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Risk Factor Pattern of Graves' Ophthalmopathy at Dr. Soetomo General Academic Hospital, Surabaya, Indonesia

Royhan Akbar[1], Sony Wibisono Mudjanarko[2*], Evelyn Komaratih[3], Deasy Ardiany[2]

[1]Faculty of Medicine, Universitas Airlangga, Surabaya, Indonesia.
[2]Department of Internal Medicine, Faculty of Medicine, Universitas Airlangga/Dr. Soetomo General Academic Hospital, Surabaya, Indonesia.
[3]Department of Ophthalmology, Faculty of Medicine, Universitas Airlangga/Dr. Soetomo General Academic Hospital, Surabaya, Indonesia.

* Correspondence: sony.wibisono@fk.unair.ac.id

ABSTRACT

Introduction: Graves' ophthalmopathy (GO) is an autoimmune condition that extends beyond the thyroid gland. The development of GO may be influenced by various risk factors, some of which may interact with each other. This study aimed to identify the most prevalent risk factors for patients with GO from 2019 to 2022 at Dr. Soetomo General Academic Hospital, Surabaya, Indonesia.

Methods: This study employed a descriptive cross-sectional design, examining 150 patients who met the inclusion and exclusion criteria. This study measured the age, gender, and systemic thyroid status of all patients. This study used Microsoft Word and Microsoft Excel for Mac version 16.87 to process data.

Results: Between 2019 and 2022, 150 patients were diagnosed with GO at Dr. Soetomo General Academic Hospital, Surabaya, Indonesia. The condition was more prevalent in females than males, and the most common age group affected was between 30 and 50 years old. Additionally, 72% of patients with GO also had hyperthyroidism.

Conclusion: Graves' ophthalmopathy was more prevalent in female patients, aged between 30 and 50 years old, with the majority having hyperthyroidism. Future studies should be conducted on the patterns of GO risk factors on a larger scale to more accurately represent the disease in the general population.

Highlights:
1. Female patients are more likely to suffer from GO.
2. Most GO patients have high thyroid levels (hypothyroidism).

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Introduction

Graves' ophthalmopathy (GO) is characterized by another condition known as thyroid-associated ophthalmopathy (TAO). Ocular abnormalities, systemic inflammation, an enlarged and overactive thyroid gland, and localized dermopathy are hallmarks of Graves' disease (GD), an autoimmune disorder. It is more prevalent in females than in males and most commonly affects adults between 20 and 50 years old.[1–3] Graves' ophthalmopathy is the most frequent cause in Western countries, with an annual incidence of 20 cases/100,000 persons.[4] Genetic influences and dietary iodine supply are significant determinants in the development of GO. An epidemiological study suggested that infections might also contribute to the development of GO, with seasonal and regional variation observed.[5]

Graves' ophthalmopathy can manifest outside of the thyroid gland in the form of an autoimmune condition known as thyroid eye disease (TED). In 80% of cases, ocular symptoms appear within 18 months of thyroid manifestations, although they may appear before or after. People without or with a history of hyperthyroidism are both susceptible to this illness.[6] The female-to-male ratio in thyroid ophthalmopathy is approximately 2.5:1.[7]

The European Group of Graves' Ophthalmopathy (EUGOGO) classifies the severity of GO as mild to sight-threatening. Patients with this condition exhibit specific symptoms and signs that may present as one or more clinical pictures. The disease presents with several clinical features, including superior palpebral retraction, lid lag, proptosis, restrictive myopathy, and neuropathy of the optic nerve due to compression.[8]

Graves' ophthalmopathy disease risk factors comprise a complex clinical picture resulting from the interaction of several endogenous (non-modifiable) and exogenous (modifiable) factors.[9] In a 2023 study in Poland, a correlation was found between serum cholesterol and patients with GO.[10] A cohort study conducted by Ferrari, *et al*. (2019) showed that patients with GO were more commonly associated with diabetes mellitus.[11] However, a study conducted at the Faculty of Medicine, Diponegoro University, Indonesia, in 2019 concluded that there was no causal relationship found between thyroid dysfunction risk factors and smoking history for patients with GO.[1]

There have been limited studies on GO in Indonesia. Although several risk factors are associated with GO, their effects may vary across different populations. Therefore, this study aimed to identify the most prevalent risk factors for patients with GO from 2019 to 2022 at Dr. Soetomo General Academic Hospital, Surabaya, Indonesia.

Methods

This study employed a descriptive, observational design with a cross-sectional approach. A descriptive study aims to accurately describe individuals, events, or conditions as they exist, without altering the variables under study.[12] Researchers describe samples and/or variables without altering them.[12] To differentiate cross-sectional research, pertinent information (data) is collected at a specific point in time.[13] Consequently, cross-sectional studies have no time dimension because all data were gathered at or near the time of data collection.[13] The dependent variables in this study include gender, age, and thyroid status of the patients. Meanwhile, the independent variables focused on the pathomechanism of GD and GO. From 2018 to 2022, data were collected from the medical records of patients with GD and GO at the Information and Communication Technology (ICT) installation of Dr. Soetomo General Academic Hospital, Surabaya, Indonesia. Graves' ophthalmology patients aged 18-75 years old were included in this study.

Results

Table 1 shows the characteristics of the distribution of age, sex, and thyroid status of the subjects. Based on age, the majority of the sample, comprising 77 patients (51.3%), were between 30 and 50 years old. Additionally, 41 patients (27.3%) were under 30 years old, and 32 patients (21.3%) were over 50 years old.

Table 1. Characteristics of the subject

Variable	Frequency (n)	Percentage (%)
Age		
<30 years old	41	27.3
30-50 years old	77	51.3
>50 years old	32	21.3
Gender		
Male	57	38.0
Female	93	62.0
Thyroid Status		
Hyperthyroid	7	4.7
Hypothyroid	108	72.0
Euthyroid	35	23.3
Total	150	100

Source: Research data, processed

In terms of gender, 93 patients (62%) were females and 57 (38%) were males. The majority of patients (72%) were found to be hyperthyroid, followed by 23.3% who were euthyroid, and only 4.7% who were hypothyroid.

Discussion

This study reveals that age, gender, and systemic thyroid status are risk factors for GO. It is essential to enhance our understanding of disease risk factor patterns to effectively manage and prevent disease progression. Objective awareness and motivation are key to treatment adherence.[14] Based on age, this study found that the most frequent age group of patients with GD and GO at Dr. Soetomo General Academic Hospital, Surabaya, Indonesia, was between 30 and 50 years old (51.3%), with fewer patients under 30 years old (27.3%) and over 50 years old (21.3%). These findings are similar to those by Mulya (2021), which indicated that the majority of respondents with GD and GO were between 30 and 50 years old (43.8%).[15] Similarly, Piya, *et al*. (2019) found that the distribution of Graves' patients with ophthalmopathy was highest among those aged 21-30 years old and 31-40

years old.[16] Thyroid levels influence GD, particularly in cases with ophthalmopathy, and are also related to age. These results align with those by Deng, *et al*. (2021), which showed a positive correlation between age and thyroid status, whether it was hyperthyroid, subclinical hyperthyroid, subclinical hypothyroidism (SCH), or normal thyroid (NTF).[17]

Kocełak, *et al*. (2022) found a significant association between age and hypothyroidism/hyperthyroidism status.[18] Tariq, *et al*. (2024) and Chen, *et al*. (2020) discovered a link between age and thyroid-stimulating hormone (TSH) levels.[19,20] According to Deng, *et al*. (2021), 77% of the 336 study subjects aged 65 years or older had normal thyroid status (euthyroid), while the remaining 20% had SCH.[17] Wardana, *et al*. (2023) discovered that thyroid function problems were more common in those aged 41-50 years old (29.9%), with hyperthyroidism more common in people aged 31-40 years old (87.6%) and 21-30 years old (87.4%).[21] Similarly, Prajayanti, *et al*. (2020) discovered that hyperthyroidism was more prevalent in people aged 40 to 59 years old (49.67%).[22] Muralidhar, *et al*. (2020) discovered that 46.23% of TED patients at tertiary eye care centers in North India were hyperthyroid.[23] Another study reported that the highest risk of hyperthyroidism occurred in younger age groups, with an average age of 30-50 years old, and those over 40 years old were at the highest risk.[24] The study results suggested a correlation between the high incidence of hyperthyroidism in GD and GO patients.[24]

Suzuki, *et al*. (2022) found that patients under the age of 40 years old were at a higher risk of severe hyperthyroidism compared to those who were 40 years old or older.[25] Although younger people tend to have TSH levels within the normal range, there is some evidence to suggest that serum TSH levels increase with age. The thyroid secretes hormones that influence metabolism and a wide range of tissues, including the nervous system, cardiovascular system, skeletal system, and muscles. While people of all ages might experience thyroid dysfunction, the condition disproportionately impacts the elderly.[26] In both males and females, TSH levels in the blood, as well as thyroid peroxidase (TPOAb) and thyroglobulin (TgAb) antibodies, rise with age. The mean TSH count increases after the age of 20 years old in all ethnic groups, even after thyroid antibody status and other risk variables were ruled out. Consequently, thyroid production also increases, and young people are more likely to have hyperthyroid status, resulting in GD.

Thyroid hormone activity, metabolism, and production vary with age. The range of thyroid hormone levels also varies, particularly in younger populations. The endocrine system is just one of many that changes as a person ages. Hormone secretion or sensitivity of the target organ may have changed, causing these modifications. Whenever the target organ changes, the release of hormones may follow suit. Additionally, changes in the metabolic rate of other hormones that affect hormone production, such as the thyroid, may occur, resulting in a person experiencing GD with GO.[27]

Free thyroxine (FT4) levels generally remain stable with age, although some studies suggest that FT4 levels may increase while free triiodothyronine (FT3) levels may decrease. Individual differences in the rate and pattern of thyroid function decline with age are substantial. Take TSH and FT4 levels, for example. Some people have high FT4 levels but low TSH. These differences may result from metabolic changes in disease, low-grade inflammation, or energy restriction. As we age, the bioactivity of TSH may decrease, resulting in less effective TSH and less functional receptors. This can lead to fluctuations in thyroid hormone levels, resulting in variations in the amount produced over time.[28] Several changes in thyroid physiology may lead to increased serum TSH levels as people age. Reduced thyrotropin sensitivity to thyroid hormone negative feedback, age-related decline in TSH bioactivity, hereditary effects, and decreased iodine uptake are among the alterations.[19]

Based on gender, this study reveals that 93 respondents (62%) were female and 57 respondents (38%) were male, indicating a notable gender difference. This finding is similar to that of Mulya (2021), which reported that the majority of GD patients with ophthalmopathy were females (80.9%).[15] Xie, *et al*. (2022) conducted a study on 204 newly diagnosed GD patients, of whom 158 were females and 46 were males.[28] The study results suggested an association between gender and GD and GO.[28] This may explain the higher incidence of GD with GO in females. Previous studies by Chen, *et al*. (2020) and Yin, *et al*. (2024) showed that females have higher TSH values than males in all age groups, which could trigger greater production of thyroid hormones and lead to hyperthyroid status.[20,29] Castello and Caputo (2019) found that hyperthyroidism was more prevalent in females than in males.[30] This gender difference may be related to differences in TSH levels, as TSH enhances polyiodine synthesis and alters thyroid function. Thyroid-stimulating hormone also acts as a risk factor for thyroid illness on its own. Impaired thyroid function can lead to various diseases, including GD with GO.[31]

As far as thyroid function indicators go, TSH is at the top of the list. Note that females have a higher prevalence of thyroid dysfunction and elevated TSH levels compared to males. This is due to several factors, including the fact that gender can influence TSH serum levels. Estrogen may be involved in the process, which could interfere with the effects of exaggerated iodine on thyroid tissue. This could explain the higher TSH values and prevalence of thyroid dysfunction in females, as estrogen receptor-mediated increased oxidative stress may be a contributing factor.[32] There are significant gender differences in the impact of metabolic and endocrine changes on the thyroid, with females being more frequently affected than males. Clinical trials and research outcomes have shown these differences. The female thyroid is especially vulnerable to the effects of estrogen environment and cyclical hormonal variations. Additionally, autoimmune diseases are more prevalent in females than males, resulting in a higher incidence of hyperthyroidism in females.[33] In males, FT3 levels gradually decrease as TSH increases. However, in females, FT3 levels fluctuate with TSH levels. Thyroid-stimulating hormone influences thyroid hormone

production and is governed by thyroid hormone negative feedback control, which is primarily impacted by circulating T3 levels. The ratio of FT3 to FT4 concentration is a good measure for monitoring thyroid hormone peripheral metabolism, which is impacted by the conversion of FT4 to FT3. Free triiodothyronine levels indirectly influence the levels of thyroid hormones produced in each sex.[20]

Hyperthyroidism, medically speaking, refers to the thyroid gland secreting more hormones than it usually does.[34–36] The vast majority of patients with GO (72%), according to the findings of the study, are hyperthyroid. The results are similar to those of Mulya (2021), who found that hyperthyroidism was present in 77.5% of patients with GO.[15] The results presented here are based on hard evidence, not personal opinions. Similarly, Piya, *et al*. (2019) found that 34.9% of GO patients had hyperthyroidism.[16] Davies, *et al*. (2020) describe GD as a systemic autoimmune condition distinguished by the infiltration of thyroid antigen-specific T lymphocytes into tissues expressing thyroid-stimulating hormone receptors (TSH-R).[2]

Thyroid hyperplasia and abnormal secretion and synthesis of thyroid hormone develop as a consequence of stimulatory autoantibodies (Ab) activating TSH-R. Pathophysiologically, thyroid-stimulating immunoglobulin (TSI), also known as thyroid-stimulating antibody (TSAb), is the primary cause of GD. According to Pokhrel and Bhusal (2023), T lymphocytes sensitized by thyroid antigens activate B lymphocytes to produce TSI in thyroid cells, lymph nodes, and bone marrow.[37] Thyroid-stimulating immunoglobulins attach to TSH receptors on the thyroid cell membrane, boosting thyroid hormone synthesis and thyroid gland development, resulting in hyperthyroidism.[37]

Graves' ophthalmopathy, the most common symptom outside of the thyroid that patients with GD have, is also associated with thyroid problems. Extraocular muscles, retro-orbital connective tissue, and adipose tissue can experience increased growth due to inflammation, cell proliferation, and cytokines produced by cytotoxic T lymphocytes (killer cells), which in turn stimulate the thyroid. In the autoimmune disease known as GO, cytokines and thyroid-stimulating antibodies activate preadipocytes and periorbital fibroblasts. Muscle edema results from the production of an excess of hydrophilic glycosaminoglycan (GAG) and the expansion of retro-orbital fat, both of which are activated by this signal. Unchangeable muscle fibrosis follows these alterations, which cause diplopia, congestion, proptosis, and periorbital edema.[38] Autoimmunity develops against antigens that are common to the thyroid gland and its pathways. One of the common pathogenetic antigens is the TSH receptor. There is a close correlation between ophthalmopathy and TSH receptor antibodies. Additionally, autoimmunity may trigger the pathogenesis of ophthalmopathy.[7]

Strengths and Limitations

The strength of this study lies in the identification of risk factors for GO based on age, gender, and systemic thyroid status, which has not been previously conducted at Dr. Soetomo General Academic Hospital, Surabaya, Indonesia. A limitation of this study was the insufficient number of samples. Therefore, the results of the study might differ from those of other studies that use more samples. Further research is needed to gain a deeper understanding of this disease.

Conclusion

The findings indicated that the highest number of patients with GO at Dr. Soetomo General Academic Hospital, Surabaya, Indonesia, fell within the age range of 30-50 years old. The age group above 50 years old had the lowest number of patients. In terms of gender, females predominated males. Regarding thyroid status, the majority of patients were hyperthyroid.

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Conflict of Interest

The authors declared there is no conflict of interest.

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Ethical Clearance

This study had received ethical clearance from the Research Ethics Committee of Dr. Soetomo General Academic Hospital, Surabaya, Indonesia (No.1289/LOE/301.4.2/IV/2023) on 04/11/2023.

Authors' Contributions

Initiated the study and wrote the manuscript: RA, SWM, and EK. Gathering information and literature review: RA and SWM. Performed statistical analysis: RA. Supervised outcomes and discussion: RA, SWM, EK, and DA. All authors reviewed and approved the final version of the manuscript.

Data Availability

N/A.

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