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Time to Normalization of Thyroid Function Tests and Associated Factors Among Thyrotoxic Patients at Saint Paul's Hospital Millennium Medical College Endocrine Clinic, Addis Ababa, Ethiopia, 2024

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ABSTRACT

Background: Thyrotoxicosis is characterized by excessively high tissue thyroid hormone levels. Untreated or inadequately managed thyrotoxicosis can lead to various complications. Understanding factors influencing the time to achieve thyroid function normalization is essential for improving treatment outcomes and patient care.

Objectives: This study aimed to assess the median time to normalization of thyroid function tests and identify factors associated with delayed euthyroidism among thyrotoxic patients attending the Endocrine Clinic at St. Paul's Hospital Millennium Medical College, Addis Ababa, Ethiopia, in 2023.

Methods: A hospital-based retrospective cohort study was conducted involving 181 patients diagnosed with thyrotoxicosis who attended the adult Endocrine Clinic from April 2023 to January 2024. Data were collected using a structured questionnaire and entered into EpiData version 7.1, then exported to STATA version 15 for analysis. Descriptive statistics summarized continuous variables as mean ± SD or median with interquartile range, and categorical variables as frequencies and percentages. The association between independent variables and time to euthyroidism was analyzed using Cox proportional hazards regression, with the log-rank test employed to compare median times across groups. Adjusted hazard ratios (AHR) with 95% confidence intervals (CI) were reported to quantify the strength of associations.

Results: Approximately 61% of patients achieved euthyroidism, with a median time of 7 months (Interquartile Range: 3–13 months). Factors significantly associated with delayed normalization included use of Propylthiouracil (AHR = 0.33; 95% CI: 0.12–0.89), poor medication adherence (AHR = 0.24; 95% CI: 0.13–0.42), higher baseline pulse rate (AHR = 0.97; 95% CI: 0.95–0.99), and elevated baseline free thyroxin levels (AHR = 0.99; 95% CI: 0.98–0.995).

Conclusion: Although more than half of the patients attained euthyroidism, the process took longer than expected. High baseline FT4 levels, elevated pulse rate, non-adherence to medication, and the use of PTU as the anti-thyroid drug delayed the achievement of euthyroidism. Patients with thyrotoxicosis require attentive and continuous monitoring until thyroid function normalizes to prevent complications.

KEYWORDS: Euthyrodism, Survival analysis, Thyrotoxicosis, Ethiopia

INTRODUCTION

Thyroid disorders, particularly thyrotoxicosis, represent a significant public health concern worldwide, affecting millions of individuals across different age groups and ethnicities. Thyrotoxicosis, characterized by elevated circulating thyroid hormones, leads to a spectrum of clinical manifestations including tachycardia, heat intolerance, weight loss, and goiter, which can substantially impair quality of life and pose risks for cardiovascular complications [1].

Globally, the prevalence of thyrotoxicosis varies, with higher rates reported in iodine-deficient regions and among females, who are disproportionately affected [2, 3]. In Ethiopia, despite the limited availability of comprehensive epidemiological data, localized studies

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suggest that thyroid disorders, including goiter and thyrotoxicosis, are common, largely attributable to iodine deficiency, autoimmune processes such as Graves' disease, and multinodular goiter [4, 5].

Effective management of thyrotoxicosis aims to restore euthyroidism swiftly to prevent complications and improve patient outcomes. Antithyroid drugs (ATDs), including propylthiouracil (PTU) and carbimazole, remain the mainstay of pharmacotherapy [6, 7]. Achieving and maintaining euthyroidism depends on timely diagnosis, adherence to medication, appropriate drug choice, and regular monitoring.

However, in low-resource settings like Ethiopia, challenges such as limited access to medications, inadequate follow-up, and variable clinical practices can delay the normalization of thyroid function. Delays in achieving euthyroidism may lead to adverse effects including atrial fibrillation, osteoporosis, and psychological disturbances [8], thus underscoring the importance of understanding factors influencing treatment outcomes.

Despite these challenges, there is a paucity of local data on the duration and determinants of time to normalization of thyroid function among Ethiopian patients with thyrotoxicosis [5, 9, 10]. Most existing studies focus on prevalence and demographic characteristics, with limited insight into treatment response dynamics and associated factors [4, 5, 9].

This study aims to assess the time to normalization of thyroid function tests (TFTs) among patients with thyrotoxicosis attending the Endocrinology Clinic at St. Paul's Hospital Millennium Medical College (SPHMMC). Additionally, it seeks to identify clinical and treatment-related predictors influencing this timeframe. The findings will provide valuable insights to optimize management strategies, improve patient outcomes, and inform health policy decisions in Ethiopia.

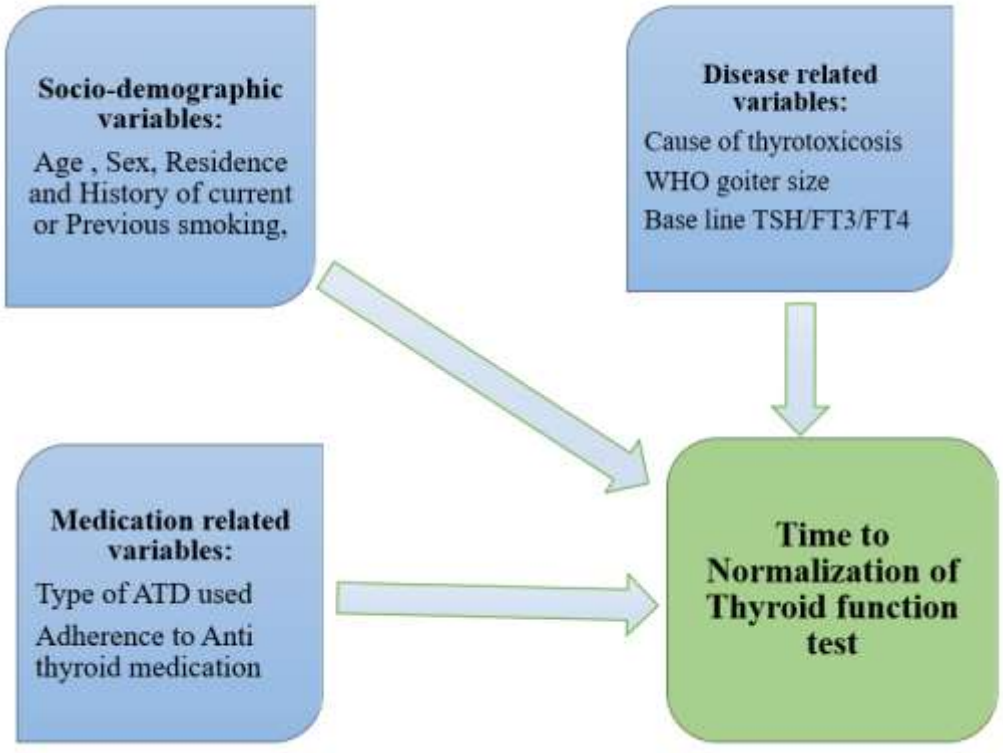

Figure 1: Conceptual framework for a study on Time to Normalization of thyroid function test and associated factors among patients with thyrotoxic patients.

METHODS AND MATERIALS

Study Area

This study was conducted at the Endocrinology Clinic of St. Paul's Hospital Millennium Medical College (SPHMMC), located in Addis Ababa, Ethiopia. SPHMMC is a major referral and teaching hospital that provides specialized services and serves as a tertiary center for Ethiopia. The Endocrinology Clinic offers both inpatient and outpatient management for various hormonal disorders,

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including thyrotoxicosis, and has a dedicated team of endocrinologists, nurses, and laboratory personnel, with an average daily patient flow of approximately 100.

Study Design and Period

A hospital-based retrospective cohort study was conducted using medical records of thyrotoxic patients attending the Endocrine Clinic at SPHMMC from April, 2023 to January, 2024.

Population

Source population included all patients diagnosed with thyrotoxicosis and attending the Endocrine Clinic at SPHMMC during the study period. The study population comprised all selected thyrotoxic patients who met the inclusion criteria and had complete follow-up data.

Sample size and sampling procedure

The sample size was calculated using the single population formula:

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

Where:

Z=1.96 (the Z-score corresponding to a 95% confidence level),

p=0.519 (proportion of euthyroid patients taken from a previous study conducted in the Tigray region),

d=0.05 (margin of error or degree of precision).

Substituting the values:

$$N_0 = \frac{1.96^2\,(0.519\times0.481)}{(0.05)^2} = 384$$

Since the total population of thyrotoxic patients under follow-up at the Endocrine Clinic was finite (N = 181), the sample size was adjusted using the finite population correction formula:

Nf = No/ (1+ No/N), Where n is the corrected sample size, N_0 is the sample size calculated using the single population proportion formula, and N is the finite population size, which in this study is the total number of hyperthyroid patients under follow-up at the Endocrine Clinic (181).

This gives us Nf= 105.

Accounting for a 10% non-response rate, the final calculated sample size was approximately 116 patients. However, given the relatively small population size, a universal sampling technique was applied, and all 181 eligible patients were included in the study.

Eligibility Criteria

The study included patients aged 18 years and older who were diagnosed with thyrotoxicosis and treated with antithyroid drugs (ATDs). Patients were excluded if they had only a single clinic visit or less than four weeks of follow-up, had incomplete medical records - particularly missing baseline or follow-up thyroid function tests (TFTs), were pregnant (due to altered thyroid physiology and trimester-specific reference ranges), or had undergone thyroid surgery or received radioactive iodine therapy, as the study focused exclusively on medically managed patients.

Variables

Dependent variable:

Time to normalization of thyroid function tests (TFTs), defined as the time from initiation of ATD therapy to the first documented euthyroid state.

Independent variables:

Socio-demographic and clinical characteristics: Age, sex, residence (urban/rural), smoking history, comorbidities

Disease-related variables: Etiology of thyrotoxicosis, World Health Organization (WHO) goiter size, baseline TSH, free T4 (FT4) and free T3 (FT3).

Medication-related variables: Initial and maintenance doses of propylthiouracil (PTU), methimazole, and carbimazole, Medication Adherence

Duration of symptoms before treatment initiation.

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Operational Definitions

Thyrotoxicosis: Defined as low serum thyroid-stimulating hormone (TSH) and elevated free thyroxine (FT4) and/or total triiodothyronine (T3) levels based on the reference ranges provided by the laboratory.

Euthyroid (event): Considered achieved when both free thyroxine (FT4) and free triiodothyronine (FT3) levels are within the normal reference range.

Normal range: The reference intervals for TSH, FT4, and FT3 as specified by the laboratory.

Time to event: The duration from initiation of antithyroid treatment to the first documented occurrence of normal thyroid function tests.

Censored: Participants who did not achieve euthyroidism during the study period or were lost to follow-up.

World Health Organization (WHO) goiter size classification:

Grade 0: No palpable or visible goiter, even when the neck is extended.

Grade 1: Goiter palpable and/or visible only when the neck is extended.

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

Grade 3: Large goiter visible from a distance.

Data Collection Procedures

Data were extracted from patients' medical records using a structured data abstraction form developed from relevant literature and expert input, capturing demographic, clinical, treatment, laboratory, and follow-up information. Trained internal medicine residents, who received one day of training on the study objectives, data collection procedures, and confidentiality, conducted the data collection. The tool was pre-tested on 5% of the sample to evaluate clarity and completeness, with adjustments made accordingly. Throughout the process, the principal investigator closely supervised data collection to ensure accuracy and completeness.

Data Analysis

In this study, time to normalization of thyroid function tests was measured in months from the initiation of therapy to the first documented euthyroid state. Kaplan-Meier survival curves were constructed to compare the cumulative probability of normalization among different patient groups, and the log-rank test was employed to assess the statistical significance of differences in median time to normalization. Variables with a p-value ≤ 0.25 in univariate analysis were entered into the multivariable Cox proportional hazards model to identify independent predictors.

The proportional hazards assumption was evaluated using the Schoenfeld residuals test, yielding a global p-value of 0.95, indicating no violation of the assumption. Model adequacy was assessed using Cox-Snell residuals, with the plot of residuals against the cumulative hazard function approximating a 45-degree line, thus supporting the model's goodness of fit. Adjusted hazard ratios (AHR) with 95% confidence intervals (CI) were reported, and a p-value ≤ 0.05 was considered statistically significant.

Ethical Consideration

Ethical approval was obtained from the Institutional Review Board of St. Paul's Hospital Millennium Medical College (Reference No. PML3/66). Permission to conduct the study was granted by the hospital administration through the academic provost. Given the retrospective nature of the study, informed consent was waived. Confidentiality was strictly maintained by anonymizing patient data and restricting access to authorized personnel only. All data were used solely for the purposes of this study in accordance with ethical guidelines and institutional policies.

RESULT

Socio-demographic Characteristics of the Study Population

The study reviewed records of patients diagnosed with thyrotoxicosis who attended the Endocrinology Clinic at SPHMMC over a 10-month period. Out of 226 sampled charts, data were successfully extracted from 181 patient records, resulting in a response rate of 80%. Among the excluded records, 13% belonged to pregnant patients, while the remainder were excluded due to incomplete data. The majority of the study participants were female, comprising 159 individuals (87.8%), and most resided in urban areas, accounting for 133 participants (73.5%). None of the participants reported a history of smoking. The median age of the cohort was 44 years (interquartile range [IQR]: 33–55 years), with 70 participants (38.7%) aged 40 years or older.

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Treatment-related Characteristics of the Study Population

The vast majority (95.6%) were treated with propylthiouracil, while carbimazole and methimazole were used in 3.9% and 0.5% of cases, respectively. The leading causes of thyrotoxicosis were toxic multinodular goiter (67.4%) and Graves' disease (26.5%). Regarding goiter size, 35.9% had Grade 3, 33.1% Grade 2, 17.1% Grade 1, and 13.8% had no palpable goiter (Grade 0).

Table 1: Frequency Distribution of Socio-demographic and Clinical Characteristics of Patients with Thyrotoxicosis at SPHMMC (April 2023 – January 2024) (n=181)

Variable	Category	Normalized, n (%)	Censored, n (%)	Total, n (%)
Age (years)	< 40	44 (24.3)	67 (37.0)	111 (61.3)
	≥ 40	37 (20.4)	33 (18.2)	70 (38.7)
Sex	Male	15 (8.2)	7 (3.8)	22 (12.1)
	Female	96 (53.0)	63 (34.8)	159 (87.8)
Residence	Urban	85 (46.9)	48 (26.5)	133 (73.5)
	Semi-urban	7 (3.8)	3 (1.7)	10 (5.5)
	Rural	19 (10.4)	19 (10.4)	38 (21.0)
Type of Medication	Carbimazole	6 (3.3)	1 (0.5)	7 (3.9)
	Methimazole	1 (0.5)	0 (0)	1 (0.5)
	Propylthiouracil	96 (53.1)	77 (42.5)	173 (95.6)
Causes of Thyrotoxicosis	Graves' disease	27 (14.9)	21 (11.6)	48 (26.5)
	Toxic multinodular goiter	77 (42.5)	45 (24.8)	122 (67.4)
	Toxic adenoma	4 (2.2)	3 (1.7)	7 (3.9)
	Others	3 (1.7)	1 (0.5)	4 (2.2)
WHO Goiter Size	Grade 0	16 (8.8)	9 (4.9)	25 (13.8)
	Grade 1	25 (13.8)	6 (3.3)	31 (17.1)
	Grade 2	36 (19.8)	24 (13.2)	60 (33.1)
	Grade 3	34 (18.7)	31 (17.1)	65 (35.9)

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Baseline Symptoms and Signs of the Study Participants

Among the 181 patients, common symptoms included palpitations (69.6%), heat intolerance (53.6%), warm moist skin (41.4%), and tremor (40.3%). Less frequent symptoms were hyperactivity (22.1%), nervousness (27.7%), and increased appetite (8.3%). Most patients (91.6%) did not report increased appetite. Regarding symptom duration before seeking treatment, the majority experienced symptoms for 1–2 years (39.8%) or 1–2 months (33.7%), while fewer patients sought care within less than one month (1.6%) or after more than five years (4.4%).

Table 2: Frequency of Baseline Signs and Symptoms among Patients with Thyrotoxicosis at SPHMMC (April 2023 – January 2024) (n=181)

Variable	Category	Normalized, n (%)	Censored, n (%)	Total, n (%)
Heat intolerance	No	53 (29.2)	31 (17.1)	84 (46.4)
	Yes	58 (32.0)	39 (21.5)	97 (53.6)
Palpitations	No	41 (22.6)	14 (7.7)	55 (30.3)
	Yes	70 (38.6)	56 (31.0)	126 (69.6)
Warm moist skin	No	66 (36.4)	40 (22.0)	106 (58.6)
	Yes	45 (24.8)	30 (16.5)	75 (41.4)
Tremor	No	66 (36.4)	42 (23.2)	108 (59.7)
	Yes	45 (24.8)	28 (15.4)	73 (40.3)
Hyperactivity	No	85 (46.9)	56 (31.0)	141 (77.9)
	Yes	26 (14.3)	14 (7.7)	40 (22.1)
Nervousness	No	79 (43.6)	52 (28.7)	131 (72.3)
	Yes	32 (17.6)	18 (9.9)	50 (27.7)
Increased appetite	No	100 (55.2)	66 (36.4)	166 (91.6)
	Yes	11 (6.0)	4 (2.2)	15 (8.3)
Duration of symptoms before seeking treatment	< 1 month	2 (1.1)	1 (0.5)	3 (1.6)
	1–2 months	38 (21.0)	23 (12.7)	61 (33.7)

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Variable	Category	Normalized, n (%)	Censored, n (%)	Total, n (%)
	1–2 years	42 (23.2)	30 (16.5)	72 (39.8)
	2–5 years	23 (12.7)	14 (7.7)	37 (20.4)
	≥ 5 years	6 (3.3)	2 (1.1)	8 (4.4)

Comorbidities of the Study Population

The majority of participants in this study had no history of congestive heart failure (91.2%), hypertension (67.9%), diabetes mellitus (91.0%), HIV infection (97.8%), or atrial fibrillation (93.4%). Comorbidities were present in a smaller subset of patients, with congestive heart failure affecting 8.8%, hypertension 32.0%, diabetes mellitus 8.8%, HIV infection 2.2%, and atrial fibrillation 6.6%. Additionally, 19.3% of patients reported other comorbid conditions, while 80.7% had none, highlighting a predominantly low burden of comorbidity within the cohort.

Table 3: Frequency of Comorbidities among Patients with Thyrotoxicosis at SPHMMC (April 2023 – January 2024) (n=181)

Variable	Category	Normalized, n (%)	Censored, n (%)	Total, n (%)
Congestive Heart Failure	No	100 (55.2)	65 (36.0)	165 (91.2)
	Yes	7 (3.9)	9 (5.0)	16 (8.8)
Hypertension	No	73 (40.3)	50 (27.6)	123 (67.9)
	Yes	38 (21.0)	20 (11.0)	58 (32.0)
Diabetes Mellitus	No	99 (54.6)	66 (36.4)	165 (91.0)
	Yes	12 (6.6)	4 (2.2)	16 (8.8)
HIV Status (RVI)	No	110 (60.7)	67 (37.0)	177 (97.8)
	Yes	1 (0.5)	3 (1.7)	4 (2.2)
Atrial Fibrillation	No	103 (56.9)	66 (36.4)	169 (93.4)
	Yes	8 (4.4)	4 (2.2)	12 (6.6)
Other Comorbidities	No	85 (47.0)	61 (33.7)	146 (80.7)
	Yes	26 (14.3)	9 (5.0)	35 (19.3)

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Medication-Related Characteristics of the Study Population

Because methimazole and carbimazole are not readily available locally, approximately 173 patients (96%) were treated with propylthiouracil (PTU). The initial PTU dose for the majority of patients (n = 111) was 100 mg orally three times daily (TID), followed by 100 mg orally twice daily (BID) for 26 patients. Most patients received PTU 100 mg orally twice daily as a maintenance dose. Only one patient was started on methimazole 10 mg once daily and maintained on 10 mg twice daily. Propranolol was the most commonly prescribed medication for comorbid conditions other than antithyroid drugs. The majority of study participants, 129 (72%), demonstrated good medication adherence, defined as taking at least 90% of prescribed doses.

Time to Normalization of Thyroid Function Test

In this study, normalization of thyroid function tests (the event) was defined as both free thyroxine (FT4) and free triiodothyronine (FT3) levels falling within the normal reference range. Accordingly, the thyroid function tests of the majority of participants, 111 (61%), normalized during the study period, while the remaining 70 (39%) were censored. The shortest and longest times to normalization were 1 month and 36 months, respectively. The median time to normalization was 7 months, with an interquartile range (IQR) of 3 to 13 months. The total person-time contributed by the study participants was 1,623 person-months. The overall incidence rate of normalization was 6.8 per 100 person-months (95% CI: 5.6–8.2). The Kaplan-Meier survival curve showed a steep decline in the probability of non-normalization during the first seven months, indicating that most patients achieved normalization within this period.

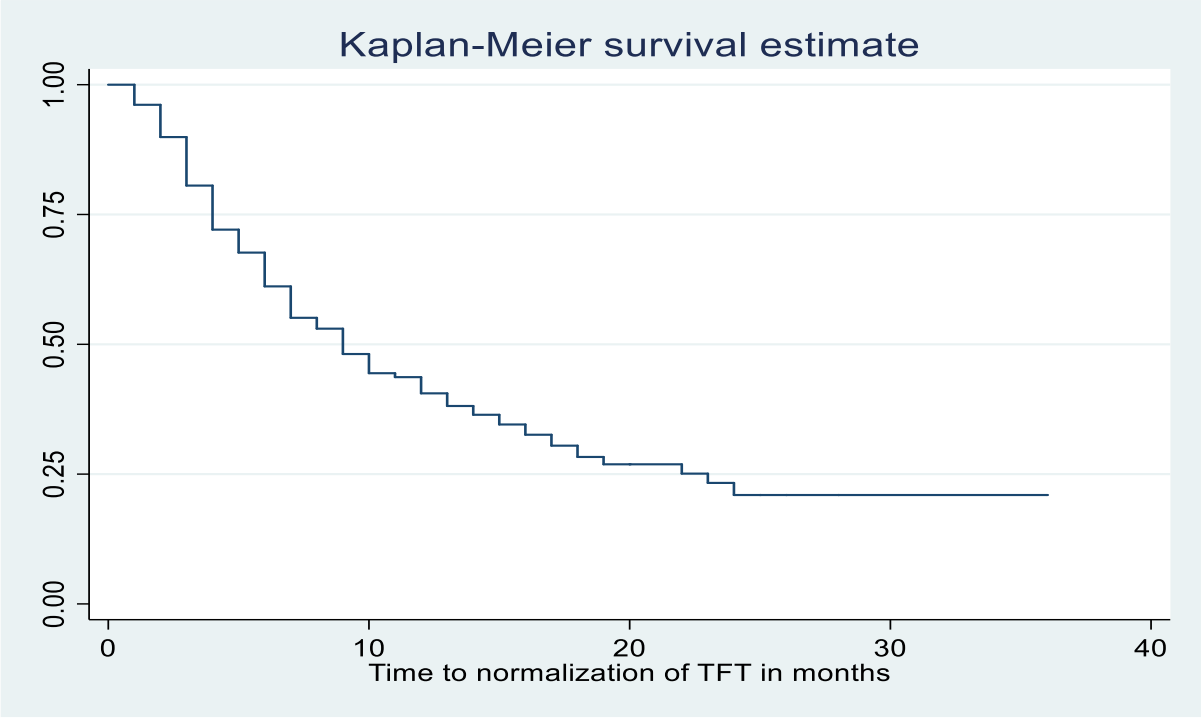

Figure 2: The overall time to normalization thyroid function test of patients with thyrotoxicosis followed at SPHMMC hospital April 2023 G.C. to January 2024 G.C. [n= 181]

Kaplan-Meier survival analysis was also used to compare time to normalization across different predictor categories. The log-rank test revealed significant differences in median time to normalization based on categorical predictors such as medication adherence and type of antithyroid medication used (Figure 3).

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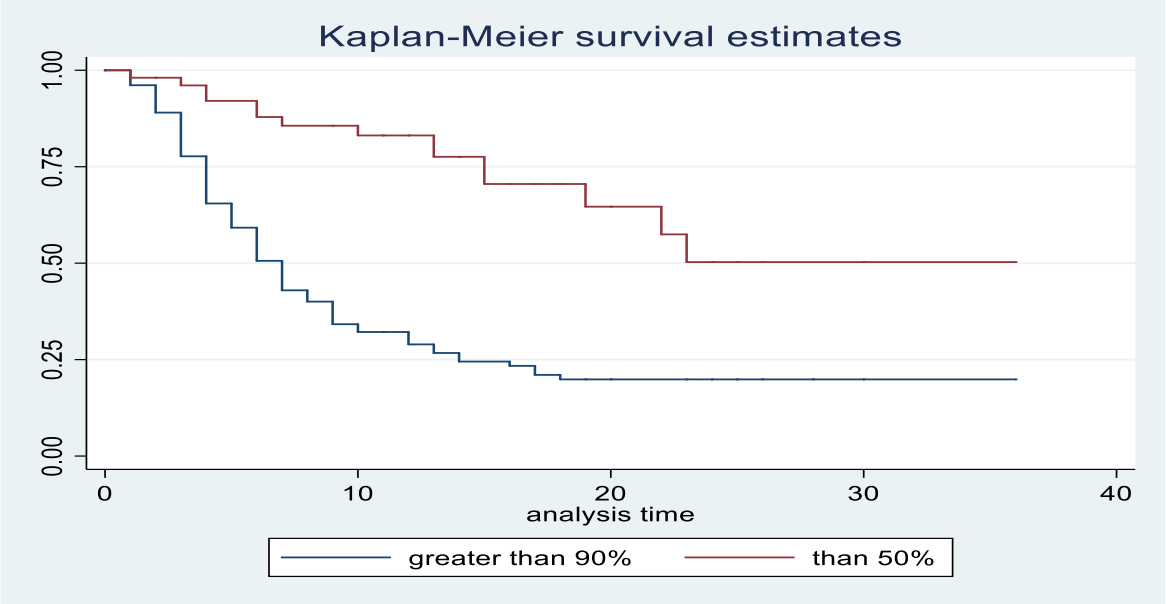

Figure 3: The overall time to normalization of thyroid function test among patient with thyrotoxicosis by drug adherence followed at SPHMMC hospital April 2023 G.C. to January 2024 G.C. [n= 181]

Proportional Hazard Assumption Test

To identify factors significantly associated with the time to normalization of thyroid function tests, the Cox proportional hazards regression model was employed. A key assumption of this model is that the hazard ratios are proportional over time, meaning the effect of covariates on the hazard is constant throughout the study period.

In this study, the proportional hazards assumption was assessed statistically using the Schoenfeld residuals test. The global test yielded a p-value of 0.95, indicating no evidence of violation of the proportional hazards assumption. Additionally, the model's adequacy was evaluated using the Cox-Snell residuals, which confirmed a good fit to the data. These diagnostic tests support the validity of the Cox regression model in this analysis.

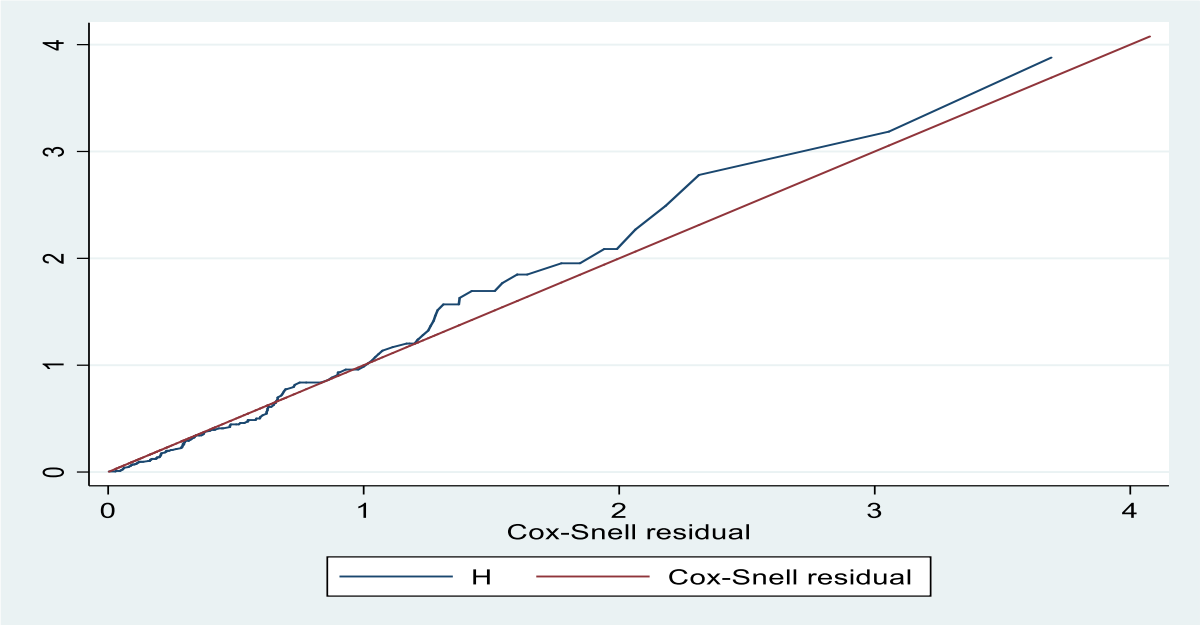

Figure 4: A cumulative hazard plot of Cox-Snell residuals for model fitness.

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Predictors of Time to Normalization of Thyroid Function Test

After performing univariate Cox regression analysis, several variables, including baseline pulse rate, respiratory rate, temperature at diagnosis, presence of palpitations, congestive heart failure, type of antithyroid medication, residence, medication adherence, age, baseline TSH, baseline FT4, WHO goiter size, and presence of other comorbidities were selected as candidate variables for multivariable Cox regression analysis.

In the multivariable Cox regression model, variables with a p-value ≤ 0.05 were considered statistically significant predictors of time to normalization of thyroid function tests. These included baseline FT4, type of antithyroid medication, medication adherence, and baseline pulse rate at diagnosis.

Patients treated with propylthiouracil (PTU) had a 66% lower hazard of normalization compared to those on carbimazole (Adjusted Hazard Ratio [AHR]: 0.33; 95% Confidence Interval [CI]: 0.12–0.89), indicating delayed normalization.

Patients with poor medication adherence (<50%) had a 76% lower hazard of normalization compared to those with good adherence (≥90%) (AHR: 0.24; 95% CI: 0.13–0.42).

Each one-unit increase in baseline pulse rate was associated with a 3% decrease in the hazard of normalization (AHR: 0.97; 95% CI: 0.95–0.99).

Each unit increase in baseline FT4 was associated with a 1% decrease in the hazard of normalization (AHR: 0.99; 95% CI: 0.984–0.995).

Table 4: Multivariable Cox Regression Analysis of Predictors of Time to Normalization of Thyroid Function Test among Patients with Thyrotoxicosis at SPHMMC (April 2023 – January 2024) (n = 103)

Variable	Category	Median Time to Normalization (IQR, months)	Status (Normalized / Censored)	Unadjusted HR (95% CI)	Adjusted HR (95% CI)	p-value
Type of Antithyroid Medication	Carbimazole	3 (1–4)	7 / 1	1 (reference)	1 (reference)	—
	Methimazole	7 (3–13)	1 / 0	1.66 (0.19–14.00)	1.07 (0.12–9.80)	0.639
	PTU	6 (3–13)	96 / 77	0.26 (0.12–0.62)	0.33 (0.12–0.89)*	0.002
Age (years)	< 40	11 (7–15)	41 / 37	1 (reference)	1 (reference)	—
	≥ 40	8 (6–10)	67 / 33	1.26 (0.68–1.84)	1.23 (0.82–1.88)	0.230
Residence	Rural	13 (9–19)	19 / 19	1 (reference)	1 (reference)	—
	Semi-urban	6 (3–14)	7 / 3	1.88 (0.79–4.50)	1.49 (0.61–3.63)	0.380

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Variable	Category	Median Time to Normalization (IQR, months)	Status (Normalized / Censored)	Unadjusted HR (95% CI)	Adjusted HR (95% CI)	p-value
	Urban	8 (6–12)	85 / 48	1.63 (0.99–2.69)	1.58 (0.93–2.71)	0.090
Palpitation	No	7 (5–10)	41 / 14	1 (reference)	1 (reference)	—
	Yes	11 (7–15)	70 / 46	0.69 (0.47–1.01)	0.71 (0.47–1.07)	0.110
Medication Adherence	≥ 90%	6 (5–8)	96 / 33	1 (reference)	1 (reference)	—
	< 50%	23 (19–27)	15 / 37	0.26 (0.15–0.45)	0.24 (0.13–0.42)**	<0.001
Congestive Heart Failure	No	9 (7–12)	108 / 65	1 (reference)	1 (reference)	—
	Yes	15 (3–8)	3 / 5	0.50 (0.16–1.59)	0.73 (0.21–1.49)	0.390
Other Comorbidities	No	5 (6–13)	85 / 61	1 (reference)	1 (reference)	—
	Yes	10 (4–8)	26 / 9	1.62 (1.04–2.51)	1.41 (0.87–2.29)	0.160
WHO Goiter Size	Grade 0	5 (3–7)	16 / 9	1 (reference)	1 (reference)	—
	Grade 1	5 (4–9)	25 / 6	0.72 (0.38–1.36)	1.35 (0.64–2.85)	0.430
	Grade 2	10 (7–16)	36 / 24	0.41 (0.22–0.75)	1.15 (0.56–2.35)	0.710
	Grade 3	13 (9–24)	34 / 31	0.33 (0.18–0.62)	0.68 (0.34–1.37)	0.290

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Variable	Category	Median Time to Normalization (IQR, months)	Status (Normalized / Censored)	Unadjusted HR (95% CI)	Adjusted HR (95% CI)	p-value
Baseline Pulse Rate (per unit increase)	—	—	—	0.98 (0.95–1.002)	0.97 (0.95–0.99)*	0.008
Baseline TSH (per unit increase)	—	—	—	1.009 (1.00–1.01)	0.99 (0.986–1.001)	0.080
Baseline Respiratory Rate (per unit increase)	—	—	—	1.03 (0.99–1.06)	1.02 (0.98–1.05)	0.300
Baseline FT4 (per unit increase)	—	—	—	0.987 (0.982–0.992)	0.99 (0.984–0.995)**	<0.001
Baseline Temperature (per unit increase)	—	—	—	0.87 (0.76–0.99)	0.90 (0.79–1.04)	0.160

Notes: HR = Hazard Ratio; CHR = Crude Hazard Ratio (unadjusted); AHR = Adjusted Hazard Ratio (multivariable model)
*p-value ≤ 0.05; **p-value ≤ 0.01
Reference categories are indicated where applicable.
Median time to normalization is presented with interquartile range (IQR).
"Normalized" refers to patients who achieved thyroid function normalization; "Censored" refers to those who did not during the study period.

DISCUSSION

This study provides important insights into the time to normalization of thyroid function among patients with thyrotoxicosis attending the Endocrinology Clinic at SPHMMC. The majority of patients were elderly females residing in urban areas, with WHO goiter size predominantly grade two, and none reported smoking. The most common presenting symptoms were diffuse goiter, palpitations, and heat intolerance, consistent with typical clinical features of thyrotoxicosis.

Comparison with Previous Studies

Our findings regarding the high female predominance align with retrospective studies conducted in Saudi Arabia, University of Gondar Comprehensive Specialized Hospital, and South Tigray General Hospitals, which reported female-to-male ratios ranging from approximately 3.8:1 to over 88% female representation [11, 12, 13]. The initial and maintenance doses of propylthiouracil (PTU) in our cohort—primarily 100 mg orally three times daily initially and 100 mg twice daily for maintenance—are comparable to

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dosing regimens reported in Ethiopian studies .This may reflect similar clinical practices and challenges such as longer intervals between patient visits and high clinic workloads[11,12].

Toxic multinodular goiter (TMNG) was the predominant etiology in 67.4% of patients, consistent with findings from Ethiopian centers. However, in contrast, Graves' disease was the leading cause in the Saudi Arabian study, accounting for 69% of cases, which may explain some differences in treatment response and time to euthyroidism [11, 12, 13].

Time to Normalization and Treatment Patterns

In this study, 61% of patients achieved euthyroidism during follow-up, a rate higher than the 51.9% reported in South Tigray but lower than the 72% reported in Saudi Arabia [12, 13]. The difference may be attributed to the predominance of TMNG in our cohort, which is generally associated with a longer time to normalization compared to Graves' disease.

Most patients (95.6%) were treated with PTU, with only a minority receiving carbimazole or methimazole. This contrasts with Ethiopian studies where PTU was exclusively used [12, 13] and a Swedish study where methimazole predominated [14]. The limited availability of methimazole and carbimazole locally likely explains this pattern.

Predictors of Time to Normalization

Multivariable Cox regression analysis identified several significant predictors of delayed normalization. Use of PTU was associated with a 66% lower hazard of achieving euthyroidism compared to carbimazole, likely reflecting the higher potency and longer half-life of carbimazole. This finding underscores the importance of medication choice in managing thyrotoxicosis.

Poor medication adherence (<50%) was associated with a 76% reduction in the hazard of normalization compared to good adherence (≥90%), highlighting adherence as a critical modifiable factor in treatment success. This is consistent with findings from a U.S. study where non-compliance significantly impaired treatment outcomes [15].

Higher baseline free thyroxine (FT4) levels and increased pulse rate at diagnosis were also associated with delayed normalization, likely reflecting greater disease severity. This aligns with studies from Ethiopia and Edinburgh reporting that elevated FT4 predicts prolonged hyperthyroidism [11,16] . However, a Swedish study did not find FT4 or FT3 to be significant prognostic factors, possibly due to differing etiologies and treatment protocols [14].

Age and Other Factors

Our study found no significant association between age and time to normalization, consistent with a Romanian study [17]. This contrasts with findings from Ethiopian and other international studies where younger patients (<40 years) had poorer response to medical treatment[12,18]. These discrepancies may relate to population differences or sample size.

Clinical and Research Implications

Our findings emphasize the importance of early diagnosis, ensuring medication adherence, and considering antithyroid drug choice to optimize time to euthyroidism. Clinicians should monitor patients with high baseline FT4 and elevated pulse rates closely, as they may require more intensive management.

Strengths and Limitations

This study has several strengths. Notably, it included patients treated with carbimazole and rigorously assessed the impact of medication adherence on the time to normalization of thyroid function—an aspect not previously explored in Ethiopian studies. Additionally, data were collected from both paper charts and electronic health records to minimize missing information.

However, the study also has limitations. Its retrospective design relied on existing medical records, many of which were incomplete or missing, resulting in a smaller sample size than initially planned. Furthermore, the study did not evaluate remission or relapse rates, limiting the understanding of the full disease course. Future prospective studies should address these gaps to provide a more comprehensive assessment of treatment outcomes. These limitations should be considered when interpreting the findings.

CONCLUSION AND RECOMMENDATIONS

Although the time to achieve euthyroidism was longer than expected, more than half of the patients in this study attained normal thyroid function. Delays in normalization were significantly associated with high baseline FT4 levels, elevated baseline pulse rate, poor medication adherence, and the use of propylthiouracil (PTU) as the antithyroid drug. Clinicians should ensure thorough and vigilant follow-up of patients with hyperthyroidism until thyroid function tests normalize, investigating potential causes of delayed

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response to prevent complications. Clear communication with patients regarding medication adherence, appropriate dosing, and possible drug interactions is essential.

To improve management, SPHMMC may consider establishing a dedicated thyroid clinic to enable more focused and frequent follow-up. Additionally, given the superior efficacy of carbimazole in achieving euthyroidism, the Federal Ministry of Health should prioritize the availability and accessibility of this medication as part of public health policy. Future prospective studies are recommended to address limitations related to missing data and to evaluate remission and relapse rates for a more comprehensive understanding of disease progression.

Consent for publication

Not applicable

Availability of data and material

The data collected for this study can be obtained from the first author based on a reasonable request.

Competing interests

No, I declare that the authors have no competing interests.

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