



**St. Paul Hospital Millennium Medical
College Graduate Study Program**

**Time to Normalization of Thyroid function test and Associated
factors among thyrotoxic patients on follow up at SPHMMC
Endocrine clinic, Addis Ababa, 2024 G.C.**

By: - Dr. Dagim Kassahun (Internal Medicine Resident)

February, 2024 G.C.

Addis Ababa, Ethiopia



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Addis Ababa, Ethiopia

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St. Paul Hospital Millennium Medical College

Graduate Study Program

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Contents

Acknowledgment	i
List of Figures	iv
List of tables.....	v
Acronyms and abbreviations.....	vi
Abstract	vii
1. Introduction.....	1
1.1 Background	1
1.2 Statement of the problem	3
1.3 Significance of the study	4
2. Literature Review	5
2.1 Time to Euthyroidism	5
2.2 Factors associated with time to Euthyroidism.....	7
2.3 Conceptual frame work	9
3. Objectives	10
3.1 General Objective:.....	10
3.2 Specific Objective:.....	10
4. Methods and Materials.....	11
4.1 Study area.....	11
4.2 Study design and period	11
4.3 Population.....	11
4.3.1 Source population	11
4.3.2 Study population.....	11
4.4 Sampling technique	12
4.4.1 Sample size and sampling procedure.....	12
4.6 Inclusion and Exclusion criteria	12
4.6.1 Inclusion criteria	12
4.6.2 Exclusion criteria.....	13
4.7 Variables.....	13
4.7.1 Dependent variables	13

4.7.2 Independent variables	13
4.8 Operational definitions	14
4.9 Data collection and procedures	15
4.9.1 Data collection tool and technique	15
4.9.2 Data collectors	15
4.9.3 Data quality control	15
4.10 Data Analysis	15
4.11 Ethical consideration	15
5. Results	16
5.1 Socio-demographic and characteristics of study populations	16
5.2 Treatment-related characteristics of study populations.....	17
5.2 Baseline sign and symptoms of the study populations.....	18
5.3. Comorbidities of the study populations	19
5.4. Medication related characteristics of the study populations	20
5.5. Time to Normalization of Thyroid Function Test.....	21
5.6. Proportional Hazard Assumption Test	22
5.7. Predictors of time normalization of thyroid function test	23
6. Discussion	26
7. Strength and limitation of the study	28
8. Conclusion	28
9. Recommendation	29
10. References	30
Annexes.....	32
Annex I: Information sheet	32
Annex II: Data collection checklist	1

List of Figures

Figure 1: Conceptual framework for a study on Time to Normalization of thyroid function test and associated factors among patients with thyrotoxic patients.

Figure 2: The overall time to normalization thyroid function test of patients with thyrotoxicosis followed at SPHMMC hospital April 2023 G.C. to January 2024 G.C. [n= 181]

Figure 3: The overall time to normalization of thyroid function test among patient with thyrotoxicosis by drug adherence followed at SPHMMC hospital April 2023 G.C. to January 2024 G.C. [n= 181]

Figure 4: A cumulative hazard plot of Cox-Snell residuals for model fitness.

List of tables

Table 1: Frequency distribution of socio-demographic and clinical-related characteristics of patients with thyrotoxicosis visited SPHMMC hospital from April 2023 G.C. to January 2024 G.C. [n=181]

Table 2: Frequency comorbidities and baseline signs and symptoms of patients of patients with thyrotoxicosis visited SPHMMC hospital from April 2023 G.C. to January 2024 G.C. [n=181]

Table 3: Frequency comorbidities of patients of with thyrotoxicosis from April 2023 G.C. to January 2024 G.C.

Table 4: Multivariable Cox regression analysis for independent predictors of time to normalization of thyroid function test among patient with visited SPHMMC hospital from April 2023 G.C. to January 2024 G.C. [n=103]

Acronyms and abbreviations

AF: Atrial fibrillation

ATD: Antithyroid drugs

BB: Beta- Blockers

CHF: Congestive heart failure

CI: Confidence Interval

DC: Data Collectors

ETB: Ethiopian Birr

FT3: Free T3

FT4: Free T4

GD: Graves' disease

IRB: Institutional Review Board

MMI: Methimazole

PI: Principal Investigator

PTU: Propylthiouracil

SPHMMC: St. Paul's Hospital Millennium Medical College

TMNG: Toxic multinodular goiter

TNG: Toxic nodular goiter

TRAb: Thyroid receptor antibody

TSH: Thyroid stimulating hormone

Abstract

Background: Thyrotoxicosis is typically brought on by excessively high tissue thyroid hormone levels. Untreated or only partially treated thyrotoxicosis can result different complications. The findings of this study will be important to address the above issue and to have plan to alleviate it thereby improving the quality of the treatment provided for our patients

Objectives: The aim of the study was to assess Time to normalization of Thyroid function test and associated factors among thyrotoxic patients of follow up at Endocrine clinic of St. Paul's Hospital Millennium Medical College, Addis Ababa, Ethiopia, 2023.

Methods: A hospital-based retrospective cohort study was conducted on 181 patients with thyrotoxicosis who had attended adult Endocrine clinic at St. Paul's Hospital Millennium Medical College from April 2023 to January of 2024. The data was collected using structured questionnaire. Data was entered using Epi data manager software version 7.1 and exported to STATA version 15 for analysis. Descriptive statistics of numeric variables was presented using mean with standard deviation or median with interquartile range, whereas categorical variables were expressed as a frequency and percentages. The association between the independent variable and time to normalization of TFT was analyzed using the Cox proportional hazard regression model. Log rank was used to identify the presence of significant difference in median time between different groups. The adjusted hazard ratio (AHR) with a 95% confidence interval (CI) was reported to show the strength of the association.

Result: One hundred eleven (61%) thyrotoxicosis patients become euthyroid with the median time to euthyroidism of 7 months, IQR (3-13) months. Type of anti- thyroid drug used (AHR = 0.33; 95% CI 0.12–0.89), Adherence to medication (AHR = 0.24; 95% CI 0.13–0.42), Base line pulse rate (AHR = 0.97; 95% CI 0.95–0.99) and baseline free thyroxin (AHR = 0.99; 95% CI 0.984–0.995) were the independent determinants of delayed time to euthyroidism.

Conclusion: More than half of the patients were euthyroid nonetheless, it took longer than anticipated. High baseline FT4, High baseline pulse rate, non- adherence to medication and use of PTU as a choice of anti-thyroid drug delayed time to euthyroidism. Patients with hyperthyroidism should get good attentive care until all thyroid function tests return to normal.

Key word: Thyrotoxicosis, survival analysis, Ethiopia

1. Introduction

1.1 Background

Thyrotoxicosis, a clinical condition caused by excessively high thyroid hormone action in tissues, is typically brought on by excessively high tissue thyroid hormone levels. The word "hyperthyroidism," is a type of thyrotoxicosis brought on by the thyroid's unnecessarily excessive synthesis and secretion of thyroid hormone. There are numerous etiologies, symptoms, and potential treatments for thyrotoxicosis(1).

In general, hyperthyroidism is categorized as overt or subclinical. Triiodothyronine (T3) and/or free thyroxine (free T4) estimates are high in serum in addition to a subnormal (often undetectable) serum thyrotropin (TSH). Low or undetectable blood TSH with T3 and free T4 readings that fall within the normal reference range is referred to as subclinical hyperthyroidism. Although subclinical hyperthyroidism is typically seen as milder, both overt and subclinical illness may result in recognizable signs and symptoms(1).

Graves' disease (70–80% of cases), toxic nodular goiter, toxic thyroid adenoma, and exogenous hyperthyroidism are the most frequent causes of Thyrotoxicosis in decreasing order of frequency (iatrogenic, factitious, iodine induced). The uncommon causes include ectopic thyroxine synthesis and excess thyroid stimulating hormone (trophoblastic and pituitary tumors)(2).

Thyrotoxicosis is frequently characterized by nervousness and increased activity, as well as sweating more than usual, heat sensitivity, palpitations, exhaustion, an increased appetite, weight loss, tachycardia, sleeplessness, weakness, and frequent bowel movements(3). Goiter, tachycardia, widening of pulse pressure, warm and wet skin, tremor, and ocular manifestations (stare, lid lag, lid retraction and photophobia) are among the usual signs. Atrial fibrillation and atrial flutter are rare signs(2).

Treatment of thyrotoxicosis include antithyroid drugs, b-blockers, radioactive iodine and thyroidectomy(1).

Atrial fibrillation, embolic events, occasionally cardiovascular collapse are some of the cardiovascular complications(4).

Weight loss, osteoporosis, , muscle weakness, tremor, neuropsychiatric symptoms, and mortality are all linked to untreated or only partially treated thyrotoxicosis(5).

Thyrotoxicosis may also end up with severe form called thyroid storm in uncontrolled patient and resulting impatient mortality, increased hospital stay, ventilation requirement, cardiovascular as well central nervous system complication(6).

1.2 Statement of the problem

Worldwide, 1-3% of the general population are affected by hyperthyroidism, and women experience it 10 times more frequently than males do. In the United States, the prevalence of hyperthyroidism is approximately 1.2% (0.5% overt and 0.7% subclinical)(1).

According to the UK Whickham study, the incidence of hyperthyroidism is between 100 and 200 cases per 100,000 people annually, with a frequency of 2.7% for women and 0.23% for males when both confirmed and suspected cases are taken into account. Similar incidence and prevalence rates have been recorded in studies from a number of other nations, including Sweden, Denmark, Norway, and Japan. An incidence rate of 51 per 100,000 per year and a mean prevalence rate of 0.75% were calculated from a meta-analysis of data from Europe(7).

Due to underdiagnosis and underreporting, the extent of thyroid diseases in Africa is unknown, although the few studies that are currently accessible note a prevalence rate of 1.2 to 9.9%(8).

A descriptive study done in Nigeria has shown that out of 78 thyroid disorders that has visited a hospital 84% were Hyperthyroidism patients(9).

Ethiopia is one of the most iodine-deficient nations in the world, despite new legislation being passed in 2011 under the National Nutrition Program, which increased access to iodized salt. The elimination of iodine deficiency disorder in Ethiopia, however, continues to be a serious challenge(10). Despite the fact that over 89.2% of salt in Ethiopia includes iodine, just 26% of salt is sufficiently iodized, according to a 2017 study(11). In Ethiopia, the prevalence of thyroid disease is reported to be 1.2%(8).

Less than one-third of participants in research conducted in Gondar had all of their TFTs normalized, implying that patients who were euthyroid were not functioning at their best and that PTU treatment delayed TFT recovery longer than predicted(12). Similarly, a study done South Tigray General Hospitals has shown time to euthyroidism was 9 months, longer than the expected time(13).

The above studies has also not taken into account patients adherence to ATD which is a major contributor to Normalization of TFTs(14).

1.3 Significance of the study

Available data are suggestive of untreated or partially treated thyrotoxicosis results in fatal and non-fatal complication. Attainment of Euthyroid state within possible defined time is crucial to prevent complication. As to my knowledge, there are only a couple of published papers about normalization of thyroid function test and factors that determine it in Ethiopia and there was no study done at our hospital.

The findings of this study are important to determine factors associated with normalization of thyroid function test at SPHMMC and to have plan to alleviate it thereby improving the quality of the treatment provided for our patients. Furthermore, the outcome of the study can be used as a basis for evidence-based guidelines to be published by the Federal Ministry of Health (FMOH), SPHMMC and also other stakeholders.

2. Literature Review

2.1 Time to Euthyroidism

Treatment options for hyperthyroidism include utilizing ATD to decrease thyroid hormone synthesis, as well as complete thyroidectomy or RAI to reduce the quantity of thyroid tissue(1).

In a well-established case of thyrotoxicosis in a single UK county (Leicestershire), a retrospective cohort analysis of 56,741 thyroid function test (TFT) results, treatment options, and outcomes revealed that, overall, T4 was more frequently controlled than thyroid stimulating hormone (TSH), and at the most recent follow-up, T4 was normal in >96%, TSH in >79%, and both in >76% of cases of different etiologies. The mean percentage control of T4 was 85% and TSH 50%. In long-term ATD courses (>2 years), this improved to 89% and 62%, respectively(15).

In a retrospective analysis of all cases of thyrotoxicosis identified at King Abdul-Aziz University Hospital in Jeddah, Kingdom of Saudi Arabia, between January 1997 and January 1999 that underwent at least one year of treatment, 140 (69%) patients had Graves' disease (GD), 59 (29%) had toxic multinodular goiter, and 2 (1%) each had toxic adenoma and subacute thyroiditis. Forty-five (45%) of patients were treated with antithyroid drugs of which 66 (72%) became Euthyroid. Of the 45 individuals who received antithyroid medication, 66 (72%) went on to develop normal thyroid function(16).

A retrospective study conducted at the Department of Endocrinology of the Royal Infirmary of Edinburgh, UK, to assess the initial response to carbimazole in patients with Graves' disease found that among patients under 30 years old, 50% of them were still biochemically hyperthyroid after 4-6 weeks of treatment, compared to 14% of those over 30(17).

A retrospective cohort study on 67 patients who underwent thyroidectomy for Graves' disease at two Canadian centers, one in Montreal and the other in Nova Scotia, between January 2006 and December 2016 revealed that 78% of patients were on methimazole, 34% on beta-blockers, 27% on potassium iodine solution, 10% on propylthiouracil, and 7% on steroids, and only 22 (33%) became euthyroid during the course of treatment(18).

In a multi-center retrospective cohort study conducted from March 30, 2020, to July 30, 2020, among adult thyrotoxicosis patients who received anti-thyroid medications in the medical and chronic ambulatory clinics of South Tigray General Hospitals, Ethiopia, it was discovered that 175 (51.9%) of these patients became euthyroid, with the median time to euthyroidism being 9 months. This study has shown also as to signs and symptoms heat intolerance and palpitation had occurred in around two-thirds of the patients (66.3%) and (62.7%), respectively. Increased appetite, nervousness, and diffuse goiter occurred in less than one-third of patients. In this study 96 individuals had comorbidities in total, with diabetes mellitus being the most prevalent (found in 11% of patients) and hypertension being the second-most prevalent (7.7% of patients). Atenolol and propylthiouracil were prescribed for patients in percentages of 100% and 58.71%, respectively. PTU was initially administered orally in doses of 200 mg to 600 mg. The majority of the patients (55.76%; n = 187) were taking a 200 mg dose as their first daily dose, while the remaining 43.7% (n = 147) were receiving a 350 mg dose. The majority of patients (76.95%) were taking a maintenance dose of 200 mg per day, with the minimum maintenance dose of PTU being 100 mg and the maximum maintenance dose being 300 mg. Metoprolol, furosemide, and spironolactone were the most commonly prescribed drugs respectively for the management of comorbidity and complications(13).

A retrospective cohort study that had been conducted on medical records of patients with thyrotoxicosis who had attended the medical inpatient ward and chronic ambulatory clinic of the University of Gondar Comprehensive Specialized Hospital in Ethiopia between June 2013 and April 2018 has shown that the most common etiology of hyperthyroidism was toxic multinodular goiter (54.90%). All of the patients were using propylthiouracil because methimazole or carbimazole were difficult to locally. The majority of patients (90.38%) experienced symptom remission at a median time of 5.37 (6.59) months. During the course of the trial, 62 (29.81%) and 122 (58.65%) patients had their TSH and FT4 levels return to normal. TSH and FT4 had respective mean times to normalization of 13 (13.28) and 11.53 (13.39) months. T3 and all three TFTs, however, were only normalized in 79 (38.16%) and 55 (26.32%) individuals, respectively(12).

2.2 Factors associated with time to Euthyroidism

In the retrospective study of single UK county remission or hypothyroidism was observed in 47.3% of autoimmune, 20.9% of nodular, and 32.5% of mixed cases after the first course of ATD, with 90% of relapses occurring within 4 years. Relapse was more common in patients with ophthalmopathy, but there was no difference between the sexes. ATD had been used in 99.2% with long- term ATD in 48%. RAI and thyroidectomy were used more commonly with nodular and mixed etiology(15).

A retrospective study conducted at the Department of Endocrinology of the Royal Infirmary of Edinburgh, UK, to assess the initial response to carbimazole in patients with Graves' disease found that patients with higher pretreatment levels of FT4, T3, TRAb, and the 4h 131I uptake responded significantly better to carbimazole(17).

On the other hand, a retrospective analysis of 219 Graves' disease patients done in Sweden revealed that the presence of a goiter predicted relapse. Patients with goiter size two had a worse prognosis compared with goiter size zero (51.2% vs 68.9% in remission after 5 years). Smoking previously helped to prevent recurrence. Age, gender, current smoking status, free triiodothyronine levels, and ophthalmopathy did not predict relapse(19).

Patients diagnosed with Graves' disease under the age of 40 had more severe hyperthyroidism than patients diagnosed with the disease over the age of 40, according to a retrospective audit of 536 new patients who presented with the condition to the thyroid clinic at the Queen Elizabeth Hospital in Birmingham between 1975 and 1998. After a course of antithyroid medication, men had a lower rate of remission than women. Those under the age of 40 also had a lower rate of remission than individuals over the age of 40(15).

In a multi-center retrospective cohort study conducted from March 30, 2020, to July 30, 2020, among adult thyrotoxicosis patients who received anti-thyroid medications in the medical and chronic ambulatory clinics of South Tigray General Hospitals, Ethiopia, Age over 40, toxic multinodular goiter, WHO goiter size three, and baseline free thyroxin were the independent factors that determined the length of time it took to reach euthyroidism(13).

Similarly, A retrospective cohort study that had been conducted on medical records of patients with thyrotoxicosis in University of Gondar Comprehensive Specialized Hospital in

Ethiopia between June 2013 and April 2018 has shown likelihood of obtaining TSH normalization is slightly decreased by older age and greater baseline FT4 levels(12).

In a very small study, which tried to assess compliance of patients of Graves' disease to anti thyroid medications who did not respond to therapy with very large doses (800 to 2000 mg/d) of propylthiouracil, it was found that, in eight patients, propylthiouracil was absorbed and metabolized normally. Five patients had no detectable propylthiouracil in their serum 2 to 3 hours after supposedly taking their medication at home, and three patients had markedly abnormal results of perchlorate discharge tests after receiving propylthiouracil under supervision. After evaluation, noncompliance was thought to be the reason for treatment failure in six of the nine patients; one patient was possibly resistant. In two patients, data were insufficient, although intermittent noncompliance could not be ruled out. Among patients who respond poorly to propylthiouracil therapy, noncompliance is the most likely reason(14).

2.3 Conceptual frame work

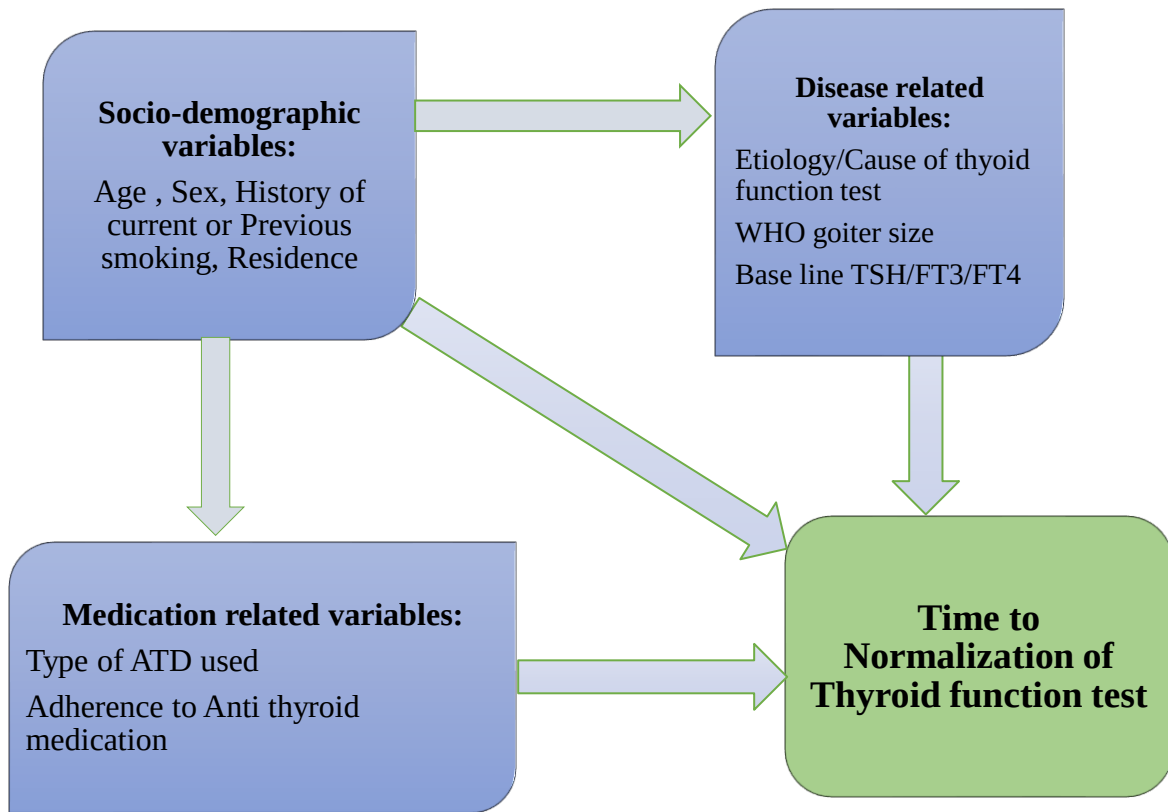


Figure 1: Conceptual framework for a study on Time to Normalization of thyroid function test and associated factors among patients with thyrotoxic patients.

3. Objectives

3.1 General Objective:

- To assess Time to normalization of Thyroid function test and associated factors among thyrotoxic patients of follow up at SPHMMC Endocrine clinic from February 2023 to June 2024

3.2 Specific Objective:

- To determine time to normalization of Thyroid function test at SPHMMC Endocrine clinic.
- To identify factors associated with normalization of Thyroid function test at SPHMMC Endocrine clinic.

4. Methods and Materials

4.1 Study area

The study was conducted at SPHMMC Endocrine clinic of St. Paul's Hospital Millennium Medical college, Addis Ababa, Ethiopia, a medical college located in Gulele sub city currently having multi-specialty treatment and teaching centers. It was founded by Emperor Haile Selassie in 1961 G.C. A medical college was additionally founded in 2007 G.C. Currently, SPHMMC serves as the primary teaching hospital for most specialties' clinical and preclinical training. It is a facility that offers the entire country specialized clinical services. In order to provide healthcare services, educate students, and conduct research, SPHMMC currently employs more than 2800 clinical, academic, administrative, and support personnel. There are many sub-specialties that fall under the department of internal medicine, including gastrointestinal, hematology, pulmonology, nephrology, endocrinology, cardiology, and neurology. The Endocrinology specialty clinic is one of the key locations where both inpatient and outpatient services as well as academic activities are provided. It could be ideal to carry out this research in one of the largest hospitals in the country, which receives referrals from all across the country for medical care, including thyroid issues. The average flow of all patients in this clinic is 100 per day.

4.2 Study design and period

A Hospital based retrospective cohort study was conducted from April 2023 G.C to January 2024 G.C

4.3 Population

4.3.1 Source population

All Thyroid patients visiting Endocrine Clinic at SPHMMC were the source population of the study.

4.3.2 Study population

All selected thyrotoxic patients who visited Endocrine clinic during the study period were the study population of the study.

4.4 Sampling technique

4.4.1 Sample size and sampling procedure

Sample size Determination for single population proportion.

$$N_0 = \frac{Z_{1/2}^2 P (1 - p)}{d^2}$$

Z=1.96 corresponding to 95% confidence interval N=sample size

α=degree of accuracy

p=proportion taken as 51.9 % that is 0.519 from previous study done in Tigray region (8).

d= degree of precision within in 5%

$$N_0 = \frac{1.96^2 (0.519 \times 0.481)}{(0.05)^2}$$

$$N_0 = 384$$

Hence, sample size determination using the finite population correction factor will be:

Nf = $N_0 / (1 + N_0/N)$, where n is the corrected sample size, N₀ is the sample size determined from the single proportion formula and N represents the finite that is the Hyperthyroid patients at follow up at Endocrine clinic which is 181.

This gives us Nf= 105

The corrected sample size is approximately considering a 10% non-response rate, the final sample size will be 116

Given the small number of patients a universal sampling technique was applied and all 181 patients will be included in the study.

4.6 Inclusion and Exclusion criteria

4.6.1 Inclusion criteria

The study included patients who are at least 18 years old, had a diagnosis of thyrotoxicosis, and had taken antithyroid drugs to treat it.

4.6.2 Exclusion criteria

Patients who visited either the medical inpatient ward or Endocrine clinic only once and do not have further follow-up history and with less than 4 weeks follow-up were excluded because of inadequate follow up time. Patients with incomplete medical records of thyroid function tests (TFTs) were also excluded for the sake completeness of the data. Pregnant patients in which the pregnancy by itself alters physiology of the thyroid gland and have their own trimester specific normal range of thyroid function test were excluded. Patients who underwent surgery for the management of thyrotoxicosis and who received radioiodine therapy were also excluded as the study only addresses those who are managed medically.

4.7 Variables

4.7.1 Dependent variables

- Time to normalization of thyroid function test

4.7.2 Independent variables

Socio-demographic and clinical characteristics

- Age
- Sex
- Urban or Rural residence
- History of past or present smoking
- Comorbid conditions
- Adherence to the medication

Disease related variables

- Etiologies of thyrotoxicosis
- World health organization (WHO) goiter size
- Baseline TSH
- Baseline FT4
- Baseline FT3

Medication related and Clinical characteristics

- Initial PTU dose

- Initial Methimazole dose
- Initial Carbimazole dose
- Maintenance PTU dose
- Maintenance Methimazole dose
- Maintenance Carbimazole dose
- Duration of symptoms

4.8 Operational definitions

Thyrotoxicosis: Low TSH and High FT4 and/or Total T3 based on the reference values given by the laboratory. (1,8)

Euthyroid (event): is considered if free thyroxin (FT4) and free triiodothyronine (FT3) are within the normal range. (1,9)

Normal range: Normal TSH, FT4 and FT3 based on the reference values given by the laboratory.

Time to event: The total time from initiation of treatment to the occurrence of normal thyroid function test.

Censored: All study participants that have not attained euthyroidism during study period.

World Health Organization (WHO) goiter size: according to WHO goiter classification goiter size was categorized as grade 0, 1, 2, and 3.

Grade 0: The goiter is not palpable or visible even when the neck is extended.

Grade 1: The goiter is detected on palpation and/ or visible when the neck is extended.

Grade 2: Goiter is visible when the neck is in the normal position.

Grade 3: Large goiter visible from distance.

4.9 Data collection and procedures

4.9.1 Data collection tool and technique

The patient's chart was retrieved from the hospital's Archives room by using HMIS documentation as a guide to identify patients who have Thyrotoxicosis as one of their diagnoses. After finding the charts, data about patients' demographics, causes, clinical signs and symptoms of thyrotoxicosis, baseline TSH, FT3, FT4, medications, adverse reactions of medication and WHO goiter size was collected by using a structured questionnaire. The data was collected inside the hospital's card room during the study period. Records of the study population was assessed for completeness before data entry and the entered data was checked by the data supervisor on a daily basis for any incompleteness and/or inconsistency.

4.9.2 Data collectors

Data collection had involved internal medical residents. Prior to data collection, the residents will be trained on how to fill the checklist and will be followed closely for completeness and validity of the data by the investigator. The checklist will be pre-tested with 5% of the total sample size to check its variability and will also be assessed for its clarity, length and completeness.

4.9.3 Data quality control

To ensure the quality of data, preceding data collection, training of the data collectors was carried out for one day by the principal investigator on the objective, relevance of the study and confidentiality of information. During the time of data collection, at the end of each day, the data was checked manually for completeness

4.10 Data Analysis

A month was used to calculate the time to normalization of thyroid function test. Kaplan Meier's plot was used to compare the survival experience of different groups of patients by using survival curves. The association between the independent variable and time to normalization of TFT was analyzed using the Cox proportional hazard regression model. Log rank was used to identify the presence of significant difference in median time between different groups.

Univariate analysis was performed and predictors that have an association with the outcome variable at a p-value of 0.25 or less were entered into the multivariable Cox regression model. A Cox proportional hazard assumption was checked statistically using the Schoenfeld residual test. The global test of (p-value = 0.95) indicated that the cox proportional hazard assumption test was not violated. The final model adequacy was assessed using the Cox-Snell residual test. The baseline distribution of the cumulative hazard function of residuals against Cox-Snell residuals followed a 45-degree line, indicating well-fitted data. Adjusted hazard ratio (AHR) with a 95% confidence interval (CI) was estimated by multivariable Cox regression and a p-value less than or equal to 0.05 was declared the presence of a statistical association between the time to normalization of TFT and explanatory variable.

4.11 Ethical consideration

After approval from the Institutional Review Board of St. Paul's Hospital Millennium Medical College by the reference number PML3/66, permission to conduct the study was requested from the school management through the academic provost of the institution. Using a systematic checklist, the data for each patient was gathered. The information gathered is confidential and be used for this specific study.

5. Results

5.1 Socio-demographic and characteristics of study populations

The study included records of patients visited Endocrinology clinic of SPHMMC hospital with a diagnosis of Thyrotoxicosis for 10 months. From the samples of 226, information was extracted from 181 patient charts making the response rate 80% from which 13% were pregnant and the rest with incomplete data. The majority of the study participant was female 159(87.8%) and 133 (73.48.28%) of the study participants came from the urban society. There were no smokers among any of the trial participants. All of the study participants were free from smoking. The median age of the study participants was 44 years with the IQR (33-55 years) and the majority 100 (55.33%) of them were under the age group of greater than or equal to 40 years.

5.2 Treatment-related characteristics of study populations

The majority 173 (95.6%) of the study subjects was on propylthiouracil (PTU). The commonest cause of thyrotoxicosis in this study were toxic multinodular goiter and grave disease accounting for 122 (67%) and 48(26.5%) respectively. The majority 65(36%) of the study participants were experience WHO grade 3 goiter size and 25(13%) of them were in grade 0 goiter size.

Table 1: Frequency distribution of socio-demographic and clinical-related characteristics of patients with thyrotoxicosis visited SPHMMC hospital from April 2023 G.C. to January 2024 G.C. [n=181]

Variable	Category	Overall Status	
		Normalized (%)	Censored (%)
Age in years	< 40	44 (24.3%)	37 (20.4%)
	≥ 40	67 (37%)	33 (18.2%)
Sex	Male	15 (8.2%)	7 (3.8%)
	Female	96 (53%)	63 (34.8%)
Residence	Urban	85 (46.9%)	48 (26.5%)
	Semi urban	7 (3.8%)	3 (1.65%)
	Rural	19 (10.4%)	19 (10.4%)
Types of medication the patients on	Carbimazole	6 (3.3%)	1 (0.5%)
	Methimazole	1 (0.5%)	0
	propylthiouracil	96 (53.08%)	77 (42.5%)
Causes of thyrotoxicosis	Graves' disease	27 (14.9%)	21 (11.6%)
	T. M. goiter	77 (42.5%)	45 (24.8%)
	Toxic adenoma	4 (2.2%)	3 (1.65%)
	Others	3 (1.65%)	1 (0.5%)

WHO Goiter size classifications	Grade 0 goiter size	16 (8.8%)	9 (4.9%)
	Grade 1 goiter size	25 (13.8%)	6 (3.31%)
	Grade 2 goiter size	36 (19.8%)	24 (13.2%)
	Grade 3 goiter size	34 (18.7%)	31 (17.1%)

5.2 Baseline sign and symptoms of the study populations

Only 3 (1.6%) of the patients visited the hospital within one month of their initial symptoms and the majority of the study participants 72 (40%) sought the treatment between 1 and 2 years of their symptoms. Heat intolerance, palpitation, and diffuse goiter were experienced in 97 (53.6%), 126 (69.6%), and 140 (77.3%) of the study participants as a baseline sign and symptoms.

Table 2: Frequency comorbidities and baseline signs and symptoms of patients of patients with thyrotoxicosis visited SPHMMC hospital from April 2023 G.C. to January 2024 G.C. [n=181]

Variable	Category	Status	
		Normalized (%)	Censored (%)
Heat intolerance	No	53 (29.2%)	31 (17.1%)
	yes	58 (32%)	39 (21.5%)
palpitations	No	41 (22.6%)	14 (7.7%)
	Yes	70 (38.6%)	56 (31%)
Warm moist skin	No	66 (36.4%)	40 (22%)
	Yes	45 (24.8%)	30 (16.5%)
Tremor	No	66 (36.4%)	42 (23.2%)
	Yes	45 (24.8%)	28 (15.4%)

hyperactivity	No	85 (46.9%)	56 (31%)
	yes	26 (14.3%)	14 (7.7%)
nervousness	No	79 (43.6%)	52 (28.7%)
	Yes	32 (17.6%)	18 (9.9%)
Increased appetite	No	100 (55.2%)	66 (36.4%)
	Yes	11 (6%)	4 (2.2%)
Duration of symptoms before seeking treatment	< 1 month	2 (1.1%)	1 (0.5%)
	1-2 months	38 (21%)	23 (12.7%)
	1-2 years	42 (23.2%)	30 (16.5%)
	2-5 years	23 (12.7%)	14 (7.7%)
	≥ 5 years	6 (3.3%)	2 (1.1%)

5.3. Comorbidities of the study populations

The major comorbidity patients with thyrotoxicosis in this follow up study was hypertension accounting for 58 (32%) of the study subjects followed by Diabetes mellitus (8.8%). Other comorbidities like dyslipidemia, pelvic organ prolapse, hepatocellular cancer, bronchial asthma, and ischemic stroke was accounting for 9(4.9%) of the study populations. Almost 177(98%) of patients with thyrotoxicosis tested non-reactive for HIV. About 129 (71%) of the study subjects had a good adherence to the antithyroid medications ($\geq 90\%$).

Table 3: Frequency comorbidities of patients of with thyrotoxicosis from April 2023 G.C. to January 2024 G.C.

Variable	Category	Status	
		Normalized (%)	Censored (%)
Congestive heart failure	NO	100 (55.2%)	65 (36%)
	Yes	7 (3.86%)	9 (5%)
Hypertension	No	73 (40.3%)	50 (27.6%)
	Yes	38 (21%)	20 (11%)
Diabetes mellites	No	99 (54.6%)	66 (36.4%)
	Yes	12 (6.6%)	4 (2.2%)
RVI	No	110 (60.7%)	67 (37%)
	Yes	1 (0.5%)	3 (1.65%)
Atrial fibrillation	No	103 (56.9%)	66 (36.4%)
	Yes	8 (4.4%)	4 (2.2%)
Other comorbidities	NO	85 (47%)	61 (33.7%)
	Yes	26 (14.3%)	9 (5%)

5.4. Medication related characteristics of the study populations

Because methimazole and carbimazole are not easily available locally, about 173 (96%) of the patients were on propylthiouracil (PTU). The initial dose of PTU in the majority of the patients (N= 111) was 100 mg PO TID and followed by 100 mg PO BID (N= 26). The majority of the patient given PTU 100 mg PO BID as a maintenance dosage. Only one patient takes initial methimazole 10 mg po per day and a maintenance of methimazole 10mg PO BID. The major

prescribed medication for comorbid condition other than antithyroid medications was Propranolol. The majority 129(72%) of the study subjects had a good drug adherence ($\geq 90\%$).

5.5. Time to Normalization of Thyroid Function Test

In this study, Normalization of thyroid function test (event) was considered if both free thyroxine (FT4) and free triiodothyronine (FT3) are lie within the normal range. Accordingly, the thyroid function test of the majority 111(61%) of the study subjects were normalized during the study period and the rest of the study subjects 70 (39%) were censored. In general, the shortest and longest time to the normalization of thyroid function was 1 and 36 months respectively. The median time to the normalization of thyroid function test was 7 months with the IQR (3 –13 months). The total person-months (person time risk) contributed by the study participants was 1,623 days. The overall incidence rate of time to normalization of thyroid function test was 6.8 per 100-person day (95% CI, 5.6 – 8.2) observation. The overall Kaplan Meier survival estimate graph shows a tendency to fall off quickly approximately in the first seven months, showing that most of the thyroid function test was normalized during this time.

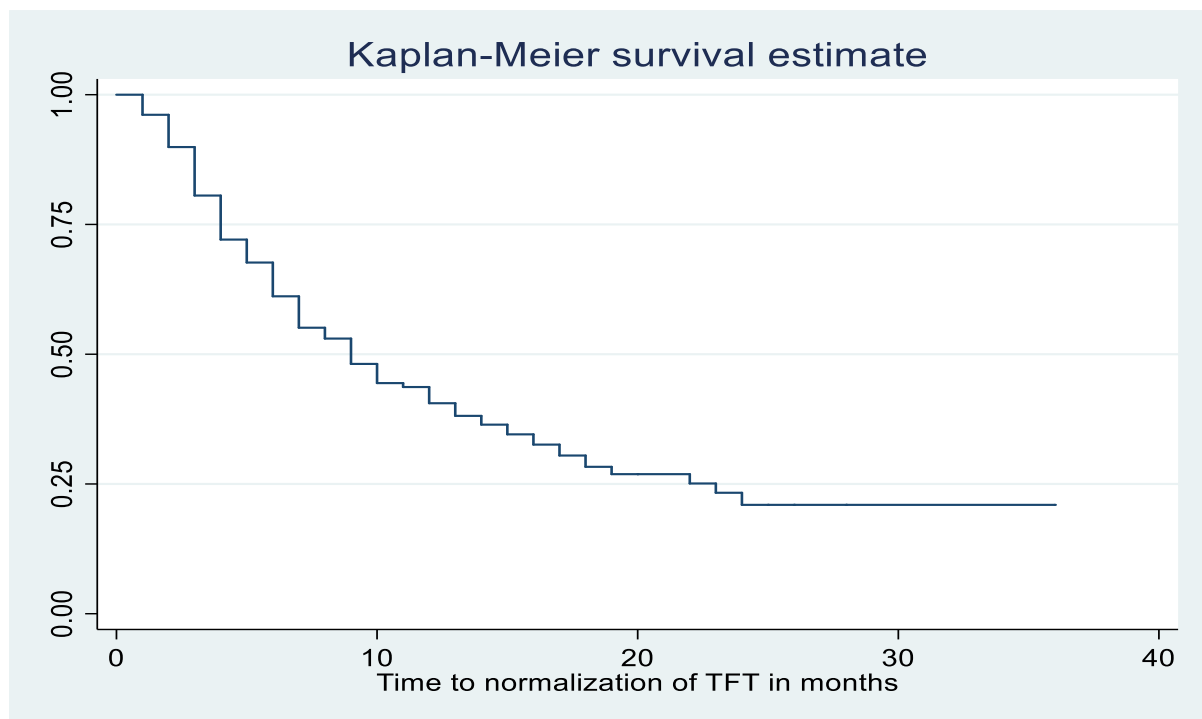


Figure 2: The overall time to normalization thyroid function test of patients with thyrotoxicosis followed at SPHMMC hospital April 2023 G.C. to January 2024 G.C. [n= 181]

Kaplan Meier Survival plot was performed to compare survival probability between categories of different predictors using survival curves. Log rank test was used to test the presence of significant differences between different categorical predictors. Accordingly, there is the significant difference between the median time to normalization of TFT by categorical predictors such as drug adherence, types antithyroid medication the patient (See Figure 3).

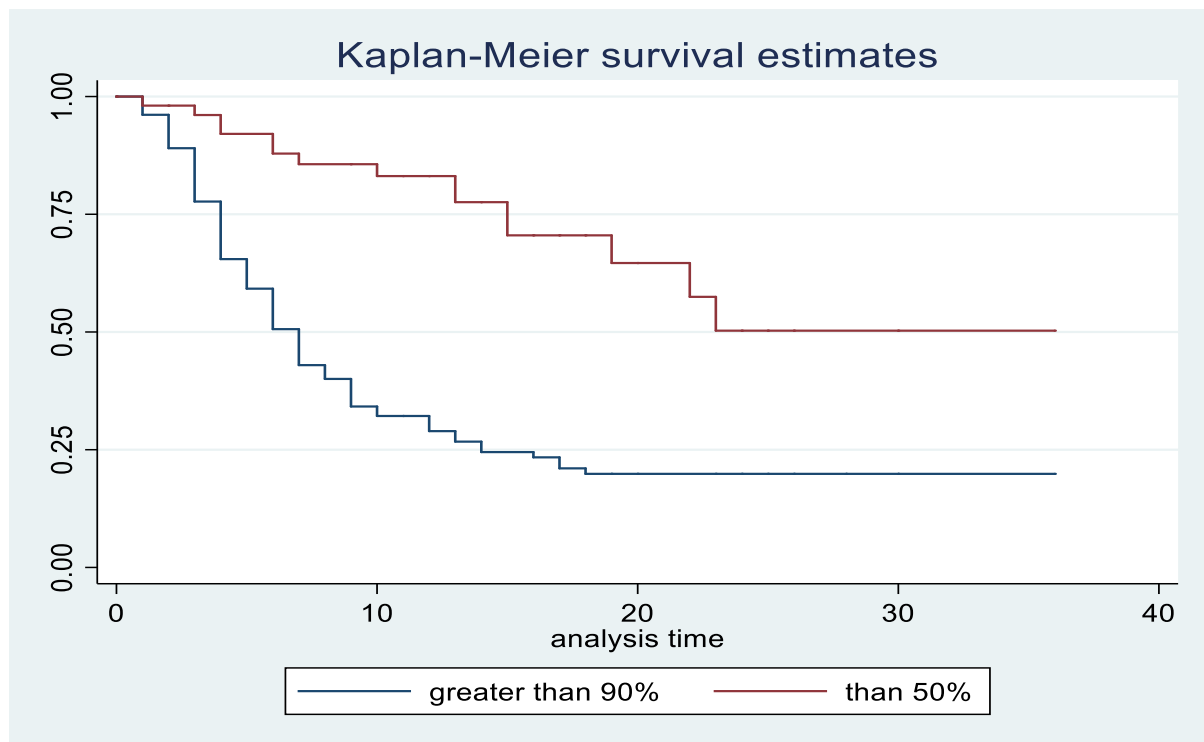


Figure 3: The overall time to normalization of thyroid function test among patient with thyrotoxicosis by drug adherence followed at SPHMMC hospital April 2023 G.C. to January 2024 G.C. [n= 181]

5.6. Proportional Hazard Assumption Test

In order to identify the factors that are significantly associated with the time to normalization of thyroid function test, the cox proportional hazard regression model was used. To do so the cox proportional hazard assumption must be satisfied (the hazard ratio is proportional over time). In this study Cox proportional hazard assumption was checked statistically using Schoenfeld residual test (Global test; p-value = 0.95 indicating the Cox proportional hazard assumption was not violated). Finally, Cox-Snell residual test was performed to check the final model adequacy and confirmed that the model is good to fit the data.

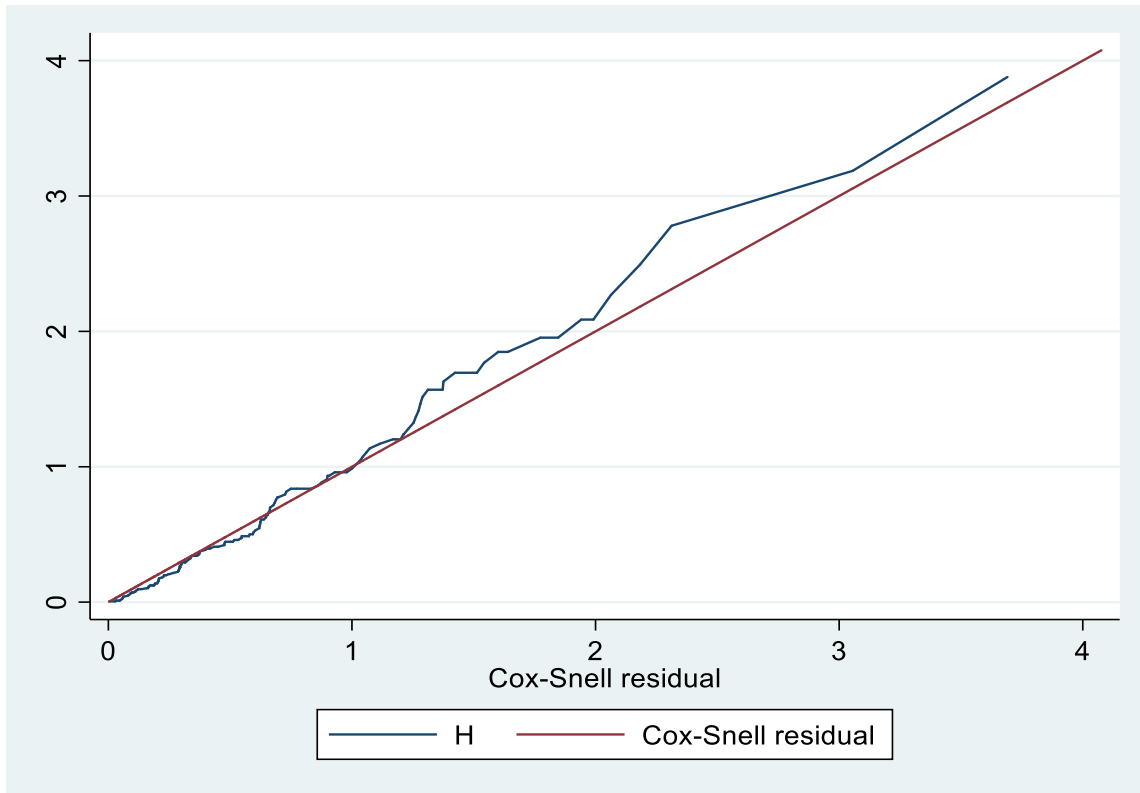


Figure 4: A cumulative hazard plot of Cox-Snell residuals for model fitness.

5.7. Predictors of time normalization of thyroid function test

After running univariate Cox regression, predictors such as baseline pulse rate, respiratory rate, temperature at the time diagnosis, palpitation, presence of congestive heart failure, type of antithyroid medication the patient on, residence, adherence of medication, age, baseline TSH. Baseline FT4, WHO goiter size, and presence of other comorbidities were selected as a candidate variable for multivariable Cox regression analysis. After carrying out the multivariable Cox regression, hazard ratios with a 95% confidence interval (CI) and a p-value less than or equal to 0.05. Thus, Variables like the baseline FT4, type of antithyroid medication the patient on drug adherence and baseline pulse rate at the time of diagnosis were statistically significant predictors of time to normalization of thyroid function test in this study.

The time to normalization of thyroid function test who has been taking propylthiouracil (PTU) was delayed by 66% as compared to patient on carbimazole (AHR; 0.33, 95% CI (0.12 – 0.89)). The time to normalization of thyroid function test among those patients who had a poor adherence to the medication (greater than 50%) was slowed by 76% as compared

to patients with a good adherence (AHR; 0.24, 95% CI (0.13 – 0.42). A one-unit increment in a pulse rate of the patient, the time to normalization of thyroid function test was delayed by 2.5 times. A unit increment in a baseline FT4, the time to normalization of thyroid function test was prolonged by 3.6 times.

Table 4: Multivariable Cox regression analysis for independent predictors of time to normalization of thyroid function test among patient with visited SPHMMC hospital from April 2023 G.C. to January 2024 G.C. [n=103]

Variable	Category	Median (IQR)	Status		p-value	CHR, (95%CI)	AHR, (95%CI)
			Normalized (%)	Censored (%)			
Type of antithyroid medication	Carbimazole	3(1-4)	6(3.3%)	1(0.5%)	1	1	1
	Methimazole		1(0.5%)	0 (0%)	0.639	1.66(0.19 -14.00)	1.07(0.12-9.80)
	PTU	7(3-13)	104 (57.4%)	69(38.1%)	0.002	0.26(0.12- 0.62)	0.33(0.12 – 0.89) *
Age	<40	11(7-15)	41(23%)	37(20%)	1	1	1
	≥40	8(6-10)	67(37%)	33(20%)	0.23	1.26(0.68-1.84)	1.23(0.82-1.88)
Residence	Rural	13(9-19)	19(10.5%)	19(10.5%)	1	1	1
	Semi urban	6(3-14)	7(3.8%)	3(1.6%)	0.15	1.88(0.79- 4.5)	1.49(0.61-3.63)
	urban	8(6-12)	85(46.9%)	48(26.5%)	0.05	1.63(0.99-2.69)	1.58(0.93-2.71)
Palpitation	No	7(5-10)	41	14	1	1	1
	Yes	11(7-15)	70	46	0.068	0.69(0.47- 1.01)	0.71(0.47 -1.07)
Medication adherence	≥90%	6(5-8)	96	33	1	1	1
	<50%	23(19-27)	15	37	0.000	0.26(0.15- 0 .45)	

							0.24 (0.13–0.42) **
Congestive heart failure	No	9(7-12)	108	65	1	1	1
	Yes	15(3-8)	3	5	0.23	0.50(0.16- 1.59)	0.73 (0.21 -1.49)
Other comorbidities	No	5(6-13)	85	61	1	1	1
	Yes	10(4-8)	26	9	0.008	1.62(1.04- 2.51)	1.41(0.87 -2.29)
WHO goiter size	Grade 0	5(3-7)	16	9	1	1	1
	Grade 1	5(4-9)	25	6	0.32	0.72(0.38-1.36)	1.35(0.64-2.85)
	Grade 2	10(7-16)	36	24	0.004	0.41(0.22-0.75)	1.15(0.56-2.35)
	Grade 3	13(9-24)	34	31	0.001	0.33(0.18-0.62)	0.68(0.34-1.37)
Baseline PR					0.008	0.98(0.95- 1.002)	0.97(0.95-0.99) *
Baseline TSH					0.04	1.009(1.00-1.01)	0.99(0.986-1.001)
Baseline RR					0.05	1.03(0.99- 1.06)	1.02(.98-1.05)
Baseline FT4					0.00	0.987(0.982-0.992)	0.99(0.984-0.995) **
Baseline temperature					0.039	0.87(0.76- 0 .99)	0.90(0.79-1.04)

P-Value =< 0.05(*) and ** for p-value < 0.01

6. Discussion

In this study, important data on the time to achieve normal thyroid function among patients with an overactive thyroid gland (thyrotoxicosis) attending SPHMMC Endocrinology clinics was collected. The majority of the patients were elderly females living in urban areas, with WHO goiter size two, and non-smokers. At the beginning of the study, the most common signs and symptoms observed were a swollen thyroid gland, heart palpitations, and intolerance to heat in most patients. Our study is similar to a retrospective study conducted in Saudi Arabia, University of Gondar Comprehensive Specialized Hospital, and South Tigray General Hospitals, which also showed a high proportion of female to male ratio of (161:42) 3.8:1, 94.31 %, 88.7% respectively(12)(13)(16).

The initial dose of PTU in the majority of the patients (N= 111) was 100 mg PO TID and followed by 100 mg PO BID (N= 26). The majority of the patient given PTU 100 mg PO BID as a maintenance dosage which is similar to doses used in both Ethiopian studies. The reason could be because of longer time interval between each patient visit which may route to the clinics heavy load of patients(12)(13).

TMNG was the common underlying cause of Hyperthyroidism (67.4%) of patients which is similar with the studies done in Ethiopia, University of Gondar Comprehensive Specialized Hospital and South Tigray General Hospitals but Graves' disease (GD) was the underlying cause in the majority of the patients, 140 (69%) patients in Saudi Arabia's study, which differs from our study(12)(13)(16).

In the current study, 111 (61%) patients became euthyroid, which is higher than the study done in South Tigray General hospitals (51.9%) but lower than a study conducted in Saudi Arabia which reported that 72 % patients became euthyroid. This difference might be, in this study the most common etiology of thyrotoxicosis was TMNG which is similar with south Tigray General hospitals study, but the study done in Saudi Arabia reported that GD was the underlying cause in the majority of patients (13)(16).

In our study, 95.6% patients were taking PTU, 3.9% Carbimazole and only 1 patient (0.6%) Methimazole for the treatment of thyrotoxicosis which is different from both studies done in Ethiopia, University of Gondar Comprehensive Specialized Hospital and South Tigray

General Hospitals, where all patients were on PTU and a Swedish retrospective study where 96.2% and 3.8% of patient were taking Methimazole and PTU respectively(12, 19).

On the multivariable cox regression analysis for independent predictors of time to normalization of thyroid function test, use of Propylthiouracil as a choice of anti-thyroid agent was associated with falling to achieve normalization of TFTs. This could be because of relative much higher potency of Carbimazole compared with PTU.

In the present study, the median (IQR) time taken to become euthyroid was 7 months, IQR (3–13) months, which is lower than the study conducted in Gondar comprehensive specialized hospital which was 11.53 (13.39) months and South Tigray general hospitals which was 9 month, IQR (6-12) months. This might be because use carbimazole as choice for anti- thyroid medication(12)(13).

In the current study, the most common etiology identified was TMNG, this may be the reason for the longer time to euthyroidism than expected. This finding was in line with the south Tigray general hospital and Gondar university comprehensive specialized hospital(12)(13).

Our study was also similar to the done at University of Gondar Comprehensive Specialized Hospital, South Tigray General Hospitals and a retrospective study conducted in Edinburgh which reported that patients with a higher baseline of FT4 were found to be hyperthyroid after they were treated with carbimazole for 4–6 weeks. In contradiction to our finding, a retrospective study conducted in Sweden reported higher FT4 and FT3 levels were not identified as significant prognostic factors. The cause of thyrotoxicosis in the current study was toxic multinodular goiter, whereas the cause of thyrotoxicosis in the Saudi Arabia study was Graves' disease, which may be the reason for FT4 to be a determinant factor in the current study(12, 19).

The present study is similar to a study conducted at a teaching hospital in Bucharest, which showed that patients' age did not seem to influence the thyroid test recovery. On the other hand, our study is contrary to a study retrospective study conducted at the University of Gondar Hospital, South Tigray general hospitals and to retrospective study conducted at

Queen Elizabeth Hospital which found patients under the age of 40 were more likely to fail to respond to medical treatment (13).

Our study has shown that the time to normalization of thyroid function test among those patients who had a poor adherence to the medication (greater than 50%) was slowed by 76% as compared to patients with a good adherence which is similar to study done in United States of America on 09 patients from which 06 patients were not compliant to the medication they were prescribed (14).

This study has shown A one-unit increment in a Base line pulse rate of the patient, the time to normalization of thyroid function test was delayed by 2.5 times. This might be because of strong relationship between Severity of Hyperthyroidism and Pulse rate.

7. Strength and limitation of the study

This study has several strengths, with a major strength being the inclusion of patients taking Carbimazole and the assessment of how adherence affects the time to achieve normal thyroid function, which was lacking in other studies conducted in Ethiopia. However, the study is not without limitations. The major limitation of this study was that it was a retrospective study and relied on the data from the medical records. Large numbers of patient medical records were also missing which made to depend on smaller sample size. In order to minimize missing records data was gathered from on paper patient chart and electronic health records also. The current study did not assess remission and relapses. To provide a more comprehensive understanding, future studies should assess remission and relapses to capture the full spectrum of the disease course. Therefore, interpretation of the findings of this study should take this limitation in to consideration.

8. Conclusion

Although treatment took longer than anticipated, more than half of the patients in this report were euthyroid. Delay in reaching euthyroidism was to High baseline FT4, High baseline pulse rate, non- adherence to medication and use of PTU as a choice of anti-thyroid drug delayed time to euthyroidism.

9. Recommendation

For physicians and other health care providers

Physicians and healthcare providers should be mindful that patients with hyperthyroidism need thorough and vigilant follow-up until their thyroid function tests are completely normal and proper Investigation and search for possible cause of delay of normalization of TFTs should be done before patients develop undesirable complications. Additionally, there has to be a detailed discussion with the patient on proper adherence to Anti thyroid medication, proper dosing, drug- drug interaction.

For fellow researchers

Further prospective and analytic studies should be conducted to address this researches limitation in regard to missing data and assess for relapse and remissions.

For SPHMMC

A separate Clinic for thyroid patients could make follow up more frequent, detailed, focused and results in desired time for normalization of TFTs.

For Federal Ministry of health

It is evident that carbimazole is more superior in attaining euthyroidism and ensuring the availability of this essential drug is a critical aspect of public health policy, and the Ministry of Health should take proactive measures to make such drugs more readily accessible to the population.

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Assurance of Principal Investigator

I the undersigned agree to accept all responsibilities for the scientific and ethical conduct of the research project. I will provide timely progress report to my advisor and seek the necessary advice and approval from my primary advisors in the course of the research. I will communicate timely to my advisors all stakeholders involved in the study including any source of funding for this research.

Name of the student: _____

Signature: _____

Date: _____

Approval of the Primary Advisor

Name of the primary advisor: _____

Signature: _____

Date: _____

Approval of the Co-Advisor

Name of the primary advisor: **Simegnew Handebo (MPH, Assistant professor)**

Signature: 

Date: February 15, 2024

Annexes

Annex I: Information sheet

Title of the Research paper: Assessment of Time to normalization of Thyroid function test and associated factors among thyrotoxic patients of follow up at SPHMMC Endocrine clinic from February to June 2023, retrospective cohort study; Addis Ababa, Ethiopia.

Name of Investigator: Dagim Kassahun (MD)

Name of the Organization: St. Paul's Hospital Millennium Medical College, department of Internal Medicine

Name of the Sponsor: SPHMMMC research office

Introduction: This information sheet is prepared for SPHMMC department of internal medicine, Endocrinology unit, Addis Ababa, Ethiopia. This information sheet will clarify the purpose of the research for the concerned office about data collection procedures and it will aid in getting permission to conduct the study.

Purpose of the Research thesis: To assess Time to normalization of Thyroid function test and associated factors among thyrotoxic patients of follow up at SPHMMC Endocrine clinic.

Procedure: In order to achieve the above objective, information will be taken from the patients their charts from February to June 2023.

Risk and /or Discomfort: As this study is non-interventional; it will not inflict any harm on the study participants. The Privacy, confidentiality and anonymity information collected from patients' chart will be maintained.

Benefits: The study participants will not benefit from this study directly. However, they may benefit from the results of the study as it may be utilized for service improvement in the future.

Confidentiality: To ensure confidentiality, the data will be collected by data collectors and the data will be handled anonymously, will be coded and entered to secure software

Person to contact: This research project will be reviewed and approved by the institutional review board of SPHMMC.

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Annex II: Data collection checklist

Card Number _____

Part I: Socio-demographic and Clinical Characteristics

1. Age in years: _____
2. Sex
 - ☐ Male
 - ☐ Female
3. History of previous Smoking
 - ☐ Yes, how many pack years _____
 - ☐ No
4. History of current smoking
 - ☐ Yes, how many pack years _____
 - ☐ No
5. Residence
 - ☐ Urban
 - ☐ Semi urban
 - ☐ Rural
6. Cause of Thyrotoxicosis
 - ☐ Graves' disease
 - ☐ Toxic Multinodular goiter
 - ☐ Toxic Adenoma
 - ☐ Other, specify _____
7. WHO Goiter size Classification
 - ☐ Grade 0 goiter size
 - ☐ Grade 1 goiter size
 - ☐ Grade 2 goiter size
 - ☐ Grade 3 goiter size

Part II: Baseline sign, symptoms and TFT

1. Base line sign and symptom experienced by the patient
 - Heat intolerance Yes ☐ No ☐

Palpitation	Yes ☐	No ☐
Hyperactivity	Yes ☐	No ☐
Tremor	Yes ☐	No ☐
Warm moist skin	Yes ☐	No ☐
Increased appetite	Yes ☐	No ☐
Nervousness	Yes ☐	No ☐
Diffuse goiter	Yes ☐	No ☐

2. Duration of Symptoms before seeking treatment

- ☐ < 01 month
- ☐ 01- 12 month
- ☐ 01 year- 2 years
- ☐ 02 years- 05 years
- ☐ > 05 years

3. Base line Vital signs at time of diagnosis

BP_____ PR_____RR_____T_____

4. Base line Vital signs at time of diagnosis

TSH_____

FT3_____

FT4_____

Part III: Common Comorbidities

1. Comorbidities among thyrotoxic patients

Congestive heart failure	Yes ☐	No ☐
Hypertension	Yes ☐	No ☐
Diabetes mellitus	Yes ☐	No ☐
RVI	Yes ☐	No ☐
Atrial fibrillation	Yes ☐	No ☐
Other, Specify_____		

Part IV: Medication related

1. Type of Anti thyroid medication that the patient is on
 - ☐ PTU
 - ☐ Methimazole
 - ☐ Carbimazole
2. Dose of initial PTU_____
3. Dose of initial Methimazole_____
4. Dose of Maintenance PTU_____
5. Dose of maintenance Methimazole_____
6. Medications prescribe for Comorbid Condition other than Anti thyroid medications_____
7. Adherence to Anti thyroid medication measured till normalization of TFT
 - ☐ >90%
 - ☐ < 50%

Part V Time to Normalization of TFT (months + weeks)

- TSH_____
- FT3_____
- FT4_____