ADDIS ABABA UNIVERSITY COLLEGE OF HEALTH SCIENCE SCHOOL OF MEDICINE DEPARTMENT OF SURGERY, ENDOCRINE AND BREAST SURGERY (EBS) SUB-UNIT

Surgical Treatment Outcomes of Graves' disease:

A Retrospective Multicenter Study in Ethiopia

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ABSTRACT

Background:

Graves' disease (GD) is the most common cause of hyperthyroidism. In general, thyroidectomy is the preferred modality in the presence of severe eye disease, failure or contraindications to other treatment options, if rapid reversal of hyperthyroidism is needed, presence of concomitant suspicious thyroid nodules, large goiters with compressive symptoms, and pregnancy or breastfeeding states. Despite advancements in medical management, total thyroidectomy remains a definitive treatment, especially in resource-limited settings. However, data on surgical outcomes and predictors of complications in low-income countries remain limited.

Objective:

To evaluate the surgical treatment outcome of GD at our centers and to identify clinical and demographic predictors of unfavorable outcomes, including recurrent laryngeal nerve injury (RLNI) and permanent hypocalcemia.

Materials and methods:

A years, multicenter retrospective study was conducted across four hospitals in Ethiopia from December 1, 2021 to December 31, 2024. A total of 43 patients for whom thyroidectomy done for GD were included. Data were analyzed using SPSS version 26. Bivariate and multivariate logistic regression analyses were employed to identify predictors of surgical outcomes. $P<0.05$ declared statistically significant. Favorable outcome was defined as the absence of RLNI or permanent hypocalcemia.

Result:

The majority of patients were female (74.4%) with a mean age of 36.4 years. Total thyroidectomy was performed in 95.3% of cases. The most frequent symptoms/signs were goiter (95.3%), palpitations (72.1%), and exophthalmos (69.8%). Postoperative complications included permanent hypocalcemia (9.3%), RLNI (4.7%), external branch of superior laryngeal injury in 1patient, temporary hypocalcemia in 1 patient and seroma in 2patients. Favorable outcomes were achieved in 86% of patients. On multivariate analysis, exophthalmos was significantly associated with favorable surgical outcome (**p = .020**), with the AOR=15.83, 95% CI [1.53 – 163.55]. Other factors such as gender, comorbidities, duration of antithyroid drug therapy, and preop-thyroid function status were not statistically significant.

Conclusion:

In well-prepared patients, surgical management of Graves' disease is safe and effective, with high rates of favorable outcomes. Exophthalmos was identified as a strong independent predictor of favorable prognosis. These findings support early surgical referral and highlight the importance of surgeon expertise and preoperative optimization. Further prospective studies are recommended to confirm these findings and guide clinical practice.

KEY WORDS: Graves' disease, Exophthalmos, hypocalcemia, recurrent laryngeal nerve injury, thyroidectomy, Ethiopia.

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Acronyms

AAU - Addis Ababa University

AHMC – Adama Hospital Medical College

BLH – Black Lion Hospital

CLD – Chronic Liver Disease

ATDs – Anti Thyroid Drugs

CTLA-4 – Cytotoxic T-Lymphocyte Antigen-4

DM – Diabetes Mellitus

EBS – Endocrine and Breast Surgery

GD – Graves' disease

GO - Graves' Orbitopathy

HIV – Human Immuno Deficiency Virus

HTN – Hypertension

IHD – Ischemic Heart Disease

LGH – Lancet General Hospital

LMICs – Low and Middle Income Countries

RAI – Radio Iodine

RLN – Recurrent Laryngeal Nerve

RLNI - Recurrent Laryngeal Nerve Injury

SLN – Superior Laryngeal Nerve

SLNI - Superior Laryngeal Nerve Injury

TSH – Thyroid Stimulating Hormone, TSHab= Thyroid stimulating receptor antibody

TSHR – Thyroid Stimulating Hormone Receptor

YGH – Yoya General Hospital

1. INTRODUCTION

1.1 Background

Graves' disease, the most common cause of hyperthyroidism, is an autoimmune disorder characterized by overproduction of thyroid hormones, diffuse goiter, and often ophthalmopathy [1]. The disease is marked by significant morbidity if left untreated, with cardiovascular and musculoskeletal complications among the most common [2]. Treatments typically include antithyroid drugs, radioactive iodine therapy (RAI), and surgery, but surgical intervention is often favored in settings with limited access to RAI or for patients who do not respond adequately to pharmacotherapy[3].

1.2 Significance of the study

In Ethiopia, the high prevalence of iodine deficiency and limited healthcare resources mean that Graves' disease is frequently diagnosed at more advanced stages, often when goiters are large and symptomatic [4], [5]. Given the lack of widespread access to RAI and challenges associated with long-term medical management in low-resource settings, thyroidectomy is often the most practical treatment option. However, variability in surgical expertise, postoperative care availability, and facility resources can significantly impact outcomes [6], [7]. This study aims to systematically examine surgical outcomes of thyroidectomy for GD in Ethiopian hospitals to inform and optimize treatment protocols for Graves' disease in similar low-resource contexts.

1.3 Statement of the problem

Graves' disease (GD) is the most common cause of hyperthyroidism, affecting individuals worldwide with an estimated prevalence of 0.5% to 2% in the general population, with a higher incidence in women [8]. It is an autoimmune disorder where the thyroid gland is overstimulated by autoantibodies to the thyroid-stimulating hormone receptor (TSHR), resulting in the excessive secretion of thyroid hormones [9]. Clinical manifestations of Graves' disease include weight loss, palpitations, tremors, exophthalmos, and goiter, which can severely impair a patient's quality of life if left untreated [3]. Although most cases of GD are managed with antithyroid drugs, radioactive iodine, or surgical treatments, a subset of patients may require surgical intervention due to failure or contraindications to these therapies[2], [10].

In Ethiopia, like in many other low- and middle-income countries (LMICs), the diagnosis and treatment of Graves' disease present significant challenges. The limited availability of diagnostic tools, the late presentation of patients, and insufficient access to advanced treatments such as radioactive iodine therapy contribute to a reliance on thyroidectomy. Thyroidectomy in Graves' disease is typically considered for patients who have not responded to medical management or in cases where other treatments are contraindicated due to factors such as pregnancy or adverse drug reactions [11]. Despite being a standard treatment approach in such cases, the surgical outcomes for Graves' disease in Ethiopia have not been extensively studied.

While thyroidectomy is generally a safe procedure, it carries risks of complications such as recurrent laryngeal nerve injury, hypoparathyroidism, injury to the external branch of superior laryngeal nerve, bleeding, tracheal injury, and esophageal injury are relatively common[6]. And, they can negatively impact patient recovery and long-term quality of life. **GD is an independent risk factor for permanent hypocalcemia [12]. Total thyroidectomy which is a standard therapy for GD , but carries higher risk of complications even among high volume surgeons** [13]**. These evidences tell the complications will be higher in GD.** More severe, but rare complications that can be life threatening include asphyxia, dspnea, and thyrotoxic crisis [14]. Furthermore, post-surgical recurrence of hyperthyroidism and the need for reoperation or long-term thyroid hormone replacement therapy are potential concerns that need thorough investigation. The burden of post-surgical complications and the absence of long-term follow-up data in Ethiopia remain significant gaps in the available medical literature, hindering the ability to form evidence-based treatment guidelines for the Ethiopian context [15].

Ethiopian healthcare settings, particularly in regions with limited resources, face challenges such as inadequate surgical expertise, lack of trained endocrinologists, and limited access to post-operative care. These factors could influence surgical outcomes and patient recovery. There is a significant need for a comprehensive analysis of the surgical treatment outcomes of Graves' disease to understand the effectiveness, complications, and long-term prognosis of patients undergoing thyroidectomy in Ethiopia. The lack of such data hinders the ability of healthcare professionals to improve clinical practices and ensure optimal care for patients with Graves' disease.

This retrospective multicenter study seeks to address this gap by evaluating the surgical outcomes of Graves' disease treatment across multiple centers in Ethiopia. Specifically, it will examine the incidence of post-surgical complications (e.g., hypocalcemia, nerve injury, bleeding), rates of recurrence of hyperthyroidism, mortality, and the need for additional treatments. The study will also explore demographic and clinical characteristics, including age, sex, comorbidities, and pre-surgical thyroid function, to identify factors that may influence surgical outcomes. The sudy mainly focusses on known determinants of thyroidectomy outcomes (Hypoparathyroidism, RLNI, and bleeding) [7]. By providing data from multiple centers in Ethiopia, this study aims to improve the understanding of thyroidectomy outcomes for Graves' disease and inform clinical practices for better patient management in resource-limited settings.

2. Literature Review

2.1 Overview and pathophysiology of Graves’ disease

Graves' disease (GD) is the most common cause of hyperthyroidism and is characterized by the overproduction of thyroid hormones due to the stimulation of the thyroid gland by autoantibodies against the thyroid-stimulating hormone receptor (TSHR). The disease predominantly affects women, with an incidence of approximately 2–3 times higher in females than males [3]. Clinical features of GD include goiter, exophthalmos, palpitations, weight loss, and nervousness, which can severely affect the quality of life and, if left untreated, lead to significant morbidity [8]. The treatment modalities for GD typically include antithyroid drugs (ATDs), radioactive iodine (RAI) therapy, and surgery [11]. The decision to pursue surgery is often based on factors such as resistance or contraindications to ATDs and RAI, patient preference, and the presence of complications.

Surgical treatments for Graves’ disease is typically total, near-total, or subtotal thyroidectomy. Near total thyroidectomy is superior to total thyroidectomy for graves’ disease regarding permanent hypoparathyroidism, but no significant differences in other post-operative complications and recurrent hyperthyroidism [16], [17]. Though the first line therapy for GD is ATDs, thyroidectomy is considered the best therapeutic option for GD with suspected malignant nodules, severe GO, failure of RAI, large goiters with compressive symptoms, or pregnant woman with hyperthyroidism [17].

2.2 Pathophysiology and Epidemiology of Graves' Disease

Graves' disease primarily affects women and is often associated with genetic and environmental risk factors, such as polymorphisms in TSH receptor and CTLA-4 genes, smoking, and iodine intake variability [18], [19], [20]. The prevalence of GD is higher in iodine-deficient areas as revealed by a number of epidemiological surveys [21]. In iodine-deficient regions like Ethiopia, the prevalence of thyroid diseases is higher, and patients often present with larger goiters due to delayed diagnosis and treatment [22], [23]. In study from China iodine deficiency was related to the high prevalence of GD [24]. A study in Danish population showed iodine supplementation resulted in reduction of hyperthyroidism by half [25].

2.3 Surgical Treatment Outcomes in Global Context

The outcomes of thyroidectomy for Graves' disease have been well-documented in high-income countries, with studies reporting a high success rate in terms of symptom resolution, low complication rates, and minimal recurrence of hyperthyroidism. To minimize the risk of hypoparathyroidism, recurrent laryngeal nerve palsy, wound infection, and hemorrhage, surgery should be performed by a skilled high volume surgeon [26]. Total thyroidectomy has been shown to be a safe, cost-effective, and successful treatment for Graves' disease, especially in the hands of high-volume, experienced endocrine surgeons [27]. Following total thyroidectomy many Graves' disease symptoms improve rapidly, with a median time to improvement of less than 1 month.

However, in low- and middle-income countries (LMICs), the outcomes of surgical treatment for Graves' disease are less well understood. Factors such as limited access to healthcare, inadequate diagnostic facilities, and variations in surgical expertise may contribute to different surgical outcomes in these settings [6]. The common complications include injury to EBSLN, injury to RLN, and hypoparathyroidism. Moreover, the long-term outcomes of these surgeries, particularly in terms of recurrence of hyperthyroidism or the need for thyroid hormone replacement were less favorable in some LMICs. Because of affordability issues for thyroxin, surgeries for hyperthyroid patients are being done in the form of subtotal thyroidectomy. Even though recent evidences support total thyroidectomy as a standard surgery for GD, subtotal thyroidectomy is still an option in resource limited settings at the expense of recurrence [28].

Key postoperative complications include:

Hypocalcemia: This can be transient or permanent due to parathyroid gland injury. Permanent hypocalcemia, while less common, has long-term quality of life implications[6], [29].

Recurrent Laryngeal Nerve Injury: RLN injury can lead to voice changes, swallowing difficulties, and, in severe cases, breathing issues, with an estimated incidence of 1-5% even in experienced centers [30], [31].

Postoperative Thyrotoxicosis or Recurrence: Recurrence is a notable issue with subtotal thyroidectomy, especially without adequate follow-up, making total thyroidectomy a preferred option to prevent recurrence.

Studies underscore that these risks are heightened in settings with limited surgical experience or inadequate postoperative monitoring, pointing to the critical need for procedural standardization and resource allocation.

2.4 Surgical treatment outcome in Ethiopia

While there is a growing body of literature on Graves' disease treatment outcomes in LMICs, there is a notable lack of comprehensive data from Ethiopia, particularly regarding surgical treatment outcomes of GD.

The surgical treatment of Graves' disease has proven to be an effective and necessary option for many patients, particularly in LMICs where access to medical therapies like radioactive iodine may be limited. However, the outcomes of thyroidectomy in these settings, including Ethiopia, remain under-explored. The available literature suggests that while thyroidectomy can effectively manage symptoms of Graves' disease, the risks of complications from thyroidectomy such as recurrent laryngeal nerve injury, hypocalcemia, and recurrence of hyperthyroidism are higher compared to high-income countries [15]. In Ethiopia, factors such as limited access to healthcare resources, delayed diagnosis, and inadequate postoperative care contribute to these suboptimal outcomes. Therefore, there is an urgent need for comprehensive studies, such as the proposed retrospective multicenter study, to assess the surgical outcomes of Graves' disease in Ethiopia and identify strategies to improve patient care and outcomes in the country.

2.5 Conceptual Framework

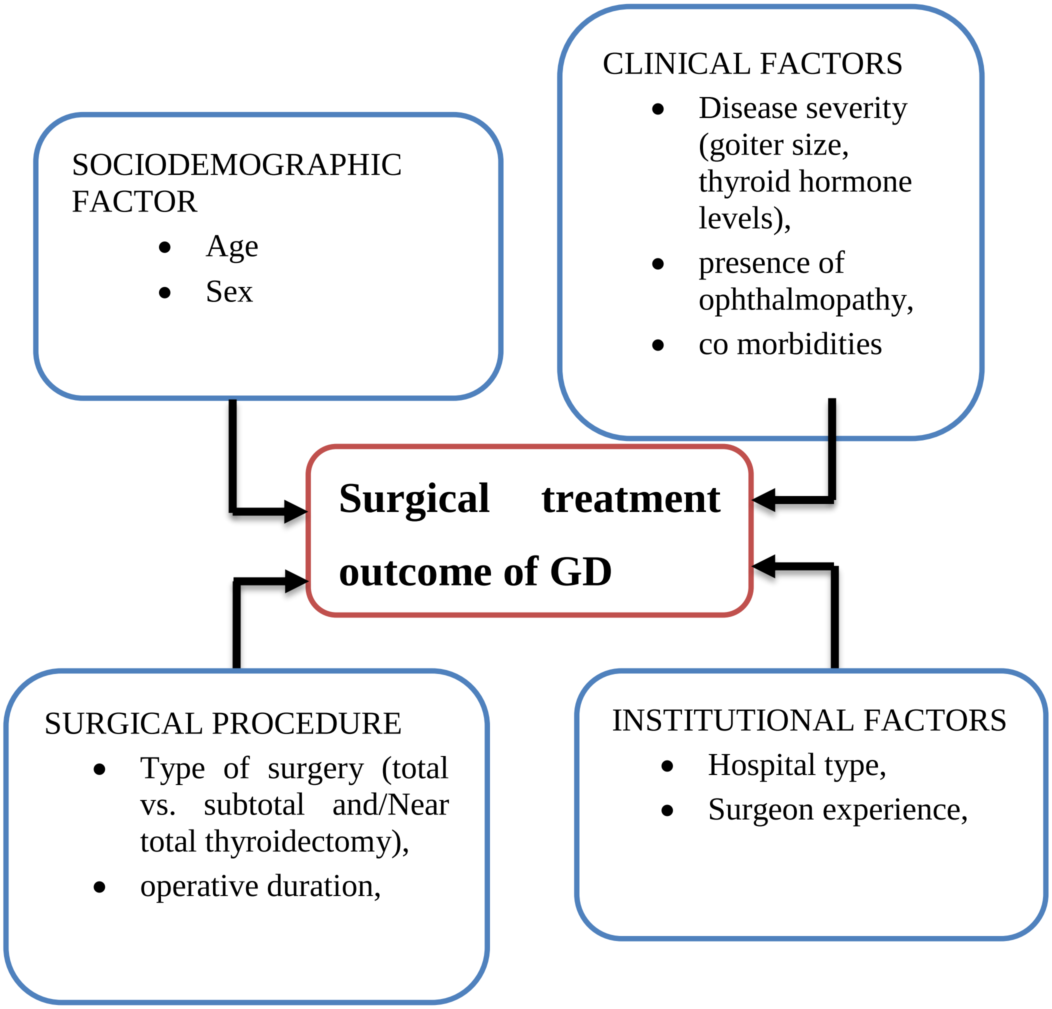

Figure 1 **Conceptual Framework for the surgical management outcome of GD based on literature review.**

3. Study Objectives

3.1General Objectives

To assess surgical treatment outcomes of Graves' disease patients in Ethiopian four hospitals, focusing on most common predictors of outcomes, i.e. complications like permanent hypocalcemia, RLNI/persistent horseness of voice or laryngoscopy confirmed, and associated factors in a multicenter setting.

3.2Specific Objectives

i. To quantify postoperative complication rates, including hypocalcemia, RLN injury, hematoma, and infection.
ii. To compare recurrence rates between subtotal/Near and total thyroidectomy.
iii. To identify demographic, clinical, and institutional factors associated with surgical outcomes.
iv. To evaluate variability in surgical outcomes across hospitals to highlight the influence of surgical expertise and healthcare infrastructure.

4. Methods and Materials

4.1 Study Design, Setting, and Period

This is a multicenter cross-sectional study that includes 4 hospitals (BLH, AHMC, LGH and YGH) in Ethiopia with diverse geographic and resource backgrounds. BLH is a prominent specialized hospital in Addis Ababa, the capital city of Ethiopia. It was estabilished in 1964, serving as a major teaching hospital affiliated with school of medicine at Addis Ababa University. The hospital provides a wide range of specialized clinical services and is a key training center for medical students and health professionals (under graduate and post graduate educations) from Ethiopia and other African countries. The hospital has over 700 beds and treats over 500,000 out patients and more than 21,000 in patient annually. AHMC was established in 1946 GC as the 1st non-governmental hospital and upgraded to college in 2011GC serving more than 6 million population. Currently it is one of the tertiary centers in the country giving clinical services and teaching medical students and postgraduate health professionals. It has more than 300 beds but when the new project under construction is finished it will have 1,200 beds. It is found in Adama city, 100km from Addis Ababa. LGH is one of the private hospitals in Addis Ababa, Ethiopia, which was estabilished in November, 2020 by 24 specialists and subspecialists of various medical fields. YGH is also one of the private hospitals in Adama, Ethiopia, which was estabilished on December, 2021 by health professionals. Cases from January1, 2017 to December 31, 2024 for BLH and AHMC **(but GD was operated only from December, 2021, probably giving priority to other patients during the past years or patients might have been labeled as controlled toxic Goiters as there were multiple toxic goiters operated during those years and after the start of Endocrine fellow ship that GD patients were operated. This shows the importance of subspecialty training in better care of patients.).** So the analysis only includes three years from December, 2021 to December, 2024. The study was conducted from May 1, 2025 to June 30, 2025.

4.2 Study Design

Multiple (four) hospital based cross sectional study conducted.

4.3 Population

4.3.1 Source Population

All patients admitted to surgical ward during the period (from December 1, 2021 to December 31, 2024 G.C). .

4.3.2 Study Population and Sample Size

All GD patients admitted to surgical ward and operated during the period (from December 1, 2021 to December 31, 2024 G.C).

4.3.3 Study Subject

The study subject comprised of all patients operated for GD and included in this particular study.

4.4 Study Unit

4.4.1 Inclusion criteria

All patients >/= 15 years diagnosed with Graves' disease undergoing near total, subtotal or total thyroidectomy with complete preoperative and postoperative documentation.

4.4.2 Exclusion criteria

Patients with concomitant thyroid cancer, incomplete records (no operation note, no post-operative follow up data for at least 6months). Most of the patient data were incomplete concerning Operation time, Parathyroid gland identification, preop serum calcium, thyroid gland size, marital status, patient BMI, EBL, post op Hct drop, and others. So analysis included other factors with adequate record.

4.5 Sample size determination and sampling technique

4.5.1 Sample size determination

The sample size was calculated using single population proportion formula for infinite population and assuming a 50% proportion for maximum variability (since exact prevalence was unknown), 95% confidence level, and 5% margin of error:

$n = (Z^2 \text{ x } p\ (1-p)) / d^2$

$n = (1.96^2 \times 0.5 \times 0.5) / 0.05^2 = 384 = n_0$

Because my sample size N=43 is small so applied the FPC formula

$n = n_{0/(1+(n_{0}-1)/N)} =$ 39, with addition of 10% attrition rate n=43=N is the final sample size

Sample size is all patients operated for GDs after inclusion and exclusion criteria applied. This work is reported in line with the STROCSS criteria [32].

4.6 Data Collection Process and Variables

Data was checked if there was any inconsistency besides training data collectors. Data is extracted from electronic medical records, patient charts and surgical log books, covering: Demographic Variables: Age, sex, and marital.

Clinical variables: Goiter, Exophthalmos/ophthalmopathy presence, hoarseness of voice/ laryngoscopy result, thyroid hormone levels (preoperative thyroid function status), serum calcium, relevant comorbidities and preop-antithyroid treatment.

Surgical Variables: Type of thyroidectomy, surgeon experience level (Endocrine surgeon/Fellow vs General surgeon).

Outcomes:

Primary outcomes: Immediate and delayed complications (e.g., hypocalcemia, RLN injury, bleeding or infection).

Favorable outcome if permanent hypocalcemia and/or RLNI, or other life threatening complications are absent, or **unfavorable** if present.

Secondary outcomes: Length of hospital stay, readmission rates, and subsequent interventions required.

4.7 Data quality control

Before data collection, pretest was done on 5% of the sample and after the pretest the findings and observation obtained was used to modify the checklist and the data collection process accordingly. The collected data was checked for completeness and accuracy on daily basis before processing and analyzing it.

4.7.1 Data Analysis

After data collection checklist checked for completeness, data was transferred from Kobotoolbox to SPSS version 26, cleaned, and analyzed using 'IBM SPSS statistics for windows, version 26 (IBM Corp., Armonk, N.Y., USA)'. Descriptive statistics like frequency tables, graphs and descriptive summaries were used to describe the study variables. A variable with $p \leq 0.05$ in multivariable analysis is considered statistically significant.

i. Descriptive Statistics: Means, medians, and frequencies will summarize demographic and clinical characteristics by surgical type.
ii. Cross tabulation - Univariate Analysis: Chi-square and t-tests for length of stay are used to examine associations between surgery type and categorical outcomes.
iii. Multivariable Logistic Regression: This model will identify factors independently associated with complications. Covariates will include demographic and clinical variables, such as goiter, exophthalmos, palpitation, type of thyroidectomy, and hospital type.
iv. Inter-Hospital Comparative Analysis: Differences in outcomes across hospitals will be assessed using ANOVA and chi-square tests to understand institutional and resource-based influences.

4.8 Operational Definitions

GD is an autoimmune disorder characterized by excess thyroid hormone production, diffuse goiter on Ultrasound, Exophthalmos/ophthalmopathy, and/or pretibial myxedema. No THR antibody or thyroid scanning in our set up. So the true magnitude of GD is under estimated.

Outcome the consequences that will occur as a result of surgical treatment of GD that can be either favorable (patients that are improved and/or cured) or unfavorable (those who develop complications postoperatively).

Favorable outcome if permanent hypocalcemia, RLNI or other life threatening complications are absent and **unfavorable** if present.

RLNI is when the patient has hoarseness of voice/laryngoscopy confirmed, permanent if persists beyond 6months, but temporary if not.

Hypocalcemia if symptoms like perioral numbness, tingling in the hands/foot, muscle cramps in addition to low serum calcium for the laboratory. It is permanent if persists beyond 6 months and the patient continued calcium and Vit D. If not it is temporary, i.e, no symptom without calcium and vitamin D and serum calcium normal within 6 months.

Subtotal thyroidectomy is removal of the thyroid leaving approximately 8 gm thyroid tissue on both sides approximately 4g each.

Near total thyroidectomy is removal of the thyroid leaving <1gm thyroid tissue near ligament of Berry on both sides.

Total thyroidectomy is removal of all macroscopic thyroid tissues.

No intraoperative nerve monitoring in our set up.

4.9 Ethical Considerations

Ethical approval was obtained from each participating institution's, but written document was obtained only from AAU, BLH, Department of Surgery Research and Ethics Committee's (Meeting No: DOS/REC/140/2025/2017). Data confidentiality is ensured by anonymizing patient identifiers and securing data in accordance with ethical guidelines for retrospective studies.

4.10 Dissemination of the study result

The result of this study will be presented to BLH, AHMC, LGH, and YGH; and to other concerned governmental and nongovernmental organization. Furthermore, it will be disseminated through publication on local and international journals.

5. Results

5.1 Socio demographic and Clinical Characteristics

During the study period, a total of 43 patients surgically treated for GD were included. Socio-demographic characteristics of the study participants showed that GD is more common in females (74.4%) as compared to the males (25.6%) with M: F ratio of 2.9 to 1. The mean and median ages of the patients were 36.44 ±9.89 (range 15-61 years) and 35 years respectively. The majority of patients, 26 (60.5%), were </= 40 years Table 1.

Table 1 Sociodemographic characteristics of the study participants, multicenter, 2025 (n=43).

Characteristics		**Frequency**	**Percentage (%)**
Age distribution (years)	</= 40 years	26	60.5
	>40 years	17	42.5
Gender	Male	11	25.5
	Female	32	74.4

5.2 Clinical Characteristics

The most common symptom was goiter in 41(95.3%) of the cases followed by palpitation (72.1%), exophthalmos (69.8%), weight loss (23.3%), insomnia (18.6%), irritability (9.3%), tremor (4.7%), and dyspnea (2.3%). The most common comorbidity seen was diabetes 9.3% followed by HIV 4.7%, HTN 4.7%, and IHD, CLD and breast cancer were also seen in 2.3% each.

Patients were euthyroid (67.4%), subclinical hyperthyroid (27.9%), and subclinical hypothyroid (4.7%) based on preoperative thyroid function status. The mean duration of preoperative antithyroid therapy was 47.4 ± 30.5 months. Duration of antithyroid therapy was >12 months in 90.7% of the cases. This shows adequate preparation preoperatively see *Table 2* below.

Table 2 Clinical Characteristics of the study groups, n= 43, Ethiopia, 2025

		Frequency	Percent
Symptom/Sign	Goiter	41	95.3
	Exophthalmos	30	69.8
	Palpitation	31	72.1
	Irritability	4	9.3
	Wt loss	10	23.2
	Dyspnea	1	2.3
	Insomnia	8	18.6
	Tremor	2	4.7
Comorbidities	Diabetes Mellitus	4	9.3
	Hypertension	2	4.7
	HIV	2	4.7
	CLD	1	2.3
	Breast cancer	1	2.3
	Ischemic Heart Disease	1	2.3
Preoperative Thyroid Function Status	Euthyroid	27	62.8
	Subclinical Hyperthyroid	14	35.6
	Subclinical Hypothyroid	2	4.7
Duration of Antithyroid drugs Prior to Surgery	</= 12 months	4	9.3
	>12 months	39	90.7

5.3 Perioperative Characteristics

Total thyroidectomy was the most common procedure in 95.3% of the cases. Near total and subtotal thyroidectomies were done in one patient each. Of the 43 patients, only 4 (9.3%) patients were operated by General surgeons. Except for the missing pathologic results in six patients, all the histopathology results were benign. No malignancy was seen. Hospital Stay was less than 4 days in 95.3% of patients, and readmission was seen in 4.7% of cases due to symptomatic post op hypocalcemia see **Error! Reference source not found.** below. An independent samples t-test revealed a statistically significant difference in surgical outcomes between patients with shorter (<4 days) and longer (≥4 days) hospital stays (**$t(41) = 4.200$, $p < 0.001$**). Patients discharged in <4 days had a mean favorable outcome rate of **0.90**, while those with stays ≥4 days had no favorable outcomes (mean = 0.00). The mean difference of **0.902** (95% CI: 0.469–1.336) indicates that extended hospital stay is strongly associated with unfavorable postoperative outcomes see **Error! Reference source not found.** below.

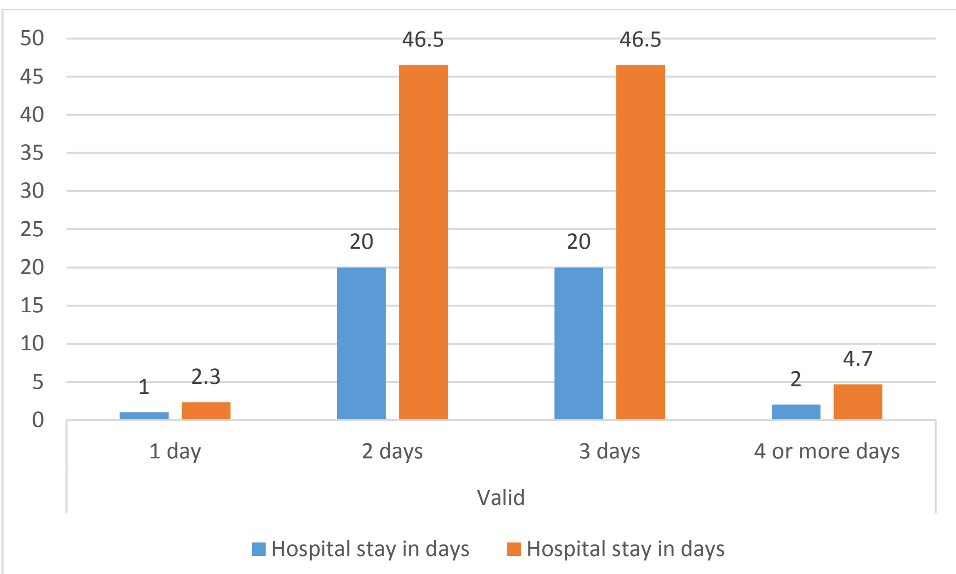

*Figure 2*Hospital stay in Days

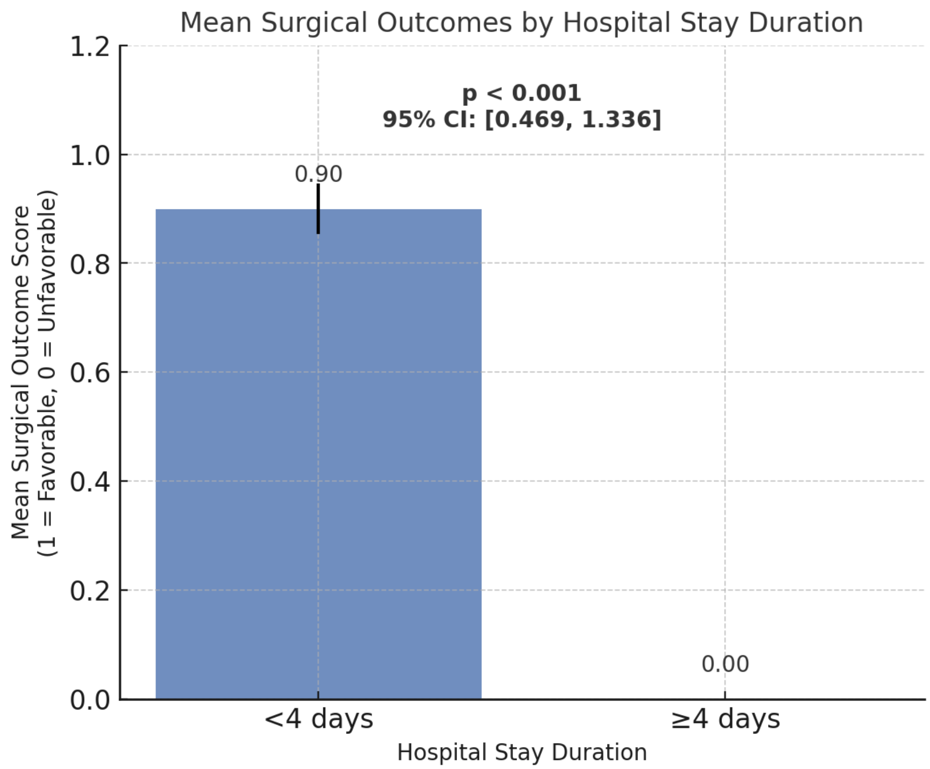

*Figure 3*Mean surgical outcomes by hospital stay of surgically treated GD patients (N=43), Ethiopia, 2025.

5.4 Postoperative complications

Among the postoperative complications permanent hypocalcemia 4 patients (9.3%), RLNI 2pts (4.7%), seroma 2pts (4.7%) and SLNI in 1patient with the RLNI (2.3%). Hypocalcemia was temporary in 1 patient see *Figure 4* below. The seromas resolved without intervension. Patients who developed permanent hypocalcemia were on calcium and vit. D.

Complication rates for hypocalcemia and RLNI were assessed among the type of surgery and hospital setting *Table 3* below.

The incidence of hypocalcemia in total thyroidectomy was 12.2% with permanent hypocalcemia being 9.8%. No hypocalcemia seen in subtotal and Near total thyroidectomies due to small numbers of patients in these groups. RLNI occurred in BLH in 2pts (9.1%). Whereas no RLNI occurred in other hospitals because of small number of patients especially AHMC and YGH, and all patients were operated by experienced endocrine surgeon in LGH. There was no recurrence in this study, due to small sample of subtotal thyroidectomy.

Table 3 Rates of Hypocalcemia and RLNI in Type of Surgery and Hospital setting, Ethiopia, 2025

		Temporary Hypocalcemia		Permanent Hypocalcemia		RLNI	
		Frequency	Percent	Frequency	Percent	Frequency	Percent
Type of Surgery	Total thyroidectomy(n=41)	1	2.4		9.8	2	4.9
	Sub/Near Total Thyroidectomy (n=2)	0	0		0		0
Hospital setting	BLH(n=22)	1	4.5	3	13.6	2	9.1
	LGH(n=17)	0	0	1	5.9	0	0
	AHMC(n=2)	0	0	0	0	0	0
	YGH(n=2)	0	0	0	0	0	0

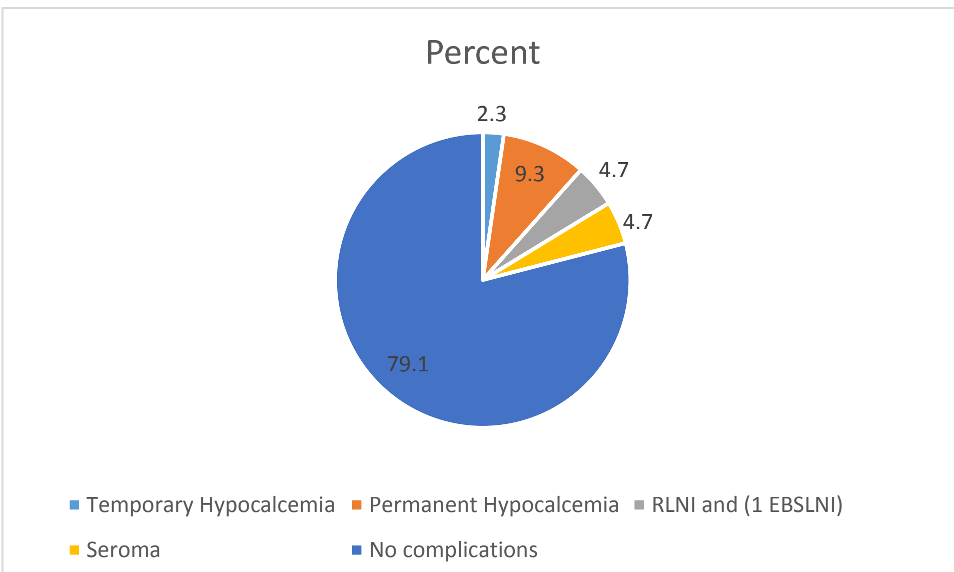

Figure 5Postoperative Complications in Patients operated for GD, Ethiopia, 2025 (N=43)

5.5 Surgical Treatment Outcomes

Of the 43 patients: - 37 (86%) had favorable outcomes, while unfavorable outcome was seen in 6 (13.95%). Unfavorable outcome is defined as: - RLN injury in 2 cases (4.7%), and permanent hypocalcemia in 4 cases (9.3%) because there were no death or significant bleeding recorded in the analyzed patients which are other rare measures of outcome.

5.6 Bivariate Analysis of Predictors VS Surgical Outcomes of GD

Bivariate analysis was done using Chi-square test for independent categorical variables VS surgical Outcomes in patients with GD, and independent-t test for continuous variables. The independent-t test was significant for the duration of hospital stay where patients who stayed <4 days had 90% rate of favorable outcome as compared to those who stayed more than 4 days. Those patients who developed hypocalcemia after discharge and readmitted were in later group. ANOVA was used to see if there were differences in outcomes among the different hospitals, and no difference is noted. In Bivariate analysis using Chi-square: the findings were significant only for exophthalmos. The association between exophthalmos and surgical outcome was statistically significant, $\chi^2(1, N = 43) = [9.322]$, $p = 0.002$; Fisher's Exact Test, **p = .007**). The result remains robust across multiple tests, including the likelihood ratio (p = .003) and linear-by-linear association (p = .003). However, since 50% of the cells had expected counts <5, **Fisher's Exact Test provides the most reliable estimate** see Table 5 below. Patients with exophthalmos were significantly more likely to have a favorable outcome compared to those without (78.4% vs. 21.6%) see Table 4 below. This suggests that the presence of exophthalmos may be linked to a better prognosis following surgery. **Possible clinical explanation can be that exophthalmos often indicates active autoimmune disease, and perhaps patients with more active disease were better selected for surgery early or followed more aggressively pre-op.**

Table 4 Summary of Crosstab Results for Exophthalmos vs outcome

Exophthalmos	**Unfavorable Outcome**	**Favorable Outcome**	**Total**
No	5 (83.3%)	8 (21.6%)	13
Yes	1 (16.7%)	29 (78.4%)	30
Total	6	37	43

Table 5 Chi-Square test results for association between Exophthalmos and Surgical treatment Outcome in Graves' disease Patients (N = 43).

Test Type	Value	df	P-value	Notes
Pearson Chi-Square	9.322	1	0.007	Significant association detected
Continuity Correction (Yates)	6.625	1	—	Conservative estimate for small sample
Likelihood Ratio	8.662	1	0.007	Supports significant association
Fisher's Exact Test	—	—	**0.007**	Preferred test due to small expected cell counts
Linear-by-Linear Association	9.105	1	0.007	Indicates a directional trend in association
Point Probability	—	—	—	Estimated likelihood of observed distribution
Valid Cases	43	—	—	Total sample used in the analysis

NB. **2 cells had expected counts < 5; min expected = 1.81 → Fisher's Exact Test is more reliable here.**

5.7 Factors associated with postoperative complications

Binary logistic regression was fitted to assess the association between postoperative complications and associated factors. In addition to factors with P-value ≤ 0.05, relevant clinical, socio demographic factors and factors with P< 0.2 in binary logistic regression were taken for further analysis to adjust for potential confounders. Model fitness was checked by Hosmer-Lemeshow goodness-of-fit.

Multivariate logistic regression was conducted using 2 predictors at a time because of small sample and small event (outcome) to examine predictors of surgical outcome in patients with Graves' Disease. Exophthalmos and palpitation; exophthalmos and gender; and gender and palpitation in multivariate analysis. The model was statistically significant, χ^2 (2) = 1.691, p = .429 (Hosmer-Lemeshow), indicating good fit for exophthalmos with gender, for other combinations it was perfect fit, maybe due to small sample. Therefore, the model is appropriate for examining predictors of surgical treatment outcomes in patients with Graves' disease in this study.

Exophthalmos was consistently the only significant independent predictor of outcome in this study. After controlling for palpitationin multivariate analysis, **Exophthalmos** is a **strong and statistically significant** independent predictor of favorable surgical outcome (**p = .020**), with the AOR=15.83, 95% CI [1.53 – 163.55], showing patients with exophthalmos are over **15 times more likely** to have a favorable outcome compared to those without. After controlling for gender, exophthalmos is significantly associated with favorable outcome (P= 0.014), with AOR= 19.192 [1.808 – 203.771]. The wide CI in these result indicates limited precision and small sample size.

To provide a more robust estimates of standard errors, confidence intervals and statistical significance a bootstrapping method applied in multivariate analysis resampling the data (here, 1000 times). A bootstrapped logistic regression model was used to explore predictors of favorable surgical outcomes in patients with Graves' disease. **Exophthalmos emerged as a statistically significant predictor** (B = 2.954, p = .014), indicating a strong positive association with favorable outcomes. However, the **confidence interval for the odds ratio [0.882 – 38.589] crossed 1**, suggesting that the **magnitude of effect may not be precisely estimated**, possibly due to small sample size. Gender was not found to be a significant predictor of outcome (p = .069). Overall, the findings support the clinical relevance of exophthalmos in guiding surgical decision-making for Graves' disease, but further studies with larger samples are recommended to validate these results. A bootstrapped logistic regression model assessing predictors of favorable surgical outcome in Graves' disease identified **exophthalmos** as a significant factor (**B = 2.76**, p = .013). However, the **bootstrap confidence interval crossed zero [**–0.231 to 22.313**]**, indicating **limited precision**. Palpitations showed a large negative effect (**B = –19.34**, p = .001), though its CI also approached zero, suggesting potential data sparsity or quasi-complete separation. These findings highlight the potential predictive value of exophthalmos but underscore the need for **larger, balanced datasets** to ensure stable estimation.

6. Discussion

This study investigated the surgical outcomes of patients with Graves' disease (GD) treated across multiple centers in Ethiopia, focusing on the association of clinical and demographic variables with postoperative complications and outcomes. The results reinforce findings from previous studies while offering new insights into the prognostic value of clinical features like exophthalmos in predicting favorable outcomes.

Graves' disease is known to disproportionately affect women, consistent with autoimmune thyroid disease patterns globally [18]. In our study, 74.4% of the surgical patients were female, with a female-to-male ratio of approximately 2.9:1. This result is consistent with the study from Ukraine in their study of "Cardiovascular Complications Secondary to Graves' Disease", 75% of patients were female [33]. This gender discrepancy aligns with previous findings that the incidence of GD is 5–10 times higher in women [28], [34], [35].

The mean age of our surgical cohort (36.4 years) also mirrors global trends, where GD most commonly presents between the third and fifth decades of life [36], [37]. The mean age was 29.2 +/- 9.8 (+/- S.D) in a study from Ethiopia [38]. The relatively young age at surgery could reflect earlier disease onset or challenges in achieving long-term medical remission in resource-limited settings.

Goiter (95.3%), palpitations (72.1%), and exophthalmos (69.8%) were the most common clinical manifestations, consistent with classic descriptions of GD by T.J. Smith, and L. Hegedüs, diffuse goiter in most and MNG in many GD patients from iodine deficient area, palpitation (>50%), exophthalmos (62%) [39], [40]. The prevalence of exophthalmos in our study is particularly notable, as this feature not only represents a diagnostic hallmark of GD but also showed a statistically significant association with favorable surgical treatment outcome of GD in our analysis. This aligns with studies suggesting that the presence of overt ophthalmopathy may lead to earlier surgical referral and better preoperative preparation for both thyroid and GO management [41], [42].

Comorbidities were not significantly associated with outcome in this study. The most common comorbidities seen were diabetes mellitus (9.3%) and hypertension (4.7%). A study from Taiwan reported DM (9.2%) and HTN (5.4%) which is similar to ours [43]. Even though comorbidities are known to be associated with GD, the relatively fewer comorbidity observed in this study is possibly due to younger age and small sample size.

The majority of patients underwent total thyroidectomy (95.3%), reflecting a growing consensus that total thyroidectomy offers the best balance of disease control and complication rates in carefully selected GD patients [44], [45], [46]. There was no recurrence or persistence of the disease observed in this study. This is due to total thyroidectomy eliminates the risk of disease recurrence associated with subtotal procedures and is increasingly preferred in centers with surgical expertise [47].

In this study, the rate of permanent hypocalcemia was 9.3%, temporary hypocalcemia was 2.3%, and permanent RLN injury occurred in 4.7% of patients. These are in line with the reported complication rates from university of Miami, Florida, that reported hypocalcemia (12.4%), and GD is at high risk of vocal cord paralysis (odds ratio [OR] = 1.36 [confidence interval (CI) 1.08-1.69]) as compared to MNG [48]. Temporary hypocalcemia was observed in only one patient in this study, suggesting a high standard of surgical technique. However, the complication rates in this study may still be considered high compared to the rates found in some literatures which range from 0.3% to 6.38% for permanent hypocalcemia, and 0.2% to 2.1% for permanent RLNI [44], [49], [50], [51]. This could be due to absence of intraoperative nerve monitoring in our setup and small sample size. But the rates of both temporary and permanent hypocalcemia was much lower than study from Denmark which was 5.6% and 31.5% respectively [52]. Their explanation was being a low volume center with no experience in parathyroid surgery. This number is even higher when only GD patients are considered.

No malignancies were reported on final histopathology in this study, which is consistent with the benign nature of GD but also underscores the value of histologic confirmation in surgical cases. In a study of 3193 GD patients treated surgically, 406 (12.7%) had incidental thyroid cancer on final pathology [53].

In our study, 86% of patients experienced favorable surgical outcomes, while 13.9% experienced unfavorable outcomes, defined as RLN injury and/or permanent hypocalcemia. Logistic regression analysis identified **exophthalmos** as a **significant independent predictor of favorable outcome** (*(**p = .020**), with the AOR=15.83, 95% CI [1.53 – 163.55]*). This may be the result of early referral and treatment of patients with exophthalmos which reduced the risk of parathyroid injuy. But this needs a confirmation with larger data. This suggests that the presence of exophthalmos may reflect a more classic or active form of GD, leading to earlier diagnosis, better preoperative optimization, or more decisive surgical intervention [41], [42]. Graves orbitopathy as an indication for surgery is an independent risk factor for permanent hypoparathyroidism in patients undergoing total or near total thyroidectomy [54]. In contrast to our findings these authors explained the presence of active and unstable disease may result in difficult dissection and hence parathyroid injury. Others reported severe GO is significantly associated with permanent hypocalcemia [55]. The treatment in our case is mainly surgery, so patients are treated earlier which can explain the discrepancy.

No other variables, including age, gender, comorbidities, or thyroid function status, were statistically significant in predicting unfavorable outcome in this study. While some previous studies have suggested that older age (>/=76) is significantly associated with post op hypocalcemia [56], our relatively small sample size and younger patient demographic may have limited the ability to detect such associations.

These findings highlight the importance of clinical evaluation in surgical decision-making for GD. Exophthalmos should not only prompt ophthalmologic management but also raise consideration for surgical referral in appropriate candidates, as favorable outcomes appear more likely in this subgroup. Furthermore, given the complication rates associated with total thyroidectomy—even in experienced hands—surgical care should ideally be delivered in high-volume tertiary centers.

6.1 Strengths and Limitations

This study is limited by its retrospective design and small sample size, which may underpower some comparisons. The low number of unfavorable outcomes also limits multivariate modeling. In addition, unmeasured confounders such as surgeon experience, intraoperative nerve monitoring, or parathyroid preservation techniques were not captured but may have impacted complication rates. Despite these limitations, the multicenter design and use of consistent surgical outcome definitions strengthen the generalizability of the findings.

7. Conclusions and Recommendations

7.1 Conclussions

The rate of favourable outcomes for GD is 86%. Despite the limited settings the complication rates are within the global reported rates. So total thyroidectomy is safe for the treatment of GD.

Among all assessed predictors, **exophthalmos was the only statistically significant independent predictor of favorable surgical outcome** (**p = .020**), with the AOR=15.83, 95% CI [1.53 – 163.55]. This finding suggests that patients with more overt or classic manifestations of GD may be selected for surgery earlier or may receive more intensive preoperative optimization, leading to better postoperative results.

7.2 Recommendations

7.2.1 Clinical Practice

1. **Prioritize surgical referral for patients with exophthalmos:** Given the favorable outcomes associated with this feature, clinicians should consider early surgical consultation for GD patients presenting with Exophthalmos.
2. **Centralize surgical care in high-volume centers:** The low rates of RLNI and hypocalcemia in experienced centers support ongoing efforts to direct GD surgeries to institutions with trained endocrine surgeons.
3. **Preoperative optimization remains critical:** Ensuring patients are euthyroid and well-prepared with antithyroid medications—as achieved in 90.7% of this study's participants—should be standard of care.
4. **Postoperative monitoring protocols:** Institutions should implement clear postoperative monitoring for calcium levels, PTH levels and vocal cord function to identify and manage complications early.

7.2.2 Health Systems and Policy

5. **Develop national GD surgical guidelines:** Clear, evidence-based protocols tailored to Ethiopia's healthcare context would help standardize care and improve outcomes across all hospitals.

6. **Enhance access to diagnostic tools:** Routine availability of thyroid function tests and laryngoscopy can improve preoperative risk assessment and postoperative evaluation.

7.2.3 Future Research

7. **Conduct prospective multicenter studies with larger sample sizes:** This would improve the ability to detect significant associations between complications and risk factors, and help validate exophthalmos as a prognostic marker.

7.2.4 Documentation

8. **There is poor documentation and document keeping which should be improved in all the hospitals especially in AHMC, where only two cards were eligible out of 9 charts found.**

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Annexes

Research Checklist

Checklist for the retrospective study on "Surgical Treatment Outcomes of Graves' Disease" over three-year period:

The aim of this checklist is to gather comprehensive data regarding the surgical treatment outcomes of Graves' disease over the past three years.

Updated_Surgical_Outcomes_Graves_Disease last

Patient Information:

Patient ID

Enter a unique identifier for the patient.

Age (years)

Enter age in years.

Gender

Choose the patient's gender.

- ◯ Male
- ◯ Female

Marital status

choose one

- ◯ single
- ◯ Married
- ◯ divorced
- ◯ widowed

Symptoms (select all that apply)

Choose from the list of common symptoms.

- ☐ Goiter
- ☐ Tremor
- ☐ Palpitations
- ☐ Exophthalmos
- ☐ Irritability
- ☐ Insomnia
- ☐ weight loss
- ☐ Dyspnea

duration of the illness before surgery in months

enter duration in months

Preoperative Thyroid function status

- [ ] Euthyroid
- [ ] Subclinical hyperthyroidism
- [ ] Subclinical hypothyroidism

preoperative_ionizedcalcium

Enter the preoperative calcium

____

Antithyroid Medications Prior to Surgery:

- [ ] PTU
- [ ] Carbimazole
- [ ] Methimazole

duration of antithyroid drugs

Enter in months

____

Betablockers prior to surgery

- [ ] propranolol
- [ ] atenolol
- [ ] metoprolol
- [ ] other

Lugol's iodine preop

- [ ] yes
- [ ] No

Co-morbid Conditions

- [ ] DM
- [ ] HTN
- [ ] cardiac disease
- [ ] others

If others, mention.

CLD, HIV, pancytopenia, etc.

____

Date of Surgery

Use the calendar to select the date.

Type of Surgery

Choose the type of surgery performed.

- ○ Total Thyroidectomy
- ○ Subtotal Thyroidectomy
- ○ near total

Hospital stay

Hospital stay in days

- ☐ 1
- ☐ 2
- ☐ 3
- ☐ 4 or more

Postoperative Complications (select all that apply)

Mark complications observed post-surgery.

- ☐ Bleeding
- ☐ Nerve Injury
- ☐ Hypocalcemia
- ☐ Thyroid storm
- ☐ Tracheal injury
- ☐ Esophageal injury

early post op complications within 30 days

choose one

- ○ yes
- ○ no

if yes to above question, specify

Enter the complication

---

late postoperative complications after 30 days

choose one

- ○ yes
- ○ no

if yes for above question, specify

Enter the complication

Estimated Blood Loss (mL)

Enter the estimated blood loss during surgery.

---

postoperative drop in Hgb

preop Hgb- Postop Hgb

Post-operative_serum calcium within 6months

Enter the postoperative calcium

---

post operative serum calcium after 6 months

enter post op serum calcium after 6 months

Histopathological Examination Results

Enter pathology result

Postoperative Temporary Hypocalcemia

Was temporary hypocalcemia observed post-surgery?

- ○ yes
- ○ no

Postoperative Permanent Hypocalcemia

Was permanent hypocalcemia observed post-surgery?

- ○ yes
- ○ no

post operativeTSH Level (mIU/L)

Enter a numeric value.

hospital

BLH=1, AHMC=2, LGH=3, YH=4

- ◯ 1
- ◯ 2
- ◯ 3
- ◯ 4

surgeon

Endocrinesurgeon=1, general Surgeon=2

- ◯ 1
- ◯ 2

duration of follow up in months

Enter follow up duration in months

____

Resolution of GD symptoms

choose one

- ☐ complete
- ☐ partial
- ☐ none

thyroid hormone replacement therapy?

- ◯ yes
- ◯ no

recurrence of GD

- ◯ yes
- ◯ no

Out come of surgical treatment for GD

Favourable if no complication and Unfavorable if complications(other than Seroma and Hypothyroidism) or death occurred

- ☐ Favourable
- ☐ Unfavorable