Eduvest – Journal of Universal Studies
Volume 5 Number 3, March, 2025
p- ISSN 2775-3735- e-ISSN 2775-3727

THE RELATIONSHIP BETWEEN AGE AND GENDER AND THE TIME TO ACHIEVE EUTHYROID CONDITION IN GRAVES' DISEASE PATIENTS WHO RECEIVE ANTITHYROID DRUG THERAPY

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ABSTRACT

Graves' disease is an autoimmune disease that most common cause of hyperthyroidism which is characterized by diffuse thyroid disease, thyrotoxicosis, and can be accompanied by orbitopathy and dermopathy. Age and gender are factors that are thought to influence the time it takes for GD patients to reach a euthyroid state who receive antithyroid drug therapy. The aim of this study was to determine the relationship between age and gender on the time to achieve euthyroidism in GD patients who received anti- thyroid drug therapy. This analytical observational study is a cohort study conducted using the Borneo Wetland Study on Thyroid 2 (BEST-T 2) Endocrine Polyclinic, Ulin Hospital Banjarmasin database. Data on 68 GD patients were taken using the total sampling method. Data were analyzed using the Cox Regression test with SPSS version 26 with a confidence level of 95%. Survival data will be displayed using the Kaplan Meier curve. This study showed that there was no relationship with age (p=0.064), but showed there was a relationship with gender (p=0.044) on the time to achieve euthyroidism in Graves' disease patients.

KEYWORDS *Graves' disease, age, sex, euthyroid, BEST-T 2, RSUD Ulin Banjarmasin.*

INTRODUCTION

Graves' disease is an autoimmune disease and the most common cause of hyperthyroidism which is characterized by diffuse thyroid and thyrotoxicosis, and can be accompanied by orbitopathy and dermopathy (Chen et al., 2014; Tan et al., 2021). Hyperthyroidism is caused by increased activity of the thyroid gland and causes excessive levels of thyroid hormone to circulate in the blood circulation, this condition characterized by increased levels of free thyroxine (fT4) and decreased thyroid stimulating hormone (TSH) (Sari et al., 2017). The most common etiology of hyperthyroidism is Graves' disease, it is estimated that 20-50 people per 100,000 people are diagnosed with Graves' disease each year. The Indonesian Society of

How to cite: Nanang Miftah Fajari, et al. (2025). The Relationship Between Age And Gender And The Time To Achieve Euthyroid Condition In Graves' Disease Patients Who Receive Antithyroid Drug Therapy. *Journal Eduvest. 5*(3), 2948-2958
E-ISSN: 2775-3727

Endocrinology Task Force for Thyroid Disease states that in Indonesia, hyperthyroidism is one of the main thyroid disorders (Musoddaq et al., 2022).

According to Basic Health Research data (RISKESDAS) in 2007, Indonesia had cases of hyperthyroidism ranging from 6.9%, while the United States and Europe each had cases of 1.2% and 0.8% (Srikandi, 2020). Then, Basic Health Research (RISKESDAS) in 2013 explained that the incidence of hyperthyroidism in residents aged 15 years and over reached more than 700,000 people or 0.4%, with Jakarta as the highest ranking at 0.7% (Amir et al., 2020; Eliana et al., 2017). Indonesia has a prevalence of Graves' disease of 0.05%, while America and Europe have a prevalence ranging from 0.5%- 1%. Graves' disease can affect anyone, but women are affected more often than men, with an age range of 30-60 years. women have a 3% risk and 0.5% of men are diagnosed with Graves' disease (Antonelli et al., 2020).

The cause of Graves' disease is still unknown, but environmental factors such as stress, psychosocial, smoking, immunity, genetically susceptible individuals such as twins are thought to trigger this disease. Therapy for Graves' disease itself includes antithyroid drugs (Methimazole (MMI), Propylthiouracil (PTU), and Carbimazole (CBZ)), radioiodine therapy, and thyroidectomy (Diker-Cohen et al., 2019). Based on research from Diker-Cohen, Talia, et al. Antithyroid drugs when used as first-line therapy were able to induce a euthyroid condition in up to 68% of a total of 235 patients with Graves' disease, which varied between regions and geographies. The euthyroid condition itself is the final successful response of the disease to therapy.

Men are more is often associated with a low level and duration of euthyroid conditions after therapy using antithyroid drugs, however, thyroid disease is more common in women. In research conducted by Anagnotis P, et al. female sex, non-smoking, no orbitopathy, duration of therapy, pharmacological hypothyroidism, higher TSH levels during completion of antithyroid drugs and 3 months after stopping taking them, and lower fT4 and fT3 levels 6 months after therapy were associated with time to achieve longer euthyroid condition. Because there is no research on the time to reach euthyroid condition relative to age and gender in Graves' disease sufferers at Ulin Hospital, Banjarmasin, this research is aimed at finding out the relationship between age and gender and the time to reach euthyroid condition in Graves' disease patients who received drug therapy. antithyroid.

RESEARCH METHOD

This research is an analytical observational study with a retrospective cohort approach. Data collection was carried out using patient data from 2012-2023 contained in the Endocrine Polyclinic database at the Ulin Banjarmasin Regional General Hospital (RSUD). The data obtained was then analyzed for the relationship between age and gender on the time to achieve euthyroidism in Graves' disease (GD) patients who received antithyroid drug therapy.

RESULT AND DISCUSSION

Research on the relationship between age and gender on the time to reach a euthyroid state in Graves' disease patients receiving antithyroid drug therapy was carried out in October-November 2023 at the Endocrine Polyclinic at Ulin Hospital, Banjarmasin. Patient data was taken from the BEST-T 2 database for the period 2012-April 2023. Based on the results of data collection, a total of 79 patients were obtained. Then, data is excluded that does not meet the criteria. Subjects taken from Graves' disease patients who met the inclusion criteria were carried out using the total sampling method, resulting in 68 people.

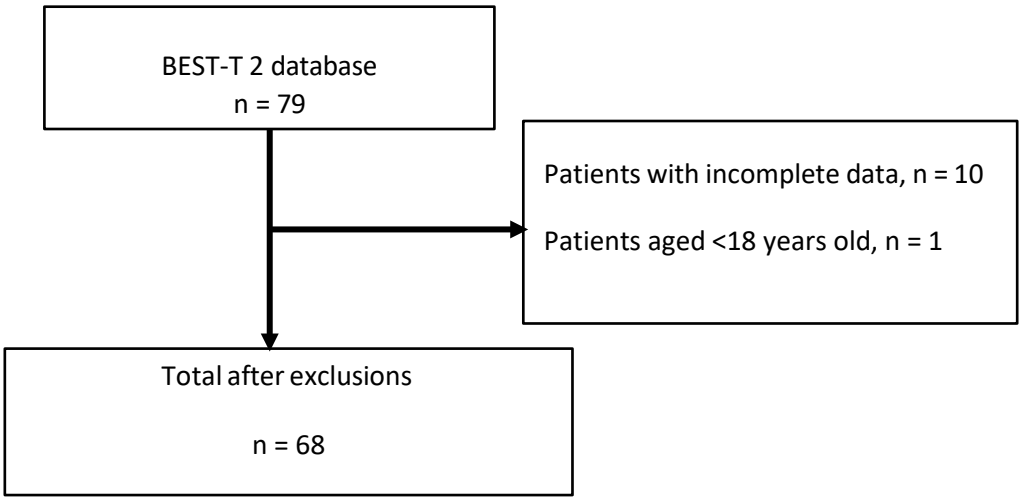

Figure 1. Sampling Stages

Table 1. Characteristics of Research Subjects on The Relationship of Age and Gender on The Time to Achieve Euthyroid in Graves' Disease Patients at RSUD Ulin Banjarmasin

Charateristics	Mean
Age, n (%)	
- 18-40 year	36 (52,9)
- >40 year	32 (47,1)
Gender, n (%)	
- Male	10 (14,7)
- Female	58 (85,2)
Patients Reaching Euthyroid <12 months, n (%)	37 (54,4)
Patients Reaching Euthyroid >12 months, n (%)	31 (45,6)
Euthyroid Monitoring in Age, n (%)	68 (100)
- 18-40 years old (Euthyroid ≤12 months)	23 (33,8)
- >40 years old (Euthyroid ≤12 months)	14 (20,5)
- 18-40 year (Euthyroid >12 months)	13 (19,2)

- >40 year (Euthyroid >12 months)	18 (26,5)
Euthyroid Monitoring in Gender, n (%)	68 (100)
- Male (Euthyroid ≤12 months)	2 (2,9)
- Female (Euthyroid ≤12 months)	35 (51,5)
- Male (Euthyroid >12 months)	8 (11,8
- Female (Euthyroid >12 months)	23 (33,8)
Time to Achieve Euthyroidism, (months)	
fT 4 rate , (pmol/l)	16,9 ± 17,9
- Beginning	39,2 ± 30,3
- End	12,1 ± 1,5
TSH rate, (uIU/ml)	
- Beginning	0,3 ± 1,2
- End	2,1 ± 1,3
fT4 rate aged 18-40 years, (pmol/l)	
- Beginning	45,7 ± 28,01
- End	11,28 ± 2,36
TSH rate aged 18-40 years, (uIU/ml)	
- Beginning	0,30 ± 1,29
- End	2,15 ± 1,45
fT4 rate aged >40 years, (pmol/l)	
- Beginning	33,76 ± 24,5
- End	12,71 ± 1,59
TSH rate aged >40 years, (uIU/ml)	
- Beginning	0,03 ± 0,04
- End	2,09 ± 1,30
fT4 rate male, (pmol/l)	
- Beginning	35,1 ± 19,1
- End	11,3 ± 1,10
TSH rate male, (uIU/ml)	
- Beginning	0,02 ± 0,01
- End	2,33 ± 0,96
fT4 rate female, (pmol/l)	
- Beginning	44,1 ± 28,9
- End	11,3 ± 3,28
TSH rate female, (uIU/ml)	
- Beginning	0,21 ± 1,05
- End	2,11 ± 1,43
fT4 rate female aged 18-40 years, (pmol/l)	
- Beginning	46,7 ± 29,2
- End	11,6 ± 1,35
TSH rate female aged 18-40 years, (uIU/ml)	
- Beginning	0,05 ± 0,08
- End	2,21 ± 1,54
fT4 rate female aged >40 years, (pmol/l)	
- Beginning	40,6 ± 28,9
- End	11,5 ± 4,13
TSH rate female aged >40 years, (uIU/ml)	
- Beginning	0,03 ± 0,04
- End	1,96 ± 1,25

fT4 rate male aged 18-40 years, (pmol/l)	
- Beginning	47,5 ± 14,5
- End	11,8 ± 1,18
TSH rate male aged 18-40 years, (uIU/ml)	
- Beginning	0,02 ± 0,02
- End	1,88 ± 0,66
fT4 rate male aged >40 years, (pmol/l)	
- Beginning	16,6 ± 5,03
- End	10,6 ± 0,25
TSH rate male aged >40 years, (uIU/ml)	
- Beginning	0,009 ± 0,007
- End	1,66 ± 1,2
Types of Antithyroid Drugs, n (%)	
- Methimazole	58 (85,2)
- Prophyltiouracil	10 (14,7)

Table 1 shows that the majority of Graves' disease patients are aged 18-40 years, namely 36 people (53%), then aged >40 years (47%). Then for gender, Graves' disease patients are more common in women, namely 58 people (85%), followed by men 10 people (15%). Then, there were 37 patients (55.5%) who achieved a euthyroid condition of <12 months, while 31 patients (45.5%) achieved a euthyroid condition >12 months. Then Graves' disease patients experienced a decrease in free Thyroxine 4 (fT4) levels from 39.2 ± 30.3 pmol/l to 12.1 ± 1.5, as well as an increase in Thyroid Stimulating Hormone (TSH) levels from 0.3 ± 1, 2 uIU/ml becomes 2.1 ± 1.3 uIU/ml. And the majority of patients used Methimazole (MMI) as the main treatment, namely 58 people (85%) and 10 people (15%) using Propylthiouracil (PTU). In order to achieve euthyroidism, the average patient takes 17 months.

Based on age distribution, ages 18-40 years are more affected by this disease. This is in accordance with research from Wardana et. al. they found that the rate of hyperthyroidism was dominated by the young age group, namely the age range 31-40 years (87.6%) followed by 21-30 years (87.4%) (Wardana et al., 2023). Other journals also stated that hyperthyroidism could occur more seriously in patients Graves' disease is young and male, and has high levels of TRAb, but the severity decreases with increasing age in both sexes (Magri et al., 2016; Suzuki et al., 2022). However, there is research that contradicts this, namely research by Smith TJ. et. al. they said that Graves' disease more often attacks patients aged 30-60 years.

Based on gender distribution, women are more affected by this disease, this is in line with research by Lestary, Ayundha Rizky et. al. who said that Graves' disease often attacks female patients aged 20-50 years (Lestary et al., 2023). A study conducted by Magri et. al. also states that the ratio of this disease in women and men is 3.4:1. Other research also says that women have a 3% risk of developing this disease and 0.5% for men. They also stated that the ratio between women and men in this disease is 4:1 (Ippolito et al., 2021).

Based on the time to achieve euthyroid conditions in Graves' disease patients, on average patients need 17 months to achieve euthyroid conditions. This is in accordance with research conducted by Magri, et. al they say that the duration of

treatment using antithyroid drugs is 12-18 months. In addition, antithyroid drug treatment should be given at the full dose (30 mg/day) after diagnosis.

Tabel 2. Analysis The Relationship of Age and Gender on The Time to Achieve Euthyroid in Graves' Disease Patients at RSUD Ulin Banjarmasin

Variable	*Hazard ratio*	CI 95%		*p-value*
		Lower bound	*Upper bound*	
Age (>40 years vs 18-40 years)	0,528	0,268	1,038	0,064
- Male	0,350	0,022	5,675	0,460
- Female	0,624	0,310	1,255	0,186
Gender (female vs male)	4,334	1,040	18,054	0,044*
- 18-40 years	3,135	0,422	23,275	0,264
- >40 years	4,478	0,580	34,547	0,150

*Statistically meaningful ($p < 0.05$)

In table 2, there is a Hazard ratio, namely the comparison ratio of variables between the controlled category and the comparison category. In terms of age, researchers compared those aged >40 years with those aged 18-40 years. Then in terms of gender, researchers compared women with men.

In the age variable, those aged >40 years have a chance of achieving euthyroidism 0.528 times that of those aged 18-40 years. In the gender variable, women have a chance of achieving euthyroidism 4.334 times that of men. And respectively, they have better chances compared to men aged 18-40 years and >40 years, amounting to 3,135 times and 4,478 times.

Table 3. Median analysis of The Relationship of Age and Gender on The Time to Achieve Euthyroid in Graves' Disease Patients at RSUD Ulin Banjarmasin

Variabel	*Median*	*Lower bound*	*Upper bound*
Age			
- 18-40 years	8,000	6,320	9,680
- >40 years	Cannot be analyzed	Cannot be analyzed	Cannot be analyzed
Gender			
- Male	Cannot be analyzed	Cannot be analyzed	Cannot be analyzed
- Female	9,000	7,350	10,650

In this median table, patients aged 18-40 years have a median value of 8,000, which means that by the 8th month half the population aged 18-40 years has reached euthyroidism, while aged >40 years the median value cannot be analyzed because not yet half the population has reached euthyroidism. reached euthyroid by the end of observation. For gender, women have a median value of 9,000, which means that by the 9th month half the population of women has reached euthyroidism, while for men the median value cannot be analyzed because not half of the population has reached euthyroidism by the end of the observation.

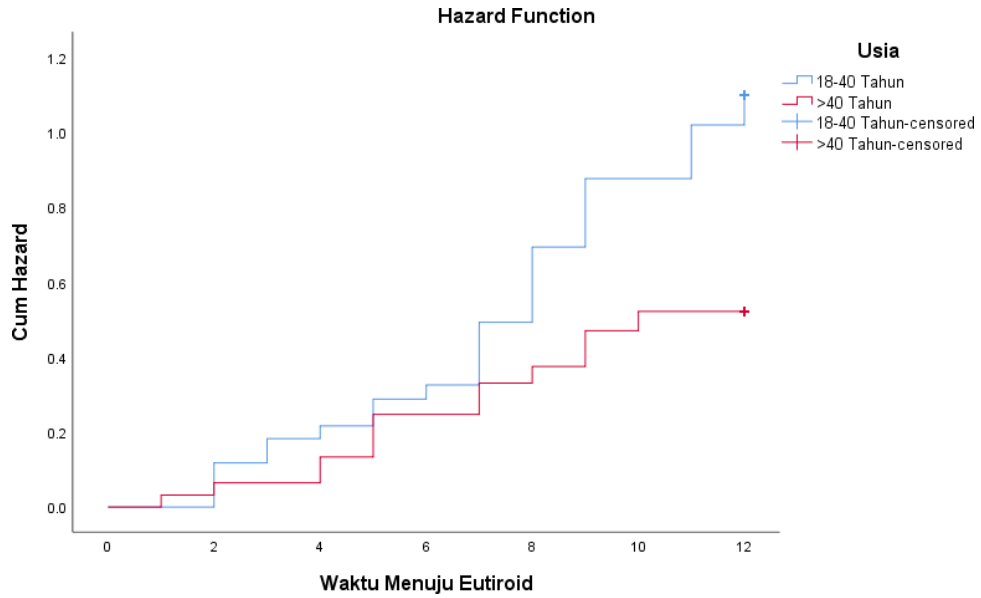

Figure 2. Kaplan-Meier curve of age versus time to reach euthyroid state

In table 2, the results of the bivariate analysis between the relationship between age and the time to achieve euthyroid conditions at the Ulin Hospital, Banjarmasin using the Cox regression test do not show a significant relationship (p=0.064). Then by presenting the data using the Kaplan Meier curve, at the 12th month, patients aged >40 years had a Hazard function value of 0.5 and those aged 18-40 years had a value of 1.1. The probability of age 18-40 years is greater than age >40 years, which means the rate of age 18-40 years is faster to reach an event or euthyroidism compared to age >40 years.

This non-meaningful result is in line with research by Dauksiene (p=0.79) in 2013. This study used 194 subjects aged >18 years, he said that patients aged <40 years had the same level of euthyroid condition as older people or there is no difference, but they say that patients aged <40 years have the potential to have a large goiter compared to those aged >40 years. Then research from Suzuki et. al. in 2021 also said the same thing, namely that there was no significance (p=0.08) between age and the time the euthyroid state was reached, but they said that fT4 levels in older patients tended to decrease due to increasing age, as well as men aged 20-30 years more likely to suffer from severe hyperthyroidism and young people are more at risk of relapse (Suzuki et al., 2021).

However, there is research from Allahabadia. et. al. in 2000 they used 536 Graves' disease patients (349 patients aged <40 years and 187 patients aged > 40 years), which showed a significant (p=0.01) relationship between age and time to reach euthyroid condition, age <40 years had The possibility of euthyroidism is lower than >40 when using ATD, and for the age category <40 years it is necessary

to consider immediate surgery or using radioactive iodine (RAI).25 Their study also used a retrospective cohort method.

The mechanism why it takes longer for people aged >40 years to reach euthyroidism is probably influenced by an aging thyroid gland, so that it cannot respond well to the stimulus of decreasing T3 and T4 levels. As age increases, the incidence of thyroid dysfunction increases, such as decreased TSH activity (Taylor et al., 2018)(Barbesino, 2019). Research from Charausia P et. al also said that the frequency of thyroid problems is more common at ages >40 years. The average TSH level in their study also showed that older people were higher than younger people. In addition, patient compliance with therapy visits is also thought to influence the results of this study.

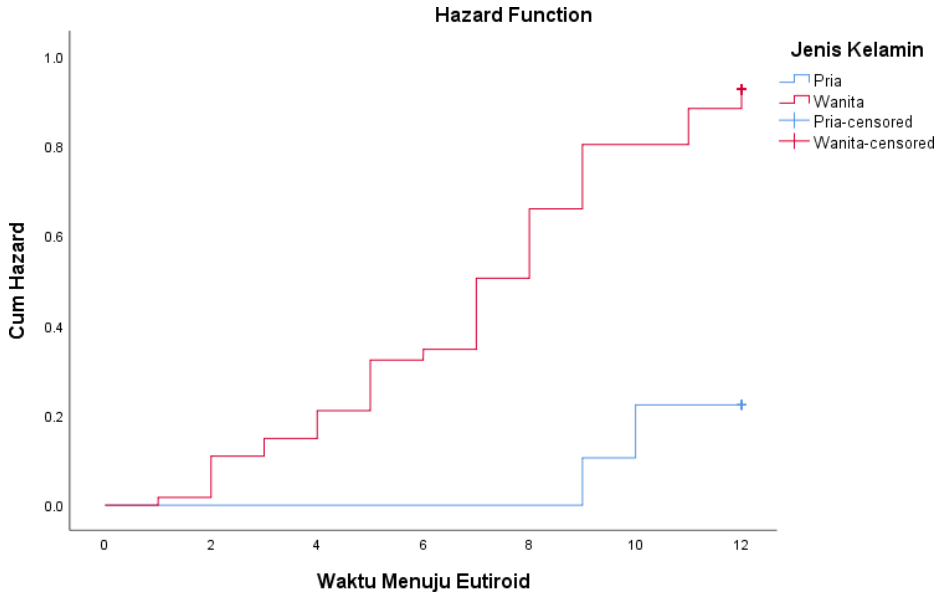

Figure 3. Kaplan-Meier curve of gender versus time to reach euthyroid state

For gender, the results of the bivariate analysis in table 2, the relationship between gender and the time to achieve euthyroid conditions using the Cox regression test shows significance (p=0.044). Then, presenting the data using the Kaplan Meier curve, at the 12th month, male patients had a Hazard function value of 0.22 and women had a value of 0.9. The probability that women are greater than men, this means that women are more likely to experience euthyroidism than men.

These results are in line with research conducted by Allahabadia et. al. (p<0.01) in 2000 they used 536 Graves' disease patients (444 female patients and 92 male patients), they said that achieving euthyroidism in men after using antithyroid drugs was less likely compared to women. Likewise, research by Gigliotti in 2021 stated that men need a longer time than women to reach a euthyroid state. This study used subjects totaling 21,633 patients with details of 81.7% women and 18.3% men. Patient data was taken from January 2005-June 2019 (Gigliotti, 2021). The American Thyroid Association 2016 also stated that after being given antithyroid drugs, men have the potential to be more low to reach

a euthyroid condition (Ross et al., 2016). Research from Suzuki et. al in 2021 with Kaplan Meier analysis ($p<0.0001$) said men need a longer time to achieve euthyroidism compared to women, the Cox proportional hazards method shows a Hazard ratio of 41% [CI] = 1.41 [1.21–1.64] for the condition euthyroid in women when compared to men.

However, there is research by Diker-Cohen et. al in 2019 at Rabin Medical, Israel. This study used 235 patients as subjects with 171 female patients and 64 male patients. This research states that there is no significant difference between men and women regarding the conditions of remission and relapse. However, they say women tend to remission more quickly, namely 58% compared to men at 47%.

This study is the first study to analyze the relationship between age and gender on the time to achieve euthyroidism in Graves' disease patients who received antithyroid drug therapy in South Kalimantan. This research can also describe the proportion of age and gender in Graves' disease patients at the Endocrine Polyclinic at Ulin Hospital, Banjarmasin.

However, there are still several limitations to this research that could influence the research results. Firstly, the number of subjects was small, resulting in a lack of power to detect the relationship between age and gender on the time to achieve euthyroid conditions in the Endocrine Polyclinic at Ulin Hospital, Banjarmasin. Second, the analysis of this study was carried out bivariately, so it could not control for other risk factors such as iodine intake, smoking status, small goiter and type and dose of ATDs treatment, because they may have an influence on the results of this study. Third, the database BEST- T 2 does not include a history of hereditary diseases, previous illnesses, physical examination. Fourth, determining the patient's euthyroid status in Graves' disease patients in the BEST-T 2 database at Ulin Banjarmasin Hospital is still based on examination of clinical symptoms, and fT4 and TSH levels are not yet equipped with examination of thyroid hormone receptor antibody (TRAb) levels from laboratory examinations.

It is hoped that this research can provide information, increase knowledge and become an additional reference for health workers, education and the public regarding the relationship between age and gender on the time to achieve euthyroidism in Graves' disease patients. This research can be used as a reference for further research with a research design that can control other risk factors (multivariate) and using other research designs, such as a randomized controlled trial (RCT), which is a procedure generally used in drug trials or medical procedures.

CONCLUSION

Based on the research that has been carried out, researchers concluded that the majority of Graves' disease patients in this study were aged 18-40 years, female, initial fT 4 levels 39.2 ± 30.3, initial TSH levels 0.3 ± 1.2, and more people use methimazole. Then the average time for reaching a euthyroid condition for Graves' disease patients at Ulin Regional Hospital, Banjarmasin is 17 months. Then, there was no statistically significant relationship between age ($p=0.064$) and the time to achieve euthyroidism, but there was a statistically significant relationship between gender ($p=0.044$) and the time to achieve euthyroidism.

It is hoped that future research can use a larger number of subjects so that the results obtained can represent the general population. Then, use a research design with a research analysis design that can control other risk factors (multivariate) so that the results obtained are more accurate. Then, the Borneo Wetland Study on Thyroid 2 (BEST-T 2) database can add more complete information regarding anamnesis and physical examination results. And finally, making a diagnosis of GD can begin using laboratory tests for thyroid hormone receptor antibody (TRAb) levels.

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