Incidence, treatments, and outcomes of Graves' disease in Thailand: a single-center study

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Research Article

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Abstract

Background: Treatment patterns and outcomes of Graves' disease (GD) are various around the world. Studies of the Asian population are lacking. The aim was to evaluate Thai patients with GD.

Methods: Patients with new diagnoses of GD between 2014-2018 were retrospectively reviewed in a single center.

Results: The age-adjusted incidence of GD was 26.57 per 100,000 per year. The analysis included 355 patients with follow-up at least 12 months and age of at least 15. Antithyroid drug (ATD) was the most popular treatment with 99.7%, followed by radioactive iodine (RAI) with 0.3%. The most effective treatment was RAI with a remission rate of 78.4% and time to failure of 54 months (p = 0.014), compared to ATD and surgery. ATD was the worst effective treatment with a remission rate of 21.5% and time to failure of 43.9 months. Multivariable Cox regression analysis showed TSH <0.01 uIU/ml was a significant factor for time to failure (HR 1.42, CI 1.03-1.96).

Conclusion: Treatment failure with ATD was frequent in this population. More effective treatment could be preferred to prevent relapse and complications of the disease.

Background

Graves' disease (GD) is the most common cause of hyperthyroidism [1]. This disease occurs in 3% of women and 0.5% in men [2, 3] with an incidence of 20–40 cases per 100,000 population per year [3, 4]. It is an autoimmune disease caused by thyroid-stimulating hormone receptor (TSHR) autoantibodies rendering the thyroid gland to produce excess thyroid hormone. Symptoms of hyperthyroidism vary from mild to severe forms including weight loss, palpitation, anxiety, and heart failure [5]. Treatments of GD comprise of antithyroid drugs (ATD), radioactive iodine (RAI), and surgery. ATD is generally the first-line treatment with a duration of 12–18 months [6]. Advantages of ATD are easily accessible and euthyroid achievable, but downsides are risk of hepatotoxicity and agranulocytosis and low remission rate of 50–55%. RAI and surgery are the latter choices with a remission rate of 90%. Even though RAI is more commonly used in the US as the first-line treatment [7, 8], it is contraindicated in patients with pregnancy and severe eye disease. ATD is the most popular treatment in Europe, Asia, and recently in the US [7, 9, 10]. The 2016 American Thyroid Association (ATA) and 2018 European Thyroid Association (ETA) guidelines recommend RAI with patients with high-risk mortality, but the recent National Institute for Health Care and Excellence (NICE) guideline in England recommends RAI as the first-line treatment due to its efficacy [11]. The benefit and risk of each modality may affect each individual's life differently, therefore the shared decision between doctors and patients is likely to fit the patients' preference [12, 13]. A trend toward ATD in Thailand was seen in the questionnaire survey [14] and a low remission rate was seen in the retrospective review in the private hospital [15]. This study aimed to explore the treatment choices and outcomes of GD in the hospital center in the suburban area.

Methods

A retrospective study was conducted to obtain newly diagnosed GD patients in Prapokklao hospital, a tertiary hospital center in the Chanthaburi province, in the eastern part of Thailand, with 5 years from 2014–2018. Patients were identified by searching in electronic medical records (EMR) with at least 1 diagnosis code of GD (ICD-10-CM E05.0). For incidence analysis, the patients with the age of 15 or more regardless of the follow-up time were included. For treatment analysis, the patients must have at least a 12-month follow-up after treatment and the age of 15 or more.

Data of age, gender, TSH, FT3, FT4, TSHR autoantibody, treatment choice, and outcome were collected. The reference range of normal values are 0.27–4.2 uIU/ml for TSH, 2.0-4.4 pg/ml for FT3, 0.93–1.71 ng/ml for FT4 and 0-1.75 IU/L for TSHR antibody.

Treatment failure was defined as being unable to withdraw ATD at the last follow-up. For ATD treatment > 60 days switching to RAI or surgery was considered a failure. ATD treatment < 60 days was considered pretreatment ATD before RAI or surgery. Remission was defined as either euthyroid or hypothyroid without ATD for at least a month.

Data analysis was performed using IBM SPSS statistics version 21. Univariable Cox regression analysis was used to explore factors associated with treatment failure with ATD. Variables with a p-value < 0.2 in univariable analysis were included in the multivariable analysis. Statistical significance was considered when a p-value < 0.05. The Kaplan-Meier curves were used to compare time to failure between ATD, RAI, and surgery. This study was approved by the institutional review board (COA No.094-2020).

Results

Incidence analysis

The available data to analyze the incidence was only in the Muang district because Thai policy in the healthcare system mandated patients to go to hospitals based on their address. The tertiary hospital received both based patients in the Muang district and referral patients from other districts. Six hundred and twenty-seven patients were found after searching for newly diagnosed GD and 169 patients were in the Muang district. From the National Statistical Office of Thailand, there were 129,113 people in the Muang district of Chanthaburi province in 2020, the survey was done once for each decade. The crude incidence rate of GD between 2014–2018 was 26.18 per 100,000 per year. Females involve 60.9% with a crude female to male ratio of 1.6:1. The standard population has a female to male ratio of 1.07:1, giving the same adjusted sex incidence of 26.18 per 100,000 per year. The age-adjusted incidence was 26.57 per 100,000 per year.

Treatment Analysis

The total cases were 355 patients (Fig. 1.). Females involve 68.2%, with a female to male ratio of 2.1:1. The mean age at diagnosis was 43 ± 15.4 years with the median follow-up time of 41 months (IQR 29–56) (Table 1.).

Table 1
Clinical characteristics

Characteristics	Overall N = 355 (%)	Remission N = 142 (%)	Failure N = 213 (%)
Sex	242 (68.2%)	113 (79.6%)	129 (60.6%)
Female	113 (31.8%)	29 (20.4%)	84 (39.4%)
Male	43 ± 15.4	42.6 ± 15	43.1 ± 15.6
Mean Age (± SD)			90 (42.3%)
Age group	156 (43.9%)	66 (46.5%)	123 (57.7%)
< 40y	199 (56.1%)	76 (53.5%)	0.005
≥ 40y			(IQR 0.005–0.009)
TFT	0.005	0.005	15.2
Median TSH	(IQR 0.005–0.01)	(IQR 0.005–0.01)	(IQR 8.7–23.6)
(N 0.27–4.2 uIU/ml)	14.3	13.8	5.1
Median FT3	(IQR 8.2–23.4)	(IQR 6.7–22.9)	(IQR 3.2–7.8)
(N 0.93–1.71 ng/ml)	4.8		158 (74.2%)
Median FT4	(IQR 3.1–7.5)	4.4	51 (23.9%)
(N 2.0-4.4 pg/ml)		(IQR 2.6–6.7)	105 (49.3%)
TSH*	250 (70.4%)		107 (50.2%)
< 0.01	96 (27%)	92 (64.8%)	93 (43.7%)
≥ 0.01		45 (31.7%)	87 (40.8%)
FT3*	185 (52.1%)		25 (11.7%)
≤ 3UNL	169 (47.6%)	80 (56.3%)	1 (0.5%)
> 3UNL		62 (43.7%)	12 (5.6%)
FT4*	165 (46.5%)		30 (14.1%)
≤ 3UNL	135 (38%)	72 (50.7%)	7 (3.3%)
> 3UNL		48 (33.8%)	19 (8.9%)
Extrathyroidal signs	42 (11.8%)		15 (7%)
GO	2 (0.6%)	17 (12%)	2 (0.9%)
Acropachy	18 (5.1%)	1 (0.7%)	

*Missing data in 9 pt of TSH, 1 pt of FT3 and 55 pt of FT4. **Including impending thyroid storm and thyroid storm. UNL, upper normal limit; GO, Graves' orbitopathy; TPP, thyrotoxic periodic paralysis; AF, atrial fibrillation.

Characteristics	Overall N = 355 (%)	Remission N = 142 (%)	Failure N = 213 (%)
TPP	48 (13.5%)	6 (4.2%)	
AF	9 (2.5%)	18 (12.7%)	
Pregnancy	30 (8.5%)	2 (1.4%)	
Severe disease**	24 (6.8%)		
Heart failure	3 (0.8%)	11 (7.7%)	
Hepatitis		9 (6.3%)	
		1 (0.7%)	

*Missing data in 9 pt of TSH, 1 pt of FT3 and 55 pt of FT4. **Including impending thyroid storm and thyroid storm. UNL, upper normal limit; GO, Graves' orbitopathy; TPP, thyrotoxic periodic paralysis; AF, atrial fibrillation.

The chosen first-line treatments were ATD in 99.7% and RAI in 0.3%. ATD was used with methimazole (MMI) of 98% and propylthiouracil (PTU) of 14.6%. The median duration of MMI was 31 months (IQR 22–46) and PTU was 1 month (IQR 0.9–13). All ATD treatments were titration regimens without block and replace regimens. RAI was used in 21.1% with a median cumulative dose of 333 MBq (9 millicurie) (IQR 222-603.1). All remission patients who underwent RAI became hypothyroidism. Surgery was done in 2.5%. There was 1 patient who chose the first-line treatment as RAI due to chronic hepatitis C infection. Overall remission at the last follow-up was 40%, the most remission rate in each intervention was seen in surgery with 88.9%, followed by RAI with 77.3% and ATD with 21.5%.

Serious adverse events of ATD included 0.6% of agranulocytosis without hepatitis or vasculitis. Surgery showed 33.3% of overall complications with 22.2% of permanent hypocalcemia, 11.1% transient hypocalcemia, and 11.1% of recurrent laryngeal nerve injury. There was 1 patient who had both permanent hypocalcemia and recurrent laryngeal nerve injury. RAI showed no complication of thyroid storm or worsening of Graves' orbitopathy.

Multivariable cox regression analysis showed a significant factor associated with time to failure in ATD patients was TSH < 0.01 uIU/ml (HR 1.42, CI 1.03–1.96) (Table 2.). The Kaplan-Meier analysis could not calculate the median time to failure of surgery due to only 1 event out of 9 patients occurred, therefore the remission probability never reached 50%. Instead, the mean time to failure was 54, 43.9, and 42.3 months for RAI, ATD, and surgery, respectively (p = 0.014) (Fig. 2.).

Table 2
Factors associated with time to failure in patients receiving ATD with univariable and multivariable cox regression analysis

Factors	Univariate p-value	HR (95% CI)	Multivariate p-value	HR (95% CI)
Sex	0.67	1.06 (0.82–1.36)	0.26	0.85 (0.64–1.13)
Female				
Male			0.054	
Age				0.67 (0.45–1.01)
< 40y	0.02*			
≥ 40y		0.76 (0.6–0.96)	0.031*	
GO	0.06			1.42 (1.03–1.96)
Present		0.71 (0.49–1.02)		
Absent				
TSH	0.004*			
< 0.01 uIU/ml		1.5 (1.14–1.97)		
≥ 0.01 uIU/ml				
FT3	0.44			
≤ 3UNL			0.49	
> 3UNL		1.1 (0.87–1.39)		1.1 (0.84–1.44)
FT4	0.12			
≤ 3UNL				
> 3UNL		1.22 (0.95–1.59)		
TPP	0.65			
Present				
Absent			0.18	
AF		1.13 (0.66–1.95)		
Present	0.09			0.76 (0.5–1.14)

GO, graves' orbitopathy; UNL, upper normal limit; TPP, thyrotoxic periodic paralysis;

AF, atrial fibrillation.

Factors	Univariate p-value	HR (95% CI)	Multivariate p-value	HR (95% CI)
Absent Severe disease Present Absent	0.52	0.74 (0.52–1.05) 1.15 (0.76–1.75)		
GO, graves' orbitopathy; UNL, upper normal limit; TPP, thyrotoxic periodic paralysis;				
AF, atrial fibrillation.				

Discussion

This study is the first report of the incidence of GD in Thailand. The age-adjusted incidence of GD in this study was 26.57 per 100,000, similar to other countries about 20–40 per 100,000, but the female to male ratio of 1.6:1 is lower than others of 10:1 [1–4].

The first-line treatment was an ATD of 99.7%, higher than the recent survey study of 90.8% [14] and retrospective review of 70.8% in Thailand [15]. The RAI treatment of 0.3% was lesser than 21% of the previous study. Like other countries in Asia and Europe [16], ATD is the most popular treatment. The median duration of ATD treatment was 32 months (IQR 22–47), almost twice longer than the recommended duration of 12–18 months [6]. Due to RAI unavailability in the local site, the leftover treatments were prolonged ATD treatment and surgery. This logistic problem probably explained the causes of much more ATD preference and duration. MMI was the most preferred ATD in general and PTU was usually used in severe disease and pregnancy. TRAB was done only 2.2%, probably due to high cost and long turn-around time.

The remission rate of ATD was 21.5%, similarly, the remission rate from the retrospective study of Thai patients in the private hospital was 30.7% [15]. This ATD remission rate was drastically different from the studies in the US and Europe of 50% [17–19], even though ATD duration was prolonged. The author suspected high iodine diet in general and genetic components were the cause of refractory disease, even though the patients were instructed to take a low iodine diet for a week before RAI. More intensive treatment such as higher dose RAI or surgery might be proper in this circumstance. RAI showed the most effectiveness in combined with remission rate and time to failure. Surgery showed the most remission rate but the worst time to failure and complication. These were probably due to non-specialized surgeons

in the countryside hospital where thyroidectomy was usually performed by Ear-Nose-Throat (ENT) or general surgeons. The small sample size of 9 out of 355 patients who underwent surgery could cause inaccurate outcomes as well. Although long-term ATD could be considered in a refractory disease [6], this strategy showed better results compared to RAI in hypothyroidism and GO [20, 21]. The remission rates were 77.3% for RAI and 88.9% for surgery, less successful than the nationwide study in the US of 93% for RAI and 99% for surgery [17].

RAI had the most safety profile without any complications, except the adverse condition of hypothyroidism. Surgery showed most complications of 33% with 3 out of 9 patients, followed by ATD of 1.1%. The risk of surgery was varied in previous studies, hypocalcemia occurred 9.4–54.4% and recurrent laryngeal nerve injury occurred 0.9–33% [22–25]. To decrease these risks, the procedure should be done by a skilled high-volume surgeon. Risk of agranulocytosis occurred far less about 0.1-1.0% [26–28].

The cost-effective treatment was seen most in RAI with about 100 USD (3,000 Thai Baht) per a single treatment, followed by subtotal thyroidectomy with 830 USD (25,000 Thai Baht) per single surgery and MMI with 54 USD (1,620 Thai Baht) per year for a dose of 15 mg per day. Thyroxin replacement cost was 12 USD (360 Thai Baht) per year for a dose of 100 mcg per day. These costs were used in public hospitals and covered by the Thai universal health care system. On the other hand, in private hospitals, the costs were usually three times higher. Costs of treatment were various in different countries, the most cost-effective modality was RAI in the UK but total thyroidectomy in the US [17].

We analyzed the predictors of the ATD time to failure and found TSH < 0.01 uIU/ml as a significant factor. We did not find any association between time to failure and FT3 and FT4. However, younger age, high FT3, FT4, orbitopathy, and large goiter size were significant factors predicting treatment failure in the past studies [15, 17, 29, 30].

Several limitations could have influenced this study. The incidence analysis included only a small number of patients due to a lack of good data management. The retrospective scheme might have confounder and bias. This study was not categorized as a controlled disease and might underestimate remission patients in a different definition.

Conclusion

This study described the epidemiology of GD in the Asian population. Treatment failure occurred more often than the western countries. RAI was the safest and most effective treatment. ATD was the worst successful treatment with a one-fourth remission rate. TSH < 0.01 uIU/ml was a predictor of the treatment failure and may need a more effective modality.

Abbreviations

GD
Graves’ disease

ATD
antithyroid drug
RAI
radioactive iodine
TSHR
thyroid-stimulating hormone receptor
ATA
American Thyroid Association
ETA
European Thyroid Association
NICE
National Institute for Health Care and Excellence
EMR
electronic medical records
TSH
thyroid-stimulating hormone
FT3
free thiiodothyronine
FT4
free thyroxine
MMI
methimazole
PTU
propylthiouracil

Declarations

Ethics approval and consent to participate:

This study was approved by the institutional review board (COA No.094-2020). No consent was done due to retrospective design.

Consent for publication:

Not applicable.

Availability of data and materials:

Datasets are available on request.

Competing interests:

The author has no potential conflict of interest associated with this research.

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Author Contributions:

The author designed the study, collected and analysed the data, and wrote the manuscript.

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Figures

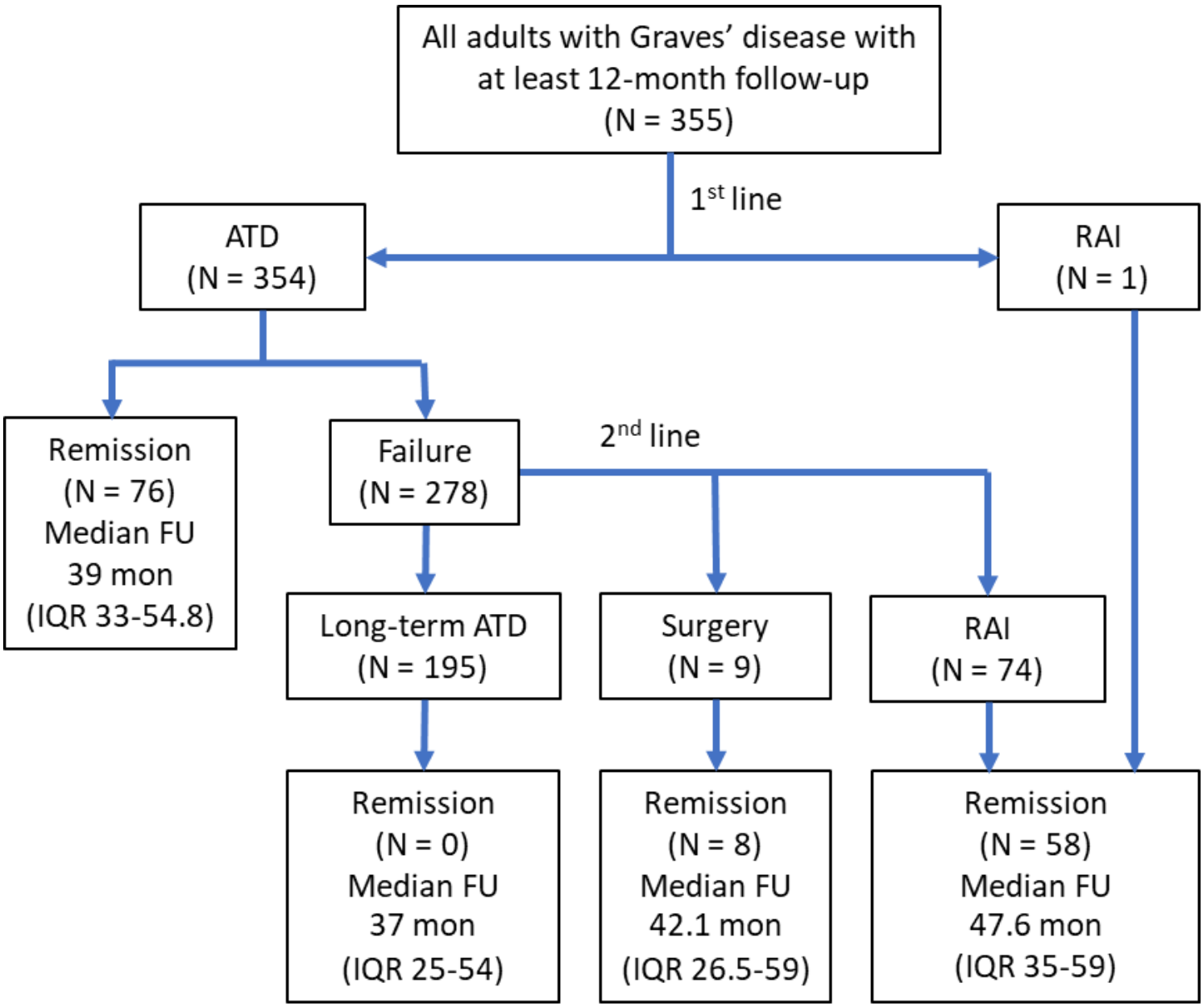

Figure 1

Study population treatment pathways.

ATD, antithyroid drug; FU, follow-up; IQR, interquartile range.

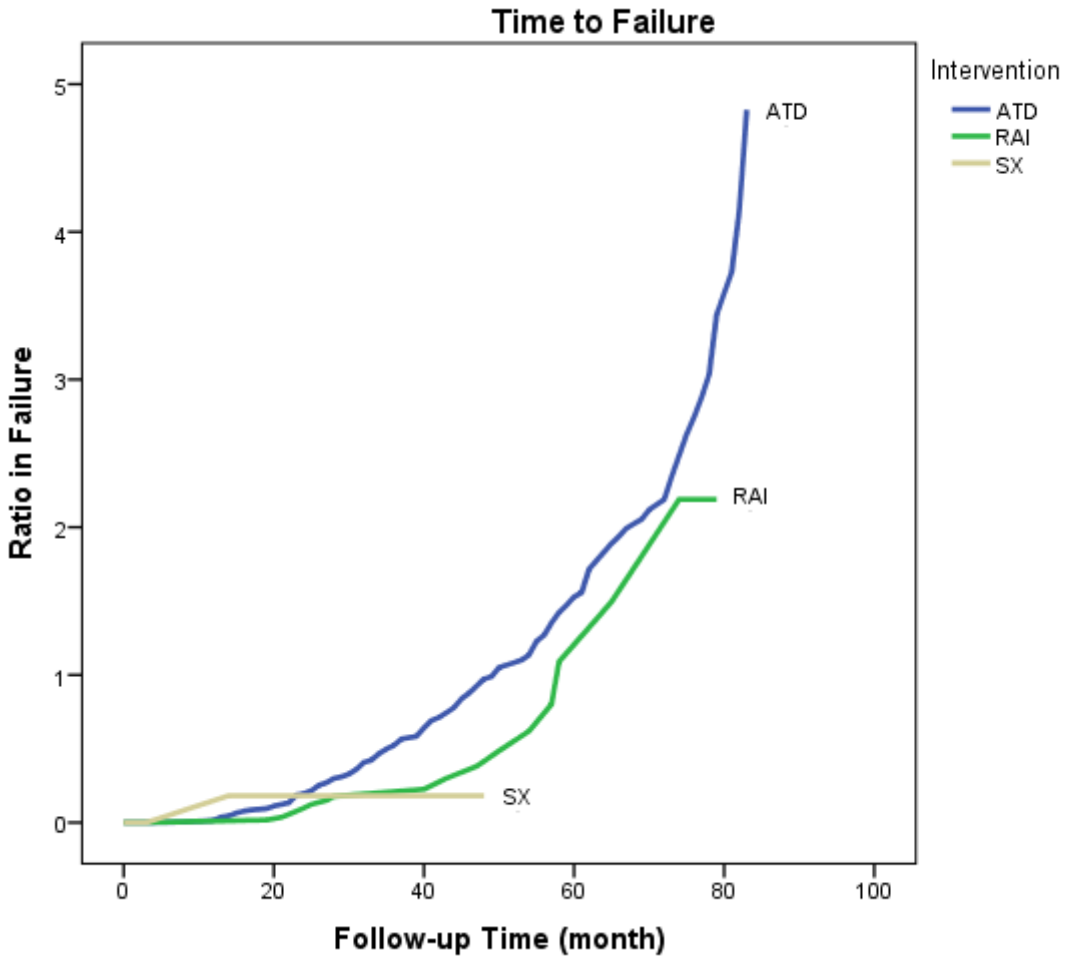

Figure 2

The Kaplan-Meier curves showed the mean time to failure was 54, 43.9, and 42.3 months for RAI, ATD, and surgery, respectively (p = 0.014). ATD, antithyroid drug; RAI, radioactive iodine; SX, surgery.