

# Clinicopathological Profile of Graves' Disease Patients At Dr. Soetomo General Hospital From January 2016 to December 2020

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## Abstract

**Background:** Graves' disease is an autoimmune disorder that is the primary trigger for excessive thyroid hormone secretion. It has three main clinical characteristics: enlargement of the thyroid gland, protrusion of the eyes (ophthalmopathy), and skin lesions (dermopathy). Laboratory examination typically reveals decreased TSH, increased FT3 and FT4, and elevated TSH receptor antibodies (TRAb). **Objective:** To evaluate the clinical, laboratory, and anatomical pathology profiles of Graves' disease patients at Dr. Soetomo General Hospital from January 2016 to December 2020. **Methods:** This retrospective observational study utilized the medical records of Graves' disease patients at the Integrated Endocrinology Service and Anatomical Pathology Laboratory of Dr. Soetomo General Hospital, spanning from January 2016 to December 2020. The study evaluated patient profiles including age, gender, clinical symptoms, TSH, FT4, total T3, total T4 levels, radiological features, and pathology findings. **Results:** Data from Dr. Soetomo General Hospital in Surabaya showed 172 Graves' disease patients from January 2016 to December 2020. The majority were female (76.2%) and aged 31-40 years (32%), with the most common complaint being palpitations (53.5%). Most patients had normal temperature, respiratory rate, and pulse, but were prehypertensive. TSH levels were below normal in 83.3% of patients, while FT4, total T3, and total T4 levels were above normal in 59.1%, 57.8%, and 50% of patients, respectively. Radiological imaging showed hyperthyroidism in 87 patients, with diffuse goiter being the most common feature. Anatomical pathology examinations in 42 patients revealed nodular colloid goiter in 24 patients. **Conclusion:** The diagnosis of Graves' disease can be made based on patient history, clinical symptoms, physical examination, and laboratory tests. Radiological and anatomical pathology examinations can be used as additional evaluations.

Keywords: Graves' disease; clinical profile; laboratory profile; anatomical pathology features; good health and well-being

## 1. Introduction

Graves' disease is an autoimmune disorder and the leading cause of hyperthyroidism, characterized by excessive thyroid hormone secretion [1]. The prevalence of hyperthyroidism in Indonesia, as reported the Ministry of Health, is 0.4%, while in the United States, it reaches 1.2% [2,3]. This condition is more common in women aged 20 to 40 years [2]. A study in the UK reported an incidence of 24.8 cases per 100,000 population, with a female-to-male ratio of 3.9:1 [4].

Graves' disease has three main clinical characteristics; thyroid gland enlargement, eye protrusion (exophthalmos), and skin lesions (dermopathy). According to the World Health Organization (WHO), the diagnosis can be confirmed by laboratory results showing increased FT3 and FT4, decreased serum TSH, and elevated TSH receptor antibodies (TRAb). The typical morphology includes diffuse and symmetric thyroid enlargement. Microscopic examination reveals hyperplastic thyroid follicles with dense, tall follicular epithelial

cells producing thyroid hormones. The colloid appears pale with a scalloping pattern due to the protrusion of follicular epithelial cells. Irregular lymphoid infiltration is found in the stroma [5].

In 2013, hyperthyroidism cases were reported by the Ministry of Health in Indonesia, yet, study on incidence and prevalence of Graves' disease in Indonesia are limited. In contrast, thyroid associations in other countries have published guidelines for the diagnosis and management of Graves' disease. This study aims to obtain data on the clinical profiles of Graves' disease patients at Dr. Soetomo General Hospital over the past five years. The collected data includes patient age, number, gender, clinical features and ultrasound findings. This information is intended as a learning resource and inform healthcare planning in Indonesia [6].

## 2. Materials and methods

This retrospective descriptive observational study aimed to examine the clinical, laboratory, and anatomical pathology profiles of Graves' disease patients. The clinical profile included age, gender, and clinical features. Laboratory tests included TSH levels, FT4, total T3, and total T4 levels. Radiological examinations using ultrasound were conducted for accurate diagnosis. Pathological examination involved thyroid tissue biopsies via fine-needle aspiration biopsy (FNAB) or histopathological examination to observe both macroscopic and microscopic characteristics and detect possible malignancies.

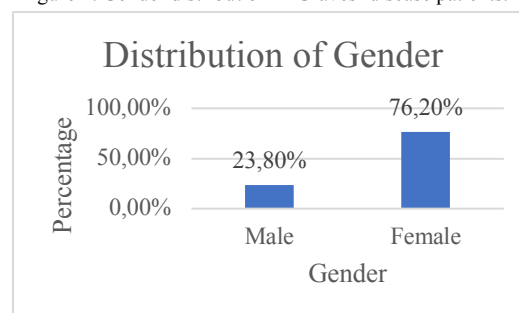
The study involved 178 Graves' disease patients registered at the Integrated Endocrinology Service and Anatomical Pathology Laboratory within the specified period. The inclusion criteria encompassed all patients diagnosed and treated for Graves' disease at Dr. Soetomo General Hospital from January 2016 to December 2020, with no exclusion criteria applied. Total sampling technique was employed to include all eligible patients. The ethics were cleared by the Ethics Committee of Dr. Soetomo General Academic Hospital, Surabaya, East Java, Indonesia. No validity and reliability tests are needed because the instruments used were medical records.

## 3. Results

A retrospective descriptive study of Graves' disease patients at Dr. Soetomo General Hospital, covering the period from January 2016 to December 2020, was conducted using data collected from the hospital medical records. A total of 172 samples met the inclusion criteria. The data collected were categorized into clinical profiles (age, gender, chief complaints, vital signs), laboratory profiles (TSH, FT4, total T3, total T4 levels, radiological features), anatomical pathology findings, and treatments. The results were presented in tables and bar charts.

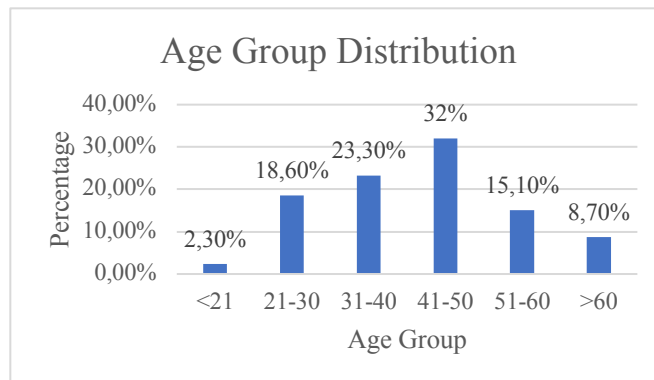
The demographic distribution shows that of the 172 patients with Graves' disease at Dr. Soetomo General Hospital from January 2016 to December 2020, the majority were female (131 patients, 76.2%), while male patients accounted for 41 (23.8%).

Figure 1. Gender distribution in Graves' disease patients.



The age range of patients was from 16 to 75 years, with the majority in the 41-50 years age group (55 patients, 32%), followed by the 31-40 years age group (40 patients, 23.3%).

Figure 2. Age distribution of Graves' disease patients.



The most common symptoms was palpitations, experienced by 92 patients (53.5%). Other symptoms included tremors (51 patients), weight loss (48 patients), heat intolerance (34 patients), fatigue (22 patients), shortness of breath (7 patients), insomnia (3 patients), and anxiety (2 patients). Goiter was observed in 74 patients, and exophthalmos in 65 patients.

Table 1. Chief complaints of Graves' disease patients.

Category		Number, n (%)
Clinical features	Tremors	51 (29,6%)
	Insomnia	3 (1,7%)
	Anxiety	2 (1,2%)
	Shortness of breath	7 (4,1%)
	Heat intolerance	34 (19,8%)
	Palpitations	92 (53,5 %)
	Fatigue	22 (12,8%)
	Weight loss	48 (27,9%)
	Goiter	74 (43%)
	Exophthalmos	65 (37,8%)

The normal range for TSH in Dr. Soetomo General Hospital is 0.55-4.78  $\mu$ IU/mL. Majority of the patients (81.4%) had TSH levels below this range, 14.5% were within the normal range, and a small percentage (1.7%) had elevated TSH levels. FT4 levels were tested in 164 patients, 97 had elevated FT4 levels, 60 were within the normal range, and 7 had levels below normal. Total T3 levels was measured in 45 patients with 26 had elevated total T3 levels, 16 were within the normal range, and 3 had levels below normal. Total T4 levels was measured in 22 patients with 11 had elevated total T4 levels, 8 were within the normal range, and 3 had levels below normal.

Table 2. Laboratory examination profile of Grave's disease patients (TSH, FT4, Total T3, Total T4).

Category	Patient number	Percentage	Valid percentage
<b>TSH levels (μIU/mL)</b>	< 0,55	140	81,4%
	0,55 – 4,78	25	14,5%
	> 4,78	3	1,7%
	No data	4	2,3%
	Total	172	100%
<b>FT4 levels (pg/mL)</b>	< 0,89	7	4,1%
	0,89 – 1,76	60	34,9%
	> 1,76	97	56,4%
	No data	8	4,6%
	Total	172	100%
<b>Total T3 levels (ng/mL)</b>	< 0,6	3	1,7%
	0,6 - 1,81	16	9,3%
	> 1,81	26	15,1%
	No data	127	73,9%
	Total	172	100%
<b>Total T4 levels (ug/dL)</b>	< 4,5	3	1,7%
	4,5 - 10,90	8	4,7%
	> 10,90	11	6,4%
	No data	150	87,2%
	Total	172	100%

Table 3. Mean value of laboratory profile of Grave's disease patients (TSH, FT4, Total T3, Total T4).

Category	Mean value
TSH (μIU/mL)	1,22 (0,001–111,04)
FT4 (ng/dL)	3,67 (0,29–23,9)
Total T3 (ng/mL)	2,9 (0,45–13,7)
Total T4 (μg/dL)	13,3 (0,5–51,9)

Doppler ultrasound was performed on 96 patients, with 87 showing characteristics of hyperthyroidism and 9 showing normal thyroid radiology. Features examined from 87 patients with hyperthyroid characteristics, 42 showed diffuse goiter, 39 showed nodular goiter, and 6 had normal-sized thyroid with hypervascularization.

Table 4. Ultrasound examination results of Grave's disease patients.

Examination impressions summary	Number, n (%)
Hyperthyroid features	87 (50,6%)
Normal features	9 (5,2%)
No data	76 (44,2%)

Table 5. Ultrasound examination impressions of hyperthyroid features in graves' disease patients

Examination impressions summary	Number of patients
Diffuse goiter	42
Nodular goiter	39
Hypervascularization without thyroid enlargement	6

Anatomical pathology was measured by FNAB method or post-thyroidectomy examination. Anatomical pathology examination using FNAB was performed on 38 patients. Of these, 24 (63.2%) showed nodular colloid goiter, 8 (21%) showed follicular hyperplasia, 5 showed thyroiditis, and 1 showed papillary thyroid carcinoma. Three patients underwent thyroidectomy, with histopathological examination revealing adenomatous goiter in 2 patients (66.7%) and Graves' disease in the involution phase in 1 patient.

Figure 3. Anatomical pathology examination results from FNAB samples.

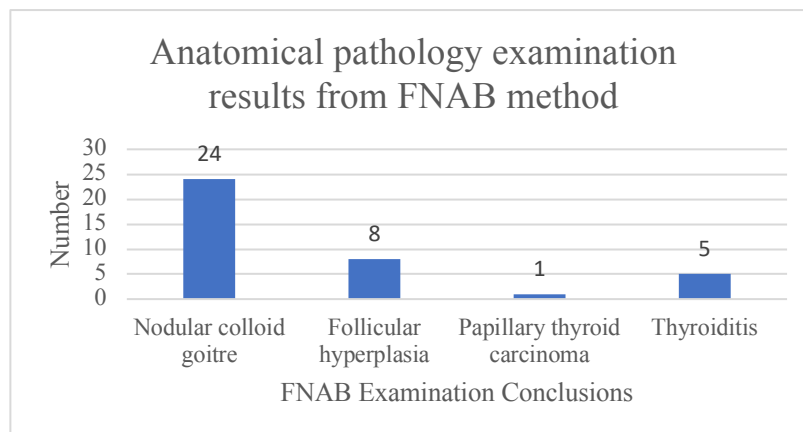
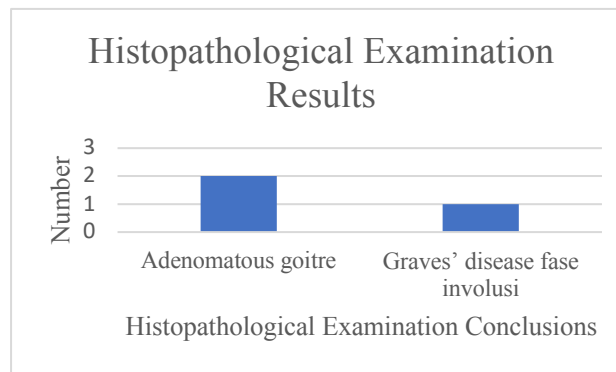


Figure 4. Histopathological examination results from thyroidectomy patients.



#### 4. Discussion

Gender distribution indicates predominance of female patients, with a percentage of 76.2%. This finding is consistent with research conducted in Ghana, which reported a female-to-male ratio of Graves' disease patients at 5.1:1 [7]. A study in 2018 further explained that autoimmunity is more prevalent in women. Sex hormones play a role in controlling innate and adaptive immune responses. The complex interaction between hormones and environmental factors in genetically susceptible individuals can disrupt immune responses, leading to autoimmune diseases [8].

The age range spans from the youngest at 16 years to 75 years. The distribution is predominantly within the age group of 41 to 50 years (32%), aligns with data analysis in 2018 showed that the majority of Graves' disease patients fall within the 31-40 years age range, although the correlation was not significant ( $p=0.311$ ) [9]. Epidemiological data from France report a similar overall incidence of Graves' disease in children and adolescents at approximately 4.58 per 100,000 per year, with an even lower incidence of 1 to 2.91 per 100,000 per year in patients under 15 [10].

In consideration of both age and gender, it was found that women who have given birth have a higher risk of developing Graves' disease [11]. Approximately 7.2% of Graves' disease cases in women begin postpartum, with parity being a notable risk factor. During the first trimester of pregnancy, excessive thyroid stimulation due to high levels of hCG and TRAb increases the risk of Graves' disease, which decreases in the second trimester due to progesterone-induced immunosuppression. However, post-delivery, the decline in progesterone levels restore the immune system, potentially triggering autoimmunity and increasing the risk in susceptible patients [12].

The clinical presentation of Graves' disease is a combination of symptoms caused by excess thyroid hormones and specific signs of Graves' disease. Symptoms vary depending on the patient's age, gender, comorbidities, disease duration and severity, and individual sensitivity to excess thyroid hormones [13]. This variation is supported by the literature and reflected in this study. The most common feature was palpitations, reported by 92 patients (53.5%). Other symptoms related to excess thyroid hormones included tremors, weight loss, and heat intolerance manifested as excessive sweating. Similar findings were reported in a 2018 study in Ghana by Sarfo-Kantanka et al., where palpitations (86%), goiter (77%), and shortness of breath (77%) were the most common symptoms [7].

Goiter, characterized by an enlarged thyroid gland, was found in 74 patients (43%). This finding aligns with a meta-analysis in 2021 which reported a 70% prevalence of goiter in Graves' disease patients [14]. The enlargement of the thyroid gland in Graves' disease is caused by the action of thyroid-stimulating immunoglobulins (TSI) and thyroid growth-stimulating immunoglobulins (TGI) on TSH receptors in thyroid follicular cells, stimulating thyroid hormone synthesis and cell proliferation, resulting in goiter [15].

Another distinctive feature of Graves' disease, exophthalmos, was reported in 65 patients (37.4%). A systematic review of 33 articles on Graves' disease by Chin showed a similar prevalence of Thyroid Eye Disease at 40% (n = 22,384 patients) [16]. Exophthalmos is the most common extrathyroidal manifestation of Graves' disease. It is influenced by genetic predisposition and modifiable risk factors, such as smoking, which plays a significant role [17].

Palpitations, a common cardiovascular symptom, were reported by more than 50% of Graves' disease patients. They are caused by the increased sensitivity and density of beta-adrenergic receptors to catecholamines in hyperthyroidism, leading to increased sympathetic activity. This results in chronotropic and inotropic effects on the sinus node, increasing heart rate and contractility [18]. Weight loss, with or without increased appetite, was reported by 48 patients, and heat intolerance by 34 patients. Excess thyroid hormones increase metabolism through the upregulation of Na<sup>+</sup>/K<sup>+</sup>-ATPase, leading to thermogenesis and heat production. This increased metabolic rate is reflected in increased appetite and heat intolerance.

Tremors, insomnia, and anxiety in some patients are explained by hyperadrenergic conditions due to increased sympathetic activity. Neurological manifestations include nervousness, emotional lability, and hyperkinesia. Severe mental disturbances such as manic-depressive reactions, schizoid, or paranoid states can also occur [11]. Fatigue reported by 22 patients may result from muscle weakness due to decreased creatine kinase activity and disruptions in muscle cell metabolism caused by excessive thyroid hormones [19]. Shortness of breath, reported by 7 patients (4.1%), often occurs in severe thyrotoxicosis due to decreased vital capacity from respiratory muscle weakness and increased oxygen consumption, which can exacerbate chronic lung conditions [11].

Thyroid function tests, primarily TSH and FT4 levels, are crucial for diagnosing Graves' disease. Occasionally, total T3 and T4 levels are also measured. A decrease in TSH or an increase in FT4, along with typical symptoms, is enough to confirm the diagnosis, although it does not determine the underlying cause. However, if physical examination points to Graves' disease and laboratory results show decreased TSH levels with normal FT4, T3 test is required [6]. In this study, the average TSH level among patients was 1.22  $\mu$ IU/mL, with a range from 0.001 to 111.04  $\mu$ IU/mL. The average FT4 level was 3.67 ng/dL, ranging from 0.29 to 23.9 ng/dL. The lowest recorded total T3 level was 0.45 ng/mL, with an average of 2.9 ng/mL and a maximum of 13.7 ng/mL. The average total T4 level was 13.3  $\mu$ g/dL, with values ranging from 0.5 to 51.9  $\mu$ g/dL.

The average TSH level was 1.22  $\mu$ IU/mL, with 81.4% of patients showing levels below the normal range. Only 1.7% of patients had TSH levels above the normal range. These findings are consistent with other epidemiological studies, which also report that the majority of Graves' disease patients have subnormal TSH levels before treatment [4, 9]. Studies have shown that TSH levels in most patients with Graves' disease are extremely low, often below 0.005  $\mu$ IU/mL [20]. In cases of such low TSH, thyrotoxicosis becomes symptomatic, and there is a marked rise in FT4. Circulating TSH typically exhibits reduced biological activity due to abnormal glycosylation, which impairs the binding of TRH to thyrotrophs [11].

In Graves' disease, measurement of serum FT4 and FT3, or total thyroid hormone is performed to differentiate between subclinical hyperthyroidism and overt hyperthyroidism. This testing also aids in identifying the cause of increased thyroid hormone concentrations in normal or slightly elevated TSH, such as in patients with TSH-secreting pituitary adenomas or peripheral thyroid hormone resistance [13]. FT4 levels were measured in 164 patients, elevated FT4 levels were found in 97 patients (59.1%). The average FT4 level

was 3.72 ng/dL, comparable to other studies showing similar results [7,14]. The extent of FT4 elevation above normal provide an estimation of the disease's severity [21].

Total T3 levels were measured in 45 patients, with 16 showing normal levels (0.6 – 1.81 ng/mL). Most patients had elevated total T3 levels, with an average of 3 ng/mL, and a maximum of 13.7 ng/mL. Similar findings have been reported in other study [22]. Total T4 levels were measured in 22 patients, with 8 having normal levels. Elevated total T4 levels were found in 11 patients, with the highest being 51.9 µg/dL. A small number of patients had total T4 levels below the normal range. This is consistent with reports indicating that total T4 levels may remain normal even in thyrotoxicosis conditions due to various factors [7, 21].

A systematic review found that the prevalence of Graves' orbitopathy (GO) in individuals with normal thyroid function ranges from 0.9% to 15.4% [23]. Diagnosing Euthyroid Graves' disease (EGD) can be challenging and relies on clinical features such as ophthalmopathy, which in EGD presents with a heterogeneous pattern, along with normal thyroid function tests (normal T3, T4, and TSH levels) and no prior history of thyroid disorders [24]. A study of Graves' disease patients in Ghana also reported that the majority (84%) were hyperthyroid at presentation, 9% were euthyroid, 4% had hypothyroidism, and 3% had subclinical hyperthyroidism [7].

Ultrasound is a crucial component in evaluating the thyroid gland in cases of hyperthyroidism. Initial imaging with color-flow Doppler USG can distinguish increased blood flow in Graves' disease from decreased flow in thyrotoxicosis due to destruction [13]. Findings in Graves' disease typically shows gland enlargement and significant vascularization, often presenting a pulsatile pattern known as "thyroid inferno," characterized by multiple small areas of increased intrathyroidal flow diffusely throughout the gland [25].

In this study, Doppler USG was performed on 96 patients, 87 displayed hyperthyroid features. A total of 42 patients had diffuse goiter, 39 had nodular goiter, and 6 had normal-sized thyroid glands with increased vascularization. Graves' disease typically shows hyperplasia or diffuse thyroid enlargement on USG, characterized by increased thyroid volume, homogeneous parenchymal echogenicity with a fine granular pattern, regular margins, and well-defined borders. Doppler USG can reveal increased symmetrical vascularization with homogeneous distribution. Approximately 80-85% of all thyroid abnormalities are diffuse thyroid gland hyperplasia [26].

Nodular goiter is defined as a thyroid lesion of any size with a visible capsule. The radiological characteristics of colloid nodules on USG include well-defined boundaries and an intact lesion capsule, with the thyroid gland capsule remaining visible [26]. This study's findings are consistent with research indicating that nodules are found in 26.4% of Graves' disease patients, with 47.1% showing hypoechoic thyroid gland [27]. Thyroid nodules are commonly detected incidentally through palpation during physical examinations across the general population, with subsequent USG evaluation revealing that most nodules are benign [28].

Pathological examinations with FNAB or histopathological examination post-thyroidectomy were conducted in 41 patients. The indications are usually the presence thyroid nodules, as most patients with thyroid nodules have normal thyroid function tests. Radionuclide scanning is recommended in patients with decreased TSH levels to determine if a nodule is a "hot nodule," which is typically benign and does not require FNAB. Further evaluation with ultrasound is performed to confirm palpable nodules and detect additional non-palpable nodules, aiding in the decision for FNAB [1].

Suspected malignant thyroid nodules exhibit characteristics such as hypoechoic gland, microcalcifications, irregular borders, height greater than width, capsular protrusion, and size greater than 1 cm. FNAB is indicated for nodules 1 cm or larger. If cytology results indicate malignancy, surgery is recommended [29]. Morphological evaluation of thyroid nodules with FNAB, combined with histopathological examination of thyroid tissue post-surgery, provides the most accurate information regarding the nature of thyroid nodules [3].



FNAB was performed on 38 Graves' disease patients, nodular colloid goiter was found in 24 patients (63.2%), follicular hyperplasia in 8 patients (21%), and thyroiditis in 5 patients. A small number of patients (1) showed papillary thyroid carcinoma. Macroscopically, Graves' disease generally presents as diffuse thyroid gland enlargement with a smooth capsule and hypervascularity. Microscopically, hypertrophic and hyperplastic follicular and papillary cells with scant colloid, along with lymphocyte and plasma cell infiltration forming lymphoid follicles, are observed. Enlarged follicular cells may resemble papillary thyroid carcinoma [15].

Previous research on 262 thyroid cancer patients with Graves' disease found that 82 had nodules in addition to thyroid malignancy, while 180 did not have additional nodules [30]. Chronic TSH stimulation can lead to the development of autonomous follicles that secrete hormones, suppressing other areas, causing focal hyperplasia, involution, and fibrosis [31]. Specific microscopic features of thyroiditis include massive lymphocytic infiltration with hyperplastic germinal centers in the thyroid parenchyma and atrophic thyroid follicular cells, making differentiation between Graves' disease and thyroiditis challenging due to frequent overlap [32].

Thyroidectomy involves the removal of all or part of the thyroid gland. Histopathological examination is conducted on the excised thyroid tissue. From January 2016 to December 2020, four Graves' disease patients underwent thyroidectomy. Adenomatous goiter was found in two patients (66.7%), while one patient exhibited involuted Graves' disease. Colloid goiter results from prolonged TSH stimulation reduction and is pathologically known as hyperplastic and colloid nodules or adenomatous goiter. Chronic TSH stimulation can lead to the formation of autonomous follicles that secrete hormones, causing other areas to undergo involution and fibrosis [6, 31]. Thyroid adenomas are benign thyroid lesions that can be inactive or active (toxic thyroid adenomas). Patients with thyroid adenomas are usually asymptomatic, but toxic adenomas can cause biochemical and clinical hyperthyroidism, defined as autonomously functioning thyroid nodules (AFTN). Reports on the incidence of adenomatous goiter in Graves' disease are rare. A study published in The Japanese Journal of Surgery in 1999 indicated that adenomatous goiter with hyperthyroidism is rare in Japan [33]. In this study, two patients with adenomatous goiter had initial presentations of subclinical hyperthyroidism and one with normal TSH and elevated FT4 levels.

## 5. Conclusion

The study on the clinical and laboratory profiles of 172 Graves' disease patients at Dr. Soetomo General Hospital, Surabaya, from January 2016 to December 2020, yielded significant findings. Demographically, the majority of patients were within the 41 to 50 years age group and predominantly female. Clinically, the most common clinical feature was palpitations, followed by goiter and symptoms of ophthalmopathy. Laboratory results showed that the average TSH level in 168 patients was 1.22  $\mu$ IU/mL, with most values below the normal range. The average FT4 level in 164 patients was 3.67 ng/dL, and the total T3 and T4 levels averaged 2.9 ng/mL and 13.3 g/dL, respectively, with most values above the normal range. Ultrasound examinations of 96 patients predominantly showed hyperthyroid features with diffuse goiter. Pathological features in 42 patients revealed that the most common findings from FNAB were nodular colloid goitre, and from histopathological examination, adenomatous goitre.

## Acknowledgements

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