in borderline (66.7%) and malignant groups (62.5%) than in benign lesions (48.8%), without significant association (p=0.367). TSHs and FT4 levels were not significantly associated with histopathological outcomes in patients undergoing thyroid surgery. These parameters should not be used as single predictors of thyroid malignancy.

Keywords : FT4, histopathology, thyroid cancer, thyroid nodules, TSH.

INTRODUCTION

Thyroid cancer is the most common endocrine malignancy worldwide, with an incidence that has continued to rise over recent decades (Forma et al., 2025). This increase has been attributed to several factors, including improved detection through advances in diagnostic technology, environmental exposure, and lifestyle-related changes that may contribute to thyroid carcinogenesis (Bray et al., 2024; Larcher de Almeida et al., 2021). Epidemiologically, thyroid cancer occurs more frequently in women than in men, with an approximate ratio of 3:1, and is generally diagnosed during adulthood (Siegel et al., 2020).

Thyroid nodules are common clinical findings, with a prevalence of 3–7% on palpation and more than 70% when assessed by ultrasonography (Durante et al., 2023; Sakajiri et al., 2022). Although most thyroid nodules are benign, approximately 5% may progress to malignancy, making risk evaluation essential in determining appropriate management. Identifying factors that can distinguish benign from malignant nodules is therefore crucial to guide treatment decisions and avoid unnecessary invasive procedures (Juweid et al., 2021; Mahendra Dewi & Saraswati Seputra, 2022).

Thyroid function tests, particularly thyroid stimulating hormone (TSH) and free thyroxine (FT4), have been widely investigated as potential parameters for assessing the risk of malignancy in thyroid nodules. Biologically, TSH is known to act as a growth factor that stimulates thyroid cell proliferation and may contribute to neoplastic (Mahendra Dewi & Saraswati Seputra, 2022; Trimboli et al., 2024). Several studies have reported that elevated TSH levels are associated with a higher risk of thyroid cancer, while lower FT4 levels have been observed in patients with malignant lesions (Trimboli et al., 2024; Xu et al., 2023).

However, findings regarding the association of TSH and FT4 with thyroid malignancy remain inconsistent. Some studies found no significant differences in thyroid hormone levels between benign and malignant nodules, indicating that the role of these parameters as predictors of malignancy remains debatable. These variations may be influenced by differences in population characteristics, study methods, and sample size (Alexander et al., 2022; Su et al., 2020).

Moreover, recent evidence suggests that the relationship between thyroid hormones and clinical outcomes in thyroid cancer is not always linear. Ghosh et al. (2025) reported that elevated FT4 levels were not associated with progression-free survival in patients with intermediate- and high-risk thyroid cancer ($p=0.69$), despite the theoretical role of thyroid hormones in tumour growth. This finding highlights a gap between biological mechanisms and currently available clinical evidence.

Thyroid cancer itself is a multifactorial disease influenced by genetic, hormonal, environmental, and chronic inflammatory processes. This complexity suggests that the relationship between laboratory parameters and malignancy cannot be explained in a simplistic manner, and further clinical research is required to clarify this association (Forma et al., 2025; Singh et al., 2021).

In Indonesia, data on the relationship between TSH and FT4 levels and thyroid malignancy remain limited. A study by Mahendra Dewi & Saraswati Seputra (2022) at Sanglah General Hospital, Denpasar, demonstrated significant differences in TSH and FT4 levels between benign and malignant thyroid nodules. However, these findings still require confirmation in different populations and over a longer observation period.

Based on this background, the present study was conducted to analyse the association between histopathological findings and TSHs and FT4 levels in patients undergoing thyroid surgery at Wangaya Regional General Hospital during 2021–2025. This study is expected to provide additional

scientific evidence regarding the role of thyroid hormone parameters in assessing the malignant potential of thyroid nodules and to support more accurate clinical decision-making.

METHODS

This study was an analytical observational study with a cross-sectional design using retrospective medical record data. The study was conducted at Wangaya Regional General Hospital, Denpasar, Bali, and included patients who underwent thyroid surgery from January 2021 to December 2025.

The target population comprised all patients who underwent thyroid surgical procedures, including lobectomy, isthmolobectomy, and total thyroidectomy, during the study period. From an initial population of 254 patients, those with complete histopathological examination and preoperative laboratory results of TSHs and FT4 were included. Patients with incomplete TSHs and/or FT4 data were excluded. After the selection process, 121 patients fulfilled the eligibility criteria and were included in the final analysis. Total sampling was used.

Data were collected retrospectively from medical records. The variables included demographic characteristics, namely age and sex, histopathological findings categorised as benign, borderline, and malignant, as well as laboratory parameters consisting of TSHs and FT4 levels. The collected data were edited, coded, entered into a statistical software package, and cleaned before analysis.

Univariate analysis was performed to describe the characteristics of the study subjects. Categorical variables were presented as frequencies and percentages, whereas numerical variables were presented as mean, standard deviation, minimum, and maximum values. Bivariate analysis was conducted using chi-square test through cross-tabulation to assess the association between histopathological outcomes and TSHs and FT4 levels. Logistic regression analysis was further performed to estimate odds ratios (ORs) with 95% confidence intervals (95% CIs). A p-value of less than 0.05 was considered statistically significant.

This study received ethical approval from the Health Research Ethics Committee of RSUD Wangaya Kota Denpasar with ethical approval number 000.9.2/217/RSUDW. As this study used secondary data obtained from medical records, informed consent was waived by the ethics committee. Patient confidentiality was strictly maintained throughout the study by removing all personal identifiers before data collection and analysis. All data were anonymised and used solely for research purposes, and access to the dataset was restricted to the research team.

RESULTS AND DISCUSSION

The characteristics of the study subjects are presented in Table 1, while the associations between histopathological outcomes and TSHs and FT4 levels are presented in Table 2 and Table 3, respectively.

Table 1. Characteristics of patients undergoing thyroid surgery at Wangaya Regional General Hospital in 2021–2025 (n=121).

Variable	Frequency (n)	Percentage (%)
Sex		
Male	19	15.7
Female	102	84.3
Histopathology		
Benign	86	71.1
Borderline	3	2.5
Malignant	32	26.4
FT4 level		
1.23–2.06	57	47.1
0.44–1.22	64	52.9
TSHs level		
1.00–41.92	60	49.6
0.01–0.99	61	50.4

Mean FT4 level was 1.23 ± 0.28 with a range of 0.44–2.06, while mean TSHs level was 1.87 ± 4.79 with a range of 0.01–41.92. Mean age was 47.13 ± 11.84 years, ranging from 19 to 75 years. The present study showed that most patients who underwent thyroid surgery were female. In addition, benign lesions accounted for the largest proportion of histopathological outcomes in this study. The distribution of histopathological outcomes is further illustrated in Figure 1, showing that benign lesions constituted the largest proportion, followed by malignant and borderline lesions.

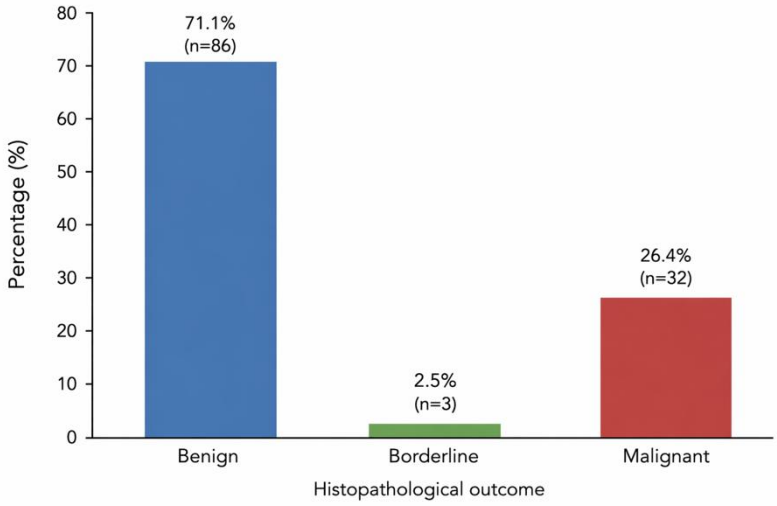

Figure 1. Distribution of histopathological outcomes in patients undergoing thyroid surgery at Wangaya Regional General Hospital, 2021–2025.

The present study showed that most patients who underwent thyroid surgery were female. This finding is consistent with the known epidemiological pattern of thyroid nodules and thyroid cancer, which are more common in women. Hormonal influences, particularly oestrogen-related mechanisms, have been suggested to play a role in thyroid cell proliferation and carcinogenesis. In addition, benign lesions accounted for the largest proportion of histopathological outcomes in this study. This result is in line with the general understanding that most thyroid nodules are non-malignant, even though surgery may still be indicated because of nodule size, compressive symptoms, indeterminate findings, or suspicion of malignancy.

Table 2. Association between histopathological outcomes and TSHs levels in patients undergoing thyroid surgery (n=121).

Histopathology	TSHs 1.00–41.92 n (%)	TSHs 0.01–0.99 n (%)	OR	95% CI	p-value
Borderline	2 (66.7)	1 (33.3)	0.435	0.038–4.976	0.503
Malignant	18 (56.3)	14 (43.8)	0.676	0.299–1.531	0.348
Benign	40 (46.5)	46 (53.5)	Ref	–	–

As shown in Table 2, the proportion of higher TSHs levels was greater in the borderline and malignant groups than in the benign group. Descriptively, this pattern may suggest a tendency toward higher TSHs values in lesions with greater malignant potential. This observation is biologically plausible, considering that TSH has been proposed to act as a growth-promoting factor in thyroid tissue.

Despite this descriptive trend, the association was not statistically significant. Logistic regression analysis showed that neither the borderline nor malignant group had significantly increased odds compared with the benign group. The wide confidence interval in the borderline category indicates substantial variability and reflects the small number of subjects in that group. Therefore, although higher TSHs appeared more common in lesions with higher malignant potential, the current data do not support TSHs as an independent predictor of histopathological malignancy.

These findings differ from some earlier studies that reported a significant relationship between higher serum TSH and thyroid cancer risk. Nevertheless, the present results are consistent with other reports that failed to identify a significant association. Differences across studies may be explained by heterogeneity in patient characteristics, sample distribution, hormone categorisation, and study methodology. Furthermore, thyroid malignancy is influenced by a complex interaction of molecular and environmental factors, which may limit the predictive value of a single hormonal parameter.

As presented in Table 3, lower FT4 levels were proportionally more frequent in borderline and malignant lesions than in benign lesions. Descriptively, this pattern suggests that relatively lower FT4 values

may be associated with lesions of greater malignant potential. However, this trend was not statistically significant in logistic regression analysis.

Table 3. Association between histopathological outcomes and FT4 levels in patients undergoing thyroid surgery (n=121).

Histopathology	FT4 1.23–2.06 n (%)	FT4 0.44–1.22 n (%)	OR	95% CI	p-value
Borderline	1 (33.3)	2 (66.7)	2.095	0.183–23.977	0.552
Malignant	12 (37.5)	20 (62.5)	1.746	0.760–4.009	0.189
Benign	44 (51.2)	42 (48.8)	Ref	–	–

The comparative proportions of TSHs and FT4 categories across benign, borderline, and malignant histopathological groups are presented in Figure 2 to facilitate visual interpretation of the findings.

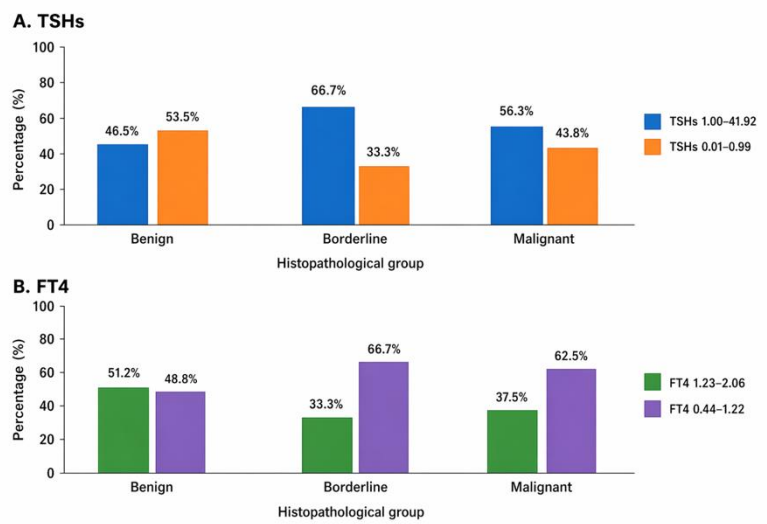

Figure 2. Comparison of TSHs and FT4 category proportions across benign, borderline, and malignant histopathological groups.

This study showed that most patients undergoing thyroid surgery were female (84.3%). This finding is consistent with previous studies reporting that thyroid cancer occurs more frequently in women than in men, with an approximate ratio of 3:1 (Forma et al., 2025; Siegel et al., 2020). This difference may be related to hormonal influences, particularly estrogen, which may affect thyroid cell proliferation and contribute to carcinogenesis (Liu et al., 2021).

The histopathological findings in this study were predominantly benign (71.1%), followed by malignant (26.4%) and borderline lesions (2.5%). This result is in line with the literature indicating that most thyroid nodules are benign and that only around 5–15% are malignant. The high proportion of benign lesions in the present study may reflect the clinical tendency to perform surgery not only in patients with suspicion of malignancy, but also in those with other indications such as large nodules or compressive symptoms (Durante et al., 2023; Juweid et al., 2021; Mahendra Dewi & Saraswati Seputra, 2022).

The mean age of patients in this study was 47.13 ± 11.84 years, indicating that most patients were in the adult age group. This finding is consistent with previous reports showing that thyroid cancer is commonly diagnosed between 30 and 50 years of age (Boucai et al., 2024; Forma et al., 2025). Age is also an important prognostic factor in thyroid cancer, with older age often being associated with poorer outcomes (Singh et al., 2021).

In terms of laboratory parameters, the mean FT4 level was 1.23 ± 0.28, with a relatively balanced distribution between the two categories. Meanwhile, the mean TSHs level was 1.87 ± 4.79, with a wide range of values. This broad variation in TSHs suggests heterogeneity in thyroid functional status among patients, which may be influenced by hormonal status, prior treatment, or other accompanying clinical conditions. Theoretically, TSH acts as a growth factor that stimulates thyroid cell proliferation, and elevated TSH levels have therefore often been associated with a higher risk of malignancy (Trimboli et al., 2024; Xu et al., 2023). In contrast, FT4, as an active thyroid hormone, has also been suggested to play a role in the regulation of cell growth, although its mechanism appears to be more complex and has not been fully elucidated (Ghosh et al., 2025). However, the descriptive distribution of FT4 and TSHs levels in this study did not show striking differences between histopathological groups. This finding suggests that thyroid hormone parameters alone may not be sufficient to clearly reflect histopathological behaviour. It is also consistent with several previous studies reporting that the relationship between TSH, FT4, and thyroid malignancy is not always consistent (Alexander et al., 2022; Su et al., 2020).

In addition, the complexity of thyroid cancer pathogenesis, which involves genetic, environmental, and molecular factors, may also influence the relationship between laboratory parameters and malignancy. Genetic alterations such as BRAF, RAS, and RET/PTC mutations are known to play important roles in thyroid cancer development, and these mechanisms may be more dominant determinants than hormonal parameters alone (Singh et al., 2021; Vija, 2025).

Based on the findings presented in Table 2, the proportion of TSHs levels of 1.00–41.92 appeared higher in the borderline (66.7%) and malignant (56.3%) groups than in the benign group (46.5%). Descriptively, this finding suggests a tendency toward higher TSH levels in lesions with greater malignant potential. This observation is in accordance with the biological concept that TSH acts as a growth factor capable of stimulating proliferation of thyroid cells, including neoplastic cells .

However, logistic regression analysis showed that this association was not statistically significant. The odds ratio for the borderline group was 0.435 (95% CI: 0.038–4.976; p=0.503), while the malignant group had an odds ratio of 0.676 (95% CI: 0.299–1.531; p=0.348), indicating no significant increase in risk compared with the benign group as the reference category. Moreover, the wide confidence interval, especially in the borderline group, suggests substantial variability in the data and the possibility of insufficient sample size in that category.

These results differ from several previous studies reporting a significant relationship between elevated TSH levels and the risk of thyroid malignancy Vinod et al. (2022) and K. Alaraifi et al. (2023) found that higher

TSH levels were associated with an increased risk of thyroid cancer. In Indonesia, Mahendra Dewi & Saraswati Seputra (2022) also reported a significant difference in TSH levels between benign and malignant thyroid nodules. On the other hand, the present findings are in agreement with other studies showing no significant relationship between TSH levels and thyroid malignancy. Cappelli et al. (2020) and Fan et al. (2024) reported that TSH could not always be used as an independent predictor of malignant thyroid nodules. Differences among studies may be explained by variations in population characteristics, research methods, and sample distribution in each histopathological group.

The absence of a significant association in this study may be explained by several factors. First, thyroid cancer is a multifactorial disease influenced by genetic, molecular, and environmental factors, which limits the role of TSH as a single predictive parameter (Singh et al., 2021; Vija, 2025). Second, the wide variability in TSH levels among study subjects may have contributed to the lack of statistical significance. Third, the relatively small sample size in the borderline group may have reduced the statistical power of the analysis. In addition, preoperative clinical conditions, such as hormone therapy, thyroid functional status, and the timing of laboratory examination, may also influence the measured TSH level. These factors may act as confounders that are difficult to control in a retrospective medical-record-based study.

Based on the findings presented in Table 3, the proportion of FT4 levels of 0.44–1.22 was higher in the malignant (62.5%) and borderline (66.7%) groups than in the benign group (48.8%). Descriptively, this suggests that lower FT4 levels were more frequently observed in lesions with greater malignant potential. This finding is consistent with several previous studies reporting that patients with thyroid cancer tend to have lower FT4 levels than those with benign nodules (Mahendra Dewi & Saraswati Seputra, 2022).

Nevertheless, logistic regression analysis in this study did not demonstrate a statistically significant association. The borderline group had an odds ratio of 2.095 (95% CI: 0.183–23.977; p=0.552), whereas the malignant group had an odds ratio of 1.746 (95% CI: 0.760–4.009; p=0.189), indicating no significant increase in risk compared with the benign group as the reference. The wide confidence intervals, particularly in the borderline group, again suggest high variability and limited sample size.

These findings differ from several earlier studies showing an association between FT4 levels and thyroid malignancy. Zhang et al. (2025) reported that lower FT4 levels were associated with a higher risk of thyroid cancer, while Trimboli et al. (2024) suggested that changes in thyroid hormone parameters may play a role in carcinogenesis. Mahendra Dewi & Saraswati Seputra (2022) also found a significant difference in FT4 levels between benign and malignant thyroid nodules in an Indonesian population. Conversely, the results of the present study are consistent with reports indicating that FT4 is not always related to thyroid cancer outcomes. Ghosh et al. (2025) demonstrated that FT4 levels were not associated with progression-free survival in patients with intermediate- and high-risk thyroid cancer. Other studies have likewise reported that the role of FT4 as a predictor of malignancy remains inconsistent and may vary across populations (Kara et al., 2026; Wang et al., 2022).

The absence of a significant association indicates that FT4 alone may not adequately differentiate benign from malignant thyroid lesions in surgical patients. Although several previous studies have suggested that lower FT4 levels are more frequently observed in malignant nodules, the available evidence remains inconsistent across different populations and study settings (Ghosh et al., 2025; Kara et al., 2026; Mahendra Dewi & Saraswati Seputra, 2022; Wang et al., 2022; Zhang et al., 2025). In the present study, the lack of statistical significance may have been influenced by the limited sample size, particularly in the borderline group, as well as by the retrospective nature of the data collection.

Overall, the findings of this study suggest that thyroid hormone parameters should be interpreted cautiously. While TSHs and FT4 may reflect thyroid functional status, histopathological behaviour is likely to be determined by broader biological mechanisms, including genetic alterations, molecular signalling pathways, and interactions within the local tumour microenvironment (Forma et al., 2025; Vija, 2025). Therefore, reliance on TSHs and FT4 as stand-alone markers of malignancy is not justified.

This study has several limitations that should be considered in interpreting the findings. Its retrospective design, based on medical records, may be affected by limitations in data completeness and accuracy, and it does not allow full control of potential confounding factors such as previous thyroid hormone therapy, preoperative thyroid functional status, and other clinical conditions that may influence TSHs and FT4 levels. In addition, the relatively small number of borderline cases may have reduced the statistical power of the analysis and contributed to wide confidence intervals. The exclusion of a number of patients due to unavailable TSHs and FT4 data may also have introduced selection bias. Variability in laboratory methods, including the possibility that some tests were performed outside the hospital, may have further affected result consistency. Therefore, these findings should be interpreted with caution and require confirmation through prospective studies with larger sample sizes.

CONCLUSION

TSHs and FT4 levels were not significantly associated with histopathological outcomes in patients with thyroid nodules undergoing surgery. Although higher TSHs and lower FT4 tended to be observed in lesions with greater malignant potential, these parameters were not sufficient to serve as independent predictors of malignancy. This study was limited by its retrospective design, dependence on the completeness and accuracy of medical records, inability to fully control potential confounding factors, relatively small number of borderline cases, and possible selection bias due to incomplete hormonal data. Therefore, future research should use prospective designs with larger and more balanced samples, while also integrating hormonal, clinical, radiological, cytological, and molecular parameters to develop a more accurate predictive model for thyroid malignancy.

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