Retrospective comparison of different therapies in the setting of ongoing thyrotoxic crisis

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RETROSPECTIVE COMPARISON OF DIFFERENT THERAPIES IN THE SETTING OF ONGOING THYROTOXIC CRISIS

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LIST OF ABBREVIATIONS

AA - Autonomous adenoma

AITD - Autoimmune Thyroid Disease

BB - Betablockers

BWPS - Burch-Wartofsky Score

D1 - Type 1 Iodothyronine Deiodinase

D2 - Type 2 Iodothyronine Deiodinase

D3 - Type 3 Iodothyronine Deiodinase

F-T3 - Free Triiodothyronine

F-T4 - Free Thyroxine

GC - Glucocorticoids

GD - Graves' Disease

HT - Hashimoto's Thyroiditis

MMI - Methimazole

NA - Irenat

PTU - Propylthiouracil

rT3 - Reverse Triiodothyronine

SMN - Struma multinodosa

SN - Struma nodosa

TA - Toxic Adenoma

TC - Tachycardia

Tg - Thyroglobulin

TGC - Thyroid Gland Cancer

TH - Thyroid Hormones

TgAb - Antibodies against Thyroglobulin

T3 - Triiodothyronine

T4 - Thyroxine

TPO - Thyroid peroxidase

TPOAb - Antibodies against thyroid peroxidase

TRAK - Thyroid hormone response element

TRH - Thyroid releasing hormone

TSAbs - Thyroid Stimulating Antibodies

TSH - Thyroid-Stimulating Hormone, Thyreotropin

TSHR - Thyrotropin Receptor

US - Ultrasound

1. INTRODUCTION

A thyrotoxic crisis or thyroid storm is an acute and severe exacerbation of hyperthyroidism that requires immediate medical attention due to its high mortality risk. In Germany, the frequency of thyrotoxic crises is estimated at around 0.2 cases per 100,000 inhabitants per year, with higher rates observed in people with pre-existing hyperthyroidism, particularly Graves' disease (GD) (1). This autoimmune disease, characterized by an overproduction of thyroid hormones, significantly increases the likelihood of a thyrotoxic crisis, especially if left untreated or poorly managed.

Despite its rarity, the severity of a thyrotoxic crisis cannot be overestimated. Patients in crisis may experience extreme symptoms such as high fever, rapid heartbeat and severe agitation, which can quickly lead to heart failure, coma or death if not treated immediately. The pathophysiological basis for these symptoms lies in the excessive levels of free triiodothyronine (FT3) and free thyroxine (FT4), which accelerate the body's metabolic processes and overstimulate the cardiovascular and nervous systems, leading to systemic decompensation (2-4).

The critical nature of this condition requires rapid diagnosis and intervention but is likely to be underdiagnosed due to the overlap of symptoms with cardiovascular emergencies such as arrhythmias and heart failure. This leads to a potentially high number of undiagnosed cases and poses an additional challenge to the effective management of this endocrine emergency.

Monitoring the progression of a thyrotoxic crisis relies heavily on biochemical parameters, particularly FT3, FT4 and thyroid stimulating hormone (TSH) (2,4). FT3 serves as the most immediate and sensitive marker for assessing the acute state and effectiveness of treatment, as it normalizes faster than FT4, whereas TSH often remains suppressed until much later (3-5). In addition, the distinction between contrast-induced and autoimmune-induced crises is crucial.

Given the urgent need for rapid and effective treatment, the choice between antithyroid drugs such as propylthiouracil (PTU) and thiamazole (in some regions called methimazole (MMI)) or its prodrug carbimazole remains crucial. However, as thyrotoxic crises are rare, there have been few solid studies on the outcome of these treatments in acute situations in the past. The present study aims to fill this gap by comparing the efficacy of PTU and thiamazole/carbimazole, thus providing new insights to optimize treatment strategies for this dangerous condition.

1.1 The thyroid gland in general

1.1.1 Anatomy of the thyroid gland

The thyroid gland is a bilobed structure located in the anterior part of the neck. It consists of two interconnected lobes joined by a narrow isthmus. Microscopically, the follicles are surrounded by a single-layered epithelium containing colloid - a substance that contains precursor molecules of thyroid hormones (6). The tissue is permeated by vessels and lymphatic vessels, which illustrates the pronounced metabolic activity of the thyroid gland. Abundantly vascularized, the thyroid gland receives its blood supply from branches of the external carotid artery, including the superior thyroid artery and the inferior thyroid artery. It is further drained by the superior, middle, and inferior thyroid veins (7). The complex anatomy of this gland forms the basis for its diverse functions (6,7).

1.1.2 Physiology of the thyroid gland

As a central component of the endocrine system the thyroid gland exerts a considerable influence on metabolic regulation. Complex processes in the thyroid follicles control the production and release of thyroid hormones, in particular thyroxine (T4) and triiodothyronine (T3) (8,9). The enzyme thyroperoxidase plays a decisive role in the conversion of iodine into hormonally active forms. Hormone secretion is controlled by the concentration of thyroid stimulating hormone (TSH) from the pituitary gland (8,10). Thyroid hormones have a profound effect on energy metabolism, thermoregulation and protein metabolism. The physiological processes in the thyroid gland are therefore of crucial importance.

1.1.3 Thyroid hormones and their functions

The hormones thyroxine (T4) and triiodothyronine (T3) are essential for the regulation of energy metabolism, influence protein metabolism and are essential for the growth and development of tissues and organs, especially the nervous system (11,12). T4 is a polyiodinated phenoxyphenyl molecule. The conversion to T3 involves deiodination of the outer ring, a process catalyzed by type 1 and type 2 iodothyronine deiodinases (D1 and D2). If deiodination happens in the inner ring, rT3 is formed, which lacks TR-mediated biological activity. The type 3 deiodinase (D3) catalyzes this inner ring deiodination and can also deactivate T3, thus terminating the hormone's action (13). T3, the more active hormone, has a direct effect on cellular metabolism by stimulating the production of adenosine triphosphate (ATP) (8,10-12). Thyroid hormone production is controlled by a negative feedback mechanism in which the

concentration of thyroid-stimulating hormone (TSH) from the pituitary gland controls the release of thyroid hormones (8,10). This complex interaction of thyroid hormones is of central importance for maintaining hormonal balance and regulating fundamental metabolic processes in the organism as depicted in Figure 1.

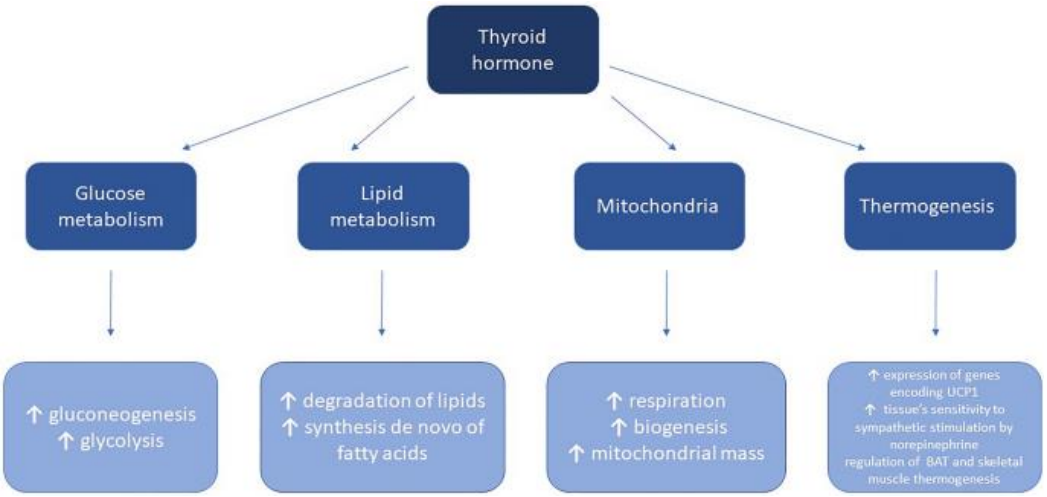


Figure 1. Thyroid hormones and their functions

Sawicka-Gutaj, N., Zawalna, N., Gut, P. *et al.* Relationship between thyroid hormones and central nervous system metabolism in physiological and pathological conditions. *Pharmacol. Rep* 74, 847–858 (2022). https://doi.org/10.1007/s43440-022-00377-w

1.1.4 Hyperthyroidism - a brief overview

Hyperthyroidism represents an endocrine disorder manifested by increased secretion of thyroid hormones, primarily due to autonomy of the thyroid gland or autoimmune processes such as Graves' disease. (15-17) This is triggered by complex processes. To summarize, Figure 2 illustrates how genetic susceptibility and environmental triggers lead to the activation of T-cells, which ultimately leads to an overproduction of thyroid hormones and the development of Graves' disease (16-18). This pathophysiological condition results in an accelerated metabolism and various systemic effects. The increased synthesis of thyroxine (T4) and triiodothyronine (T3) causes clinical features such as weight loss, tachycardia, increased heat intolerance and nervous agitation (19). Diagnosis is based on clinical evaluation, serologic tests, especially thyroid-stimulating hormone (TSH), and imaging techniques (19,20). The therapeutic approach varies and includes antithyrotoxic medication, radioiodine therapy or, in selected cases, thyroid ablation (20).

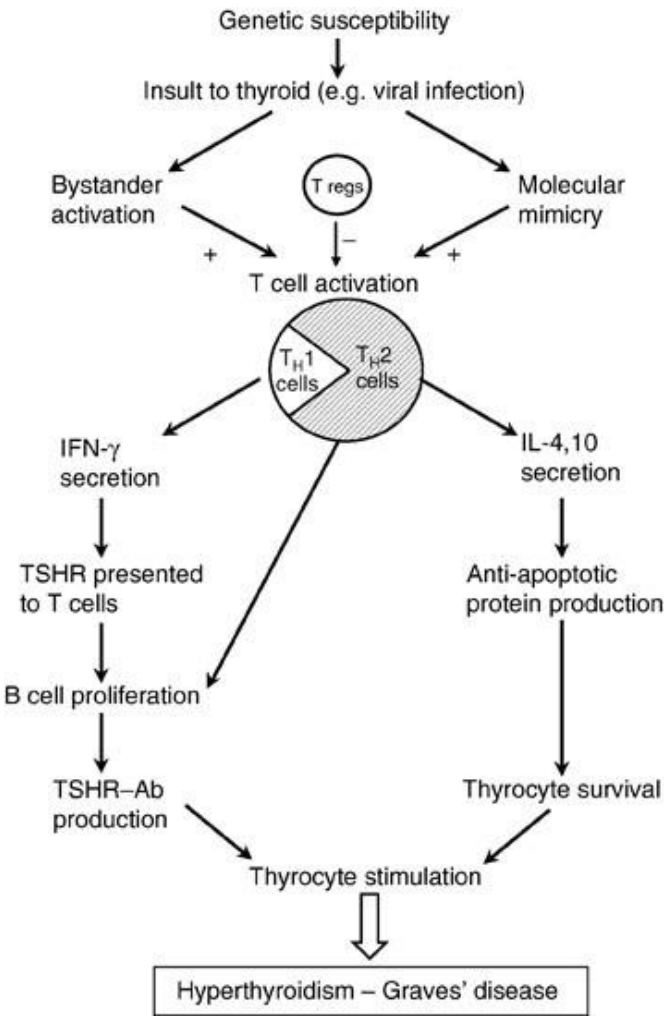


Figure 2. Hyperthyroidism – Grave´s disease
Kraiem, Z., Tomer, Y., Davies, T.F. (2009). Graves' Disease. In: Lang, F. (eds) Encyclopedia of Molecular Mechanisms of Disease. Springer, Berlin, Heidelberg. https://doi.org/10.1007/978-3-540-29676-8_734

1.1.5 Differences between autoimmune-induced, contrast-induced and amiodarone-induced hyperthyroidism

Autoimmune-induced hyperthyroidism, which is primarily caused by conditions such as Graves' disease, results from the immune system producing antibodies that stimulate the thyroid gland to overproduce thyroid hormones (16,18). This continuous over-stimulation leads to persistent hyperthyroidism, which is characterized by a number of systemic symptoms such as weight loss, heat intolerance, and tachycardia (18). In contrast, contrast-induced hyperthyroidism typically occurs after the administration of iodine-containing contrast agents used in imaging procedures (21,22). This often-transient condition is due to the sudden availability of excess iodine, which can temporarily increase thyroid hormone production in

individuals with underlying thyroid autonomy or subclinical hyperthyroidism (15,18). Iodine-induced hyperthyroidism, known as the “Jod-Basedow phenomenon”, occurs when an excess iodine supply stimulates increased thyroid hormone production, leading to elevated hormone levels in the bloodstream (23,24). While most people can adapt to sudden iodine exposure, certain groups, such as those with thyroid nodules or a history of iodine deficiency, are more susceptible. This increased risk is likely due to impaired thyroid regulation in these individuals (23-25). Pre-existing thyroid disorders often first become apparent after the administration of a contrast agent. While autoimmune hyperthyroidism usually requires long-term treatment with thyroid medication, radioiodine therapy or surgery, the duration of therapy for contrast-induced hyperthyroidism is much shorter or partially resolves on its own once the iodine excess is reduced, although short-term medical treatment may be required to control acute symptoms (26-28). The distinction between these two forms is crucial, as their etiology, clinical course and treatment strategies differ considerably. Amiodarone is an antiarrhythmic agent that primarily affects potassium channels and prolongs the repolarization phase of the action potential (class III effect) (29,31). In addition, it inhibits several ion channels, which affects the conduction velocity (class I effect), has beta-blocking properties and a weak calcium antagonistic effect. Amiodarone accumulates in fatty tissue and is excreted via the liver with a half-life of 50-100 days (29,31). Due to its high iodine content, amiodarone often affects the thyroid gland. In the first month of treatment, free thyroxine (F-T4) levels usually rise by 20-40%, free triiodothyronine (F-T3) levels fall by 30% and thyroid stimulating hormone (TSH) rises slightly and may exceed the upper limit of normal (30,31). After three to six months, a new equilibrium is established in which TSH normalizes, F-T4 is slightly elevated or in the upper normal range and F-T3 is in the lower normal range (30,31). This effect is more pronounced in areas with low dietary iodine, which may increase sensitivity to exogenous iodine (30). There are two main types of amiodarone-induced thyrotoxicosis: type I, which is caused by increased thyroid hormone synthesis, and type II, which is due to hormone release resulting from destructive thyroiditis. Mixed forms can also occur. Type I usually affects individuals with pre-existing thyroid disease such as nodular goiter or latent Graves' disease, while type II can occur without prior thyroid disease (32).

1.2 Thyrotoxic crisis

1.2.1 Pathophysiology of Thyrotoxic crisis

Thyrotoxic crisis is a serious clinical entity within the spectrum of hyperthyroidism and

arises as the culmination of complex pathophysiologic events. The diagnosis of thyrotoxic crisis involves identifying the presence of thyrotoxicosis, recognizing the appropriate clinical signs, and providing evidence of a precipitating event (33,34).

The path to a thyrotoxic crisis begins with an underlying thyroid dysfunction, often due to autoimmune processes, structural abnormalities or iatrogenic factors. As this dysfunction progresses, a tipping point is reached, characterized by an increase in thyroid hormone release that exceeds the body's compensatory mechanisms (35).

The transition from hyperthyroidism to thyrotoxic crisis is accompanied by a cascade of molecular and systemic disturbances. Key factors include autoimmune mechanisms in which the immune system mistakenly targets thyroid tissue and triggers a release of thyroid hormones. At the same time, inflammatory mediators further exacerbate thyroid dysfunction and create an environment that favors the development of a thyrotoxic crisis.

Thus, there are immunological triggers and downstream effects that lead to the inexorable progression of thyroid dysfunction into the acute and life-threatening state of thyrotoxic crisis.

1.2.2 Autoimmune processes in the pathophysiology of thyrotoxic crisis

Thyrotoxic crisis is often caused by a dysregulated immune response directed against the thyroid gland, leading to disruption of its normal function. Autoimmune thyroid diseases, such as Graves' disease, contribute significantly to the development of a thyrotoxic crisis. In Graves' disease, the immune system produces autoantibodies, particularly thyrotropin receptor antibodies (TRAb), which mimic the action of thyroid stimulating hormone (TSH). These autoantibodies bind to the thyrotropin receptors on the follicular cells of the thyroid gland and trigger an uncontrolled production and release of thyroid hormones (39-41). This autoimmune attack not only stimulates thyroid hormone synthesis, but also disrupts the feedback mechanisms that normally regulate thyroid function. In toxic adenomas (TA), autonomous hormone production may be due to somatic activating mutations in genes that control thyroid growth and hormone synthesis. Germline mutations in the gene encoding the TSH receptor can lead to sporadic or familial non-autoimmune hyperthyroidism, often associated with diffuse thyroid enlargement (40,42).

The result of both is hyperthyroidism, which can quickly escalate into a thyrotoxic crisis characterized by a sudden and sharp increase in circulating thyroid hormones (40,41). Understanding the intricacies of these autoimmune processes is important to understand the

specific molecular processes that move people from a state of hyperthyroidism to the critical state of thyrotoxic crisis.

1.2.3 Clinical manifestations of thyrotoxic crisis

A thyrotoxic crisis is manifested by several clinical features that require a comprehensive understanding for timely intervention. Laboratory values show an increase in circulating thyroid hormones, particularly free thyroxine (T4) and triiodothyronine (T3), which often exceed the normal range (35,43,44). This is coupled with a decrease in thyrotropin (less than 0.05 μU/mL (17).

Clinically, patients may exhibit increased sympathetic activity, which manifests itself in symptoms such as severe tachycardia, high blood pressure and hyperpyrexia. Gastrointestinal symptoms, including nausea, vomiting and diarrhea, contribute to the overall clinical picture. Central nervous system involvement can lead to agitation, delirium and, in severe cases, coma (35,44). Recognizing the subtle early symptoms, such as unexplained weight loss, heat intolerance, and anxiety, is paramount for rapid diagnosis and intervention. The use of scoring systems such as the Burch-Wartofsky scale helps to objectively assess the severity of a thyrotoxic crisis (4,35,45). This scientific understanding of the intricate interplay between laboratory findings and clinical symptoms provides the basis for healthcare professionals to improve early detection, optimize diagnostic accuracy, and initiate timely therapeutic measures in the management of this critical endocrine emergency (34).

1.2.4 The importance of distinguishing between thyrotoxicosis and thyrotoxic crisis

An understanding of the difference between thyrotoxicosis and thyrotoxic crisis is critical enabling rapid clinical responses and provides a subtle perspective on the spectrum of thyroid dysfunction and its implications for effective patient management.

Thyrotoxicosis and thyrotoxic crisis are two distinct clinical entities within the spectrum of thyroid dysfunction, each characterized by different degrees of severity and physiological impact (3,43). Thyrotoxicosis refers to a state of elevated circulating thyroid hormones, often due to hyperthyroidism (43,46). While thyrotoxicosis includes a range of symptoms such as weight loss, palpitations, and heat intolerance, it does not necessarily equate to a life-threatening condition (46,47).

On the other hand, a thyrotoxic crisis, also known as a thyroid storm, is an acute exacerbation of thyrotoxicosis characterized by a sudden and severe release of thyroid hormones that overwhelms the body's compensatory mechanisms (11).

Thus, the difference lies not only in the intensity of symptoms, but also in the possible multi-organ failure and hemodynamic instability observed in a thyrotoxic crisis. Scientifically, thyrotoxicosis serves as a broader umbrella term for hyperthyroid states, while thyrotoxic crisis refers to the critical end of the spectrum that requires immediate and intensive medical intervention to alleviate life-threatening conditions.

1.2.5 Key drugs in thyrotoxic crisis management

Thionamides (propylthiouracil and methimazole (MMI)) are the first to be mentioned. They are fundamental in the management of thyrotoxic crises due to their ability to directly inhibit thyroid hormone synthesis. As seen in Figure 3, propylthiouracil (PTU) and methimazole (MMI) exert their effect by blocking the activity of thyroperoxidase, an enzyme crucial for the synthesis of thyroid hormones. PTU not only inhibits thyroid hormone synthesis, but also interferes with the peripheral conversion of T4 into T3 (48). This dual mechanism makes PTU beneficial in severe cases or in situations requiring rapid reduction of circulating thyroid hormones. Conversely, methimazole's longer half-life often allows it to be administered once daily, which improves patient compliance (48).

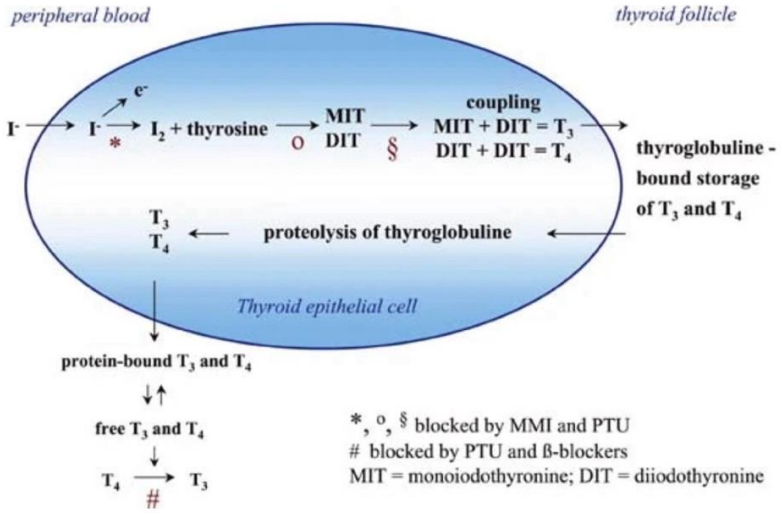


Figure 3. Synthesis and secretion of thyroid hormones and mechanisms of action of antithyroid drugs.
Source: (2004). Antithyroid Drugs. In: Encyclopedic Reference of Molecular Pharmacology. Springer, Berlin, Heidelberg. https://doi.org/10.1007/3-540-29832-0_157
https://link.springer.com/referenceworkentry/10.1007/3-540-29832-0_157

Secondly, beta-adrenergic blockers (propranolol) particularly propranolol, play a critical role in relieving the adrenergic symptoms associated with thyrotoxicosis (11,47,49). By

competitively antagonizing beta-receptors, propranolol effectively relieves tachycardia, palpitations, and tremors. In addition, propranolol has been shown to reduce the peripheral conversion of T4 to T3, contributing to its multiple therapeutic benefits. The fast onset of action and effective relief of symptoms make it the preferred choice for the treatment of cardiovascular manifestations during a thyrotoxic crisis.

The third drug used in management is iodine compounds. They work by inhibiting the release of thyroid hormones. Potassium iodide and Lugol's solution are particularly useful in preparing the thyroid gland for subsequent procedures such as surgery or radioactive iodine therapy (2,44). Its fast onset of action, particularly with Lugol's solution due to its higher concentration of iodine, makes it a valuable tool to immediately reduce the release of thyroid hormones (2). There is a need for caution, though, as their indiscriminate administration can exacerbate thyrotoxicosis. They also have a whole array of side effects, ranging from acne and malaise to anaphylaxis and esophageal ulcers (44).

Lastly, glucocorticoids (dexamethasone) serve a role in the treatment of thyrotoxic crises by suppressing the peripheral conversion of T4 to T3 (2,44). Their anti-inflammatory effect is particularly beneficial in attenuating the systemic effects of thyroid hormone excess (2). Dexamethasone, with its minimal mineralocorticoid activity, is often preferred to prevent fluid retention. Furthermore, glucocorticoids may be of benefit in situations where a patient has contraindications to beta-blockers or when beta-blockers alone are not sufficient to control symptoms.

2. OBJECTIVES

2.1 Aims of the study

The main objective of this study is to evaluate the response rates of different thyrostatic drugs in the treatment of thyrotoxic crises. In particular, the study will investigate which thyrostatic drug shows the fastest response. It will also investigate how independent variables such as smoking status, gender, body weight (BMI), and pre-existing conditions (e.g. Graves' disease) influence treatment outcomes. The study will also look at thyroid hormone levels (FT3 and FT4) to determine the benefits of each treatment and how these factors might influence the effectiveness of the drugs.

2.2 Hypothesis

1. Different thyrostatic drugs respond differently in the treatment of thyrotoxic crisis.
2. The response rate to thyrostatic drugs is influenced by age, BMI, smoking status, gender and pre-existing conditions such as Graves' disease.
3. The levels of thyroid hormones (FT3 and FT4) are influenced by the previously mentioned variables and the efficacy and benefits of the respective thyrostatic treatment.
4. The administration of additional therapies, such as glucocorticoids, beta-blockers or irenate, influences the response rates of thyrostatic drugs in the treatment of thyrotoxic crisis.

3. SUBJECTS AND METHODS

3.1 Data source and study subjects

For this retrospective study, subjects were obtained from a database of previously anonymized patients who were undergoing inpatient treatment for the thyrotoxic crisis at the District Hospital Upper Franconia/South Thuringia, Coburg Clinic in the years from the beginning of 2018 to the end of 2022 and were cared for by the endocrinology department of the clinic. The patients were hospitalized on the following wards: Cardiology, Gastroenterology/Internal Medicine, Intensive Care Unit and Pediatrics. The database was established from information gathered during the stay and then collected from the patients' electronic medical records. Blood samples as well as measurements of heart rate, weight and height, and anamnesis about smoking habits, previous illnesses, and previous medication were taken on the ward and in the emergency room. In both cases, the documented data was contained in doctor's letters, which were confirmed and signed by the assistant doctor, senior doctor, and head physician of the respective ward. Furthermore, an ultrasound examination was carried out for each patient by the endocrinology department. In some cases, scintigraphy was additionally performed by the nuclear medicine department.

The study was approved by the Ethics Committee of the University of Split and the Internal Review Board of the Faculty of Medicine REGIOMED.

3.2 Inclusion and exclusion criteria

In our study, we included all hospitalized patients with a Burch-Wartofsky score above 25 and follow-up parameters of thyroid function tests (TSH, FT3, FT4). We included both subjects who became euthyroid during the crisis and those whose values were considered stable enough for their individual condition to be discharged to outpatient treatment. The inclusion of subjects who were not euthyroid by definition was due to individual variance. The variability of FT3 and FT4 values is relatively low in healthy individuals and remains within a narrow range around the mean value. In patients with Graves' disease and other thyroid pathologies the fluctuations are much more significant.

At the time of crisis onset, the patients were in a state of manifest and, in very few cases, latent hyperthyroidism. All included patients were treated with thyrostatic drugs, eiter PTU or MMI. We also recorded additional acute treatment with glucocorticoids, beta-blockers and, in contrast-induced cases, Irenat. Furthermore, we recorded whether a thyroidectomy was performed during or after the inpatient stay. We included patients with concomitant diseases. We included minors who had almost reached the age of 18. We included patients with malignant

thyroid disease.

We excluded pregnant patients. We excluded patients who lacked the required monitoring values (TSH, fT3, fT4).

3.3 Measurements

All clinical measurements such as pulse, height, and weight were performed by trained staff of the respective department or experienced admission physicians in the emergency room. Blood samples for determination of ft3, ft4, and TSH were taken by nurses trained in this skill. Weight was measured in kg for all patients. Height and weight are not listed individually in this database but were used to calculate the patients' BMI. With the metric system, the formula for BMI is weight in kilograms (kg) divided by height in meters (m) squared.

The hospital laboratory in Coburg carried out the analysis of thyroid parameters, while the analysis of thyroid antibodies was outsourced to external laboratories. The serum levels of TSH, fT3 and fT4 were measured in the hospital laboratory using the electrochemiluminescence immunoassay (ECLIA). There was a change in the external laboratory which took place at the beginning of May 2018. Up to this point, the examination was carried out by MVZ Labor PD Dr. Volkmann and colleagues in Karlsruhe. From May 2018, the MedLab in Bamberg took over responsibility. The thyroid autoantibodies were determined by MVZ Labor PD Dr. Volkmann und Kollegen, Karlsruhe, and MedLab, Bamberg. The reference intervals used by MVZ Labor PD Dr. Volkmann und Kollegen, Karlsruhe, are TPOAb: < 9 IU/ml, TgAb: < 4 IU/ml, TSAb: < 1.5 IU/L. MedLab, Bamberg, uses the following reference ranges: TPOAb: 1-16 IU/ml, TgAb: 5-100 IU/ml, TSAb: < 1.8 IU/L. For this study, the reference range of the MedLab Bamberg was evaluated as the normal range, as this corresponds to the international standard range. If the antibody measurements were above the reference range, they were indicated as elevated in the data.

3.4 Definitions

3.4.1 Definition of the Burch-Wartofsky Score

For this study, the Burch-Wartofsky Score was used as the main assessment of the severity of the clinical picture. The Burch-Wartofsky scoring scale (BWPS) is a clinical tool used to assess the likelihood and severity of a thyrotoxic crisis (4). This scoring system assigns points based on the severity of various clinical signs and symptoms associated with severe hyperthyroidism. Several criteria are included in this scoring system. Criteria are Temperature

with a maximum of 30 points, Central Nervous Effects with a maximum of 30 points, Hepatogastrointestinal Dysfunction with a maximum of 20 points, Cardiovascular Dysfunction 1 (heart rate) with a maximum of 25 points, Cardiovascular dysfunction 2 (leg edema, bibasilar rales, pulmonary edema) with a maximum of 15 points, Cardiovascular dysfunction 3 (absent/present) with a maximum of 10 points and Suggestive anamnesis with a maximum of 10 points (50), as seen in Figure 4.

Criteria	Score	Criteria	Score
Thermoregulatory dysfunction		**Gastrointestinal-hepatic dysfunction**	
Temperature (^{0}C)	5	Manifestation	0
37.8 – 38.2	10	Absent	10
38.3 – 38.8	15	Moderate (diarrhea, abdominal	
38.9 – 39.3	20	pain	20
39.4 – 39.9	25	nausea/vomiting)	
≥ 40	30	Severe (jaundice)	
Cardiovascular		**Central nervous system disturbance**	
Tachycardia (beats/minute)		Manifestation	0
100 – 109	5	Absent	10
110 – 119	10	Mild (agitation)	20
120 – 129	15	Moderate (delirium, psychosis,	
130 – 139	20	extreme lethargy)	30
≥ 140	25	Severe (seizure, coma)	
Atrial fibrillation			
Absent	0		
Present	10		
Congestive heart failure			
Absent	0		
Mild	5		
Moderate	10		
Severe	20		
Precipitating event		**Total score**	
Status	0	> 45	Thyroid crisis
Positive	10	25-44	Impending
Negative		< 25	storm
			Storm unlikely

Figure 4. Diagnosis criteria for thyroid crisis (Burch-Wartofsky, 1993)
Source: Thyroid Crisis and Septic Suspected Sepsis in the First Trimester of Pregnancy - Scientific Figure on ResearchGate. https://www.researchgate.net/figure/Diagnosis-criteria-for-thyroid-crisis-Burch-Wartofsky-1993_tbl2_347400713 [accessed 4 Jul, 2024]

3.4.2 Standard laboratory quality procedures were used for the blood values

The laboratory parameters included were FT3, FT4 and TSH. The following laboratory-evaluated reference intervals were used for diagnostics: 0.4-4 mIU/l for TSH, 3.1-6.8 pmol/l for FT3, 10-23 pmol/l for FT4.

As the laboratory cannot record measured TSH values below 0.05mI/U and therefore

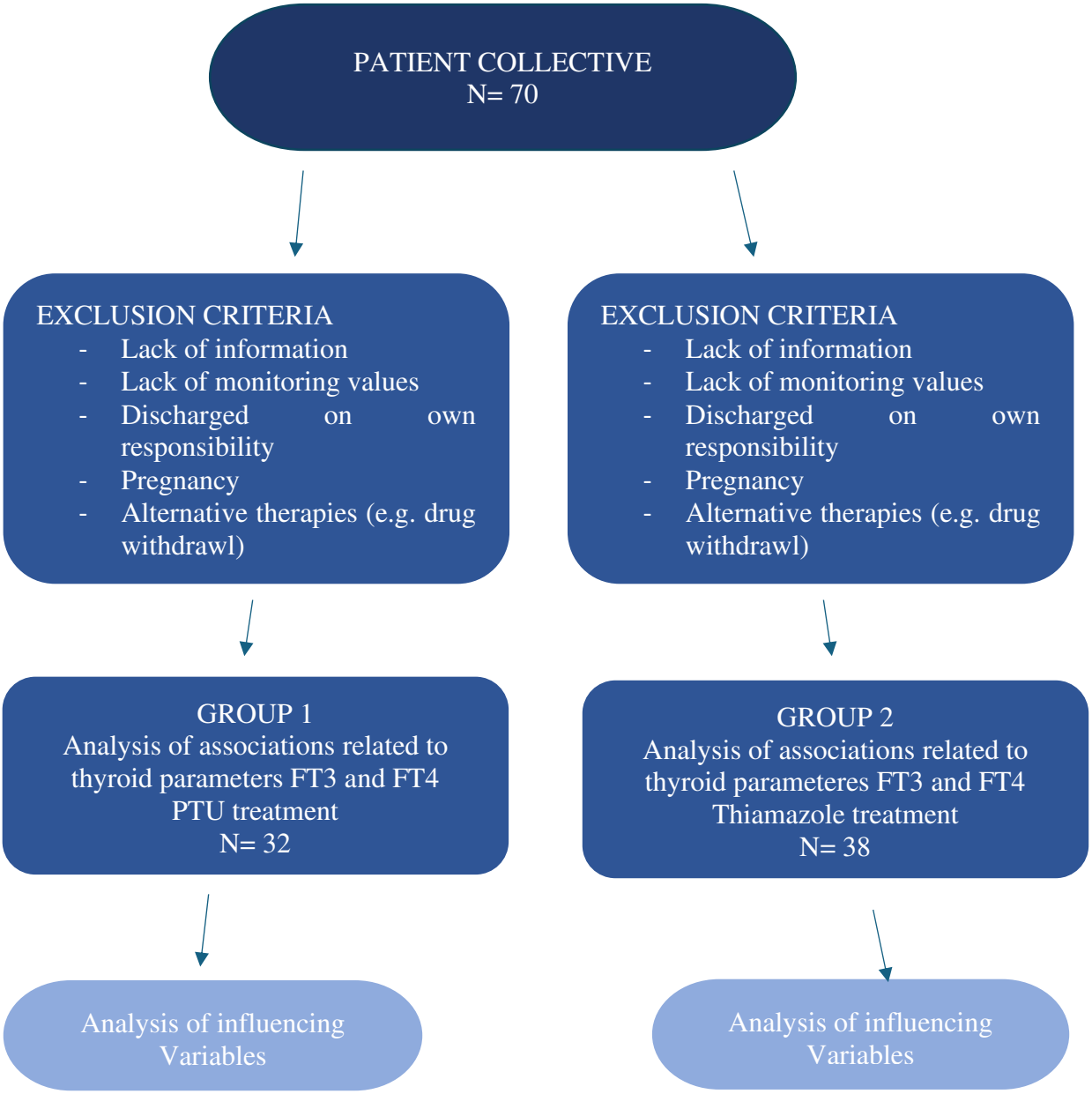
indicates them as (<), these TSH values were recorded as 0.05mI/Ufor statistical evaluation. We classified the state of nutrition according to the NIH/WHO classification for obesity using the BMI formula (50):

1. Severely underweight - BMI less than 16.5kg/m^2
2. Underweight - BMI under 18.5 kg/m^2
3. Normal weight - BMI greater than or equal to 18.5 to 24.9 kg/m^2
4. Overweight – BMI greater than or equal to 25 to 29.9 kg/m^2
5. Obesity – BMI greater than or equal to 30 kg/m^2

We classified our study population into different thyroid function groups using the following reference ranges:

1. Euthyroidism: TSH levels between 0.27-4.2 μIU/ml, fT3 levels between 3.1-6.8 pmol/L, and fT4 levels between 10.0-23.0 pmol/L
2. Hypothyroidism: TSH levels greater than 4.2 μIU/ml, with fT3 levels below 3.1 pmol/L or fT4 levels below 10.0 pmol/L.
3. Hyperthyroidism: TSH levels less than 0.27 μIU/ml, with fT3 levels above 6.8 pmol/L or fT4 levels above 23 pmol/L.
4. Subclinical Hypothyroidism: TSH levels greater than 4.2 μIU/ml, while maintaining euthyroid fT3 and fT4 values.
5. Subclinical Hyperthyroidism: TSH levels less than 0.27 μIU/ml, while maintaining euthyroid fT3 and fT4 values.

3.5 Groups for statistical analysis



3.6 Statistical Analysis

SPSS Statistics from IBM, version 29 was used to process and analyze our data. Descriptive statistics were calculated to summarize the data. Inferential statistics, including t-tests and Mann-Whitney-U-Tests were performed to analyze the relationships and differences between the variables. A p-value less than 0.05 was considered significant.

4. RESULTS

4.1 Description of study group

4.1.1 Baseline characteristics of subjects

The total population for this study comprised 70 patients (n=70). The average age was 57.87 years. 32 patients (n=32, 45.7%) were over 60 years old and 38 patients (n=38, 54.3%) were under 60 years old. There was an age range from 17 to 89 years. The mean BMI was 27.4 and the mean Burch-Wartofsky score was 34.9. There were 22 male patients (n=22, 31.4%) and 48 female patients (n=48, 68.6%) (Figures 5-7). The average number of inpatient days was 13.9. There were 2 underage patients (n=2, 2.9%). 1 patient had a previous operation in the last three months (n=1, 1.4%). The total population is further divided into two groups. The first group is the group treated with propylthiouracil and the second group is the group treated with thiamazole.

There was a total of 32 patients in the PTU-treated patient group (n=32). The average age was 55.19 years. 11 patients (n=11, 34.4%) were over 60 years old and 21 patients (n=21, 65.6%) were under 60 years old. The mean BMI was 27.2 and the mean Burch-Wartofsky score was 33.0 (Figures 8-10). There were 10 male patients (n=10, 31.2%) and 22 female patients (n=22, 68.8%). The average number of inpatient days was 12.0. There were 2 underage patients (n=2, 6.2%). 1 patient had undergone surgery in the last three months (n=1, 3.1%). In the PTU group, it should be noted that 8 patients (n=8, 25,0%) were initially treated with thiamazole. They were switched to PTU before their values stabilized or because their values did not improve on thiamazole. One patient in the PTU group was switched to thiamazole after 6 days, although their values had already stabilized on PTU. There are no patients (n=0, 0,0%) in the thiamazole group who were started or continued on PTU.

There was a total of 38 patients in the thiamazole-treated patient group (n=38). The average age was 60.13 years. 21 patients (n=21, 55.3%) were over 60 years old and 17 patients (n=17, 44.7%) were under 60 years old. The mean BMI was 27.5 and the mean Burch-Wartofsky score was 36.6 (Figures 11-13). There were 12 male patients (n=12, 31.6%) and 26 female patients (n=26, 68.4%). The average number of inpatient days was 15.4. There were no underage patients (n=0, 0.0%). The proportion of patients who had a previous operation in the last three months was 0 (n=0, 0.0%).

Ethnic backgrounds from other continents than Europe were not documented, and all study participants lived within a 25 km radius to Coburg.

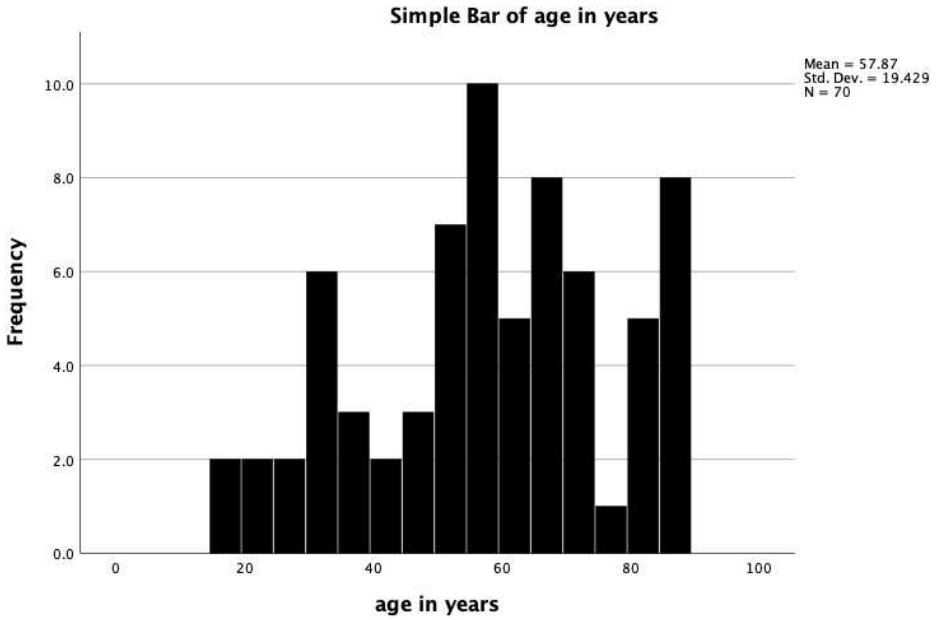


Figure 5. Simple Bar of age in years total population

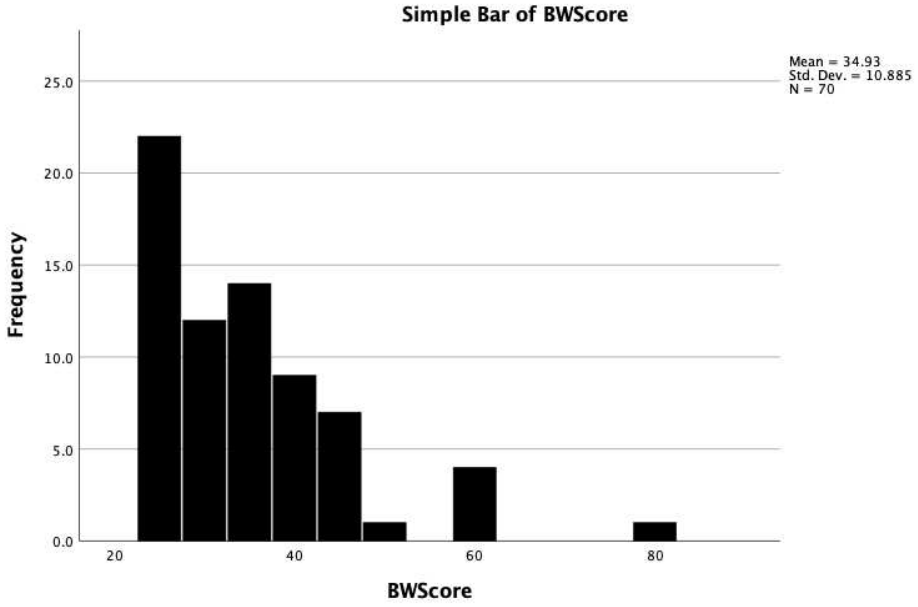


Figure 6. Simple Bar of Burch-Wartofsky- Score total population

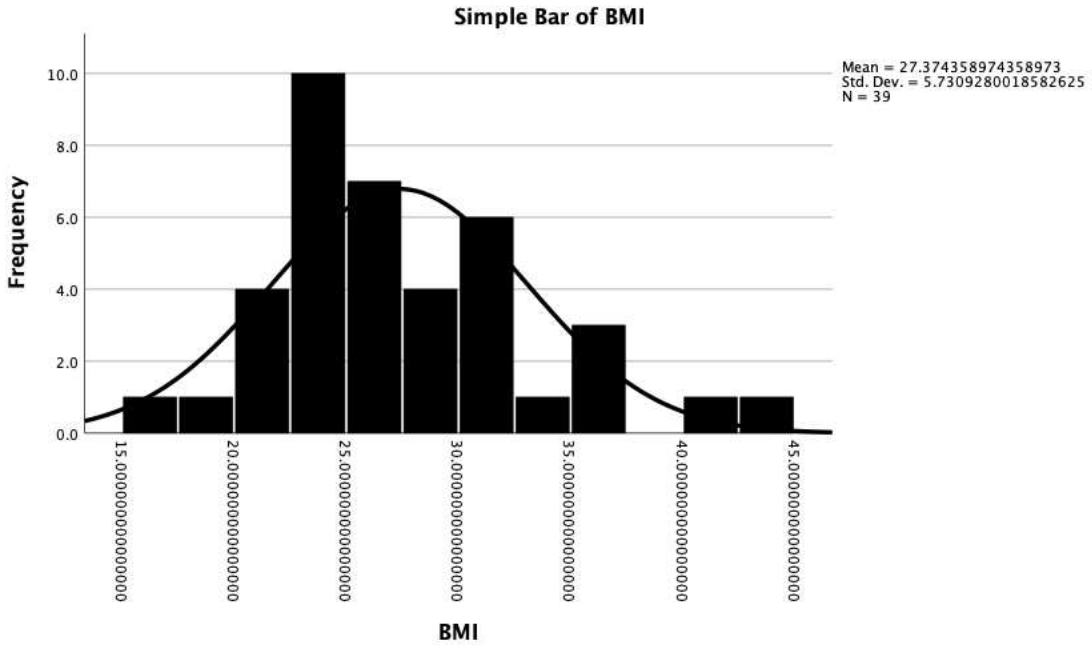


Figure 7. Simple Bar of BMI total population

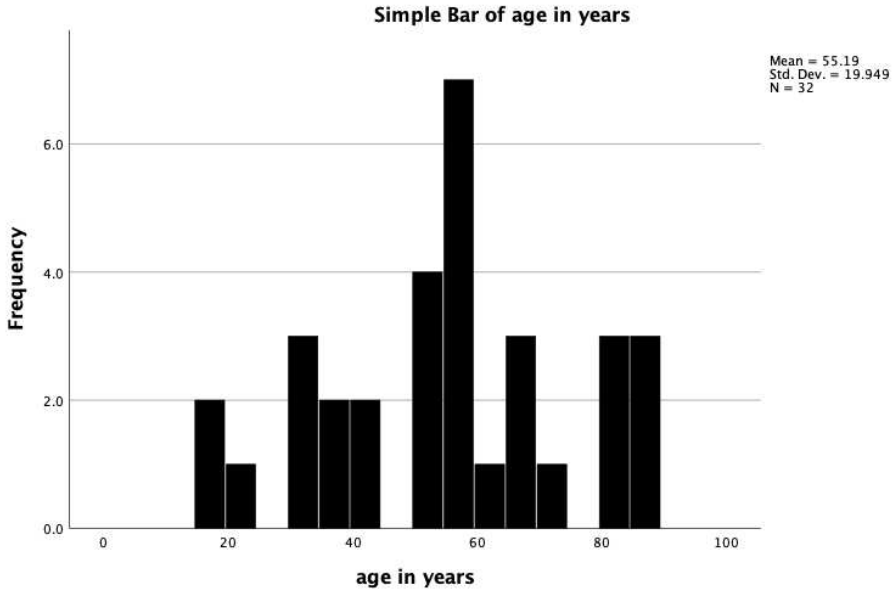


Figure 8. Simple bar of age in years PTU group

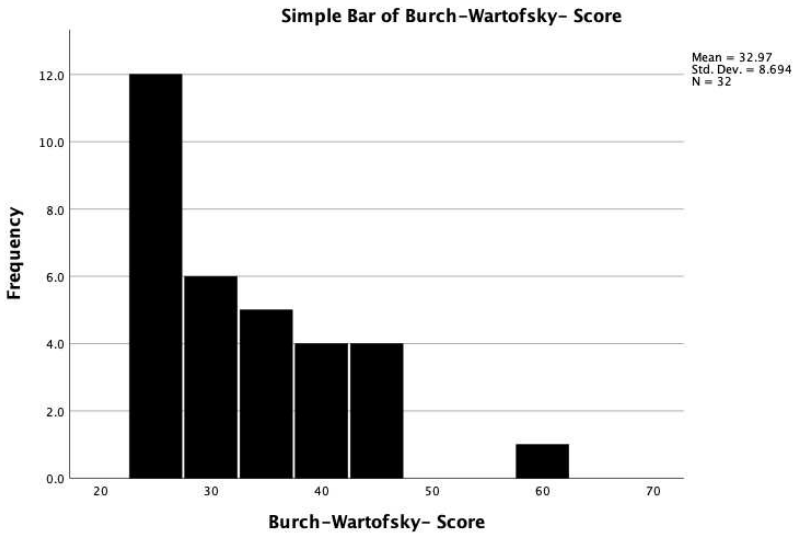


Figure 9. Simple bar of Burch- Wartofsky- Score PTU group

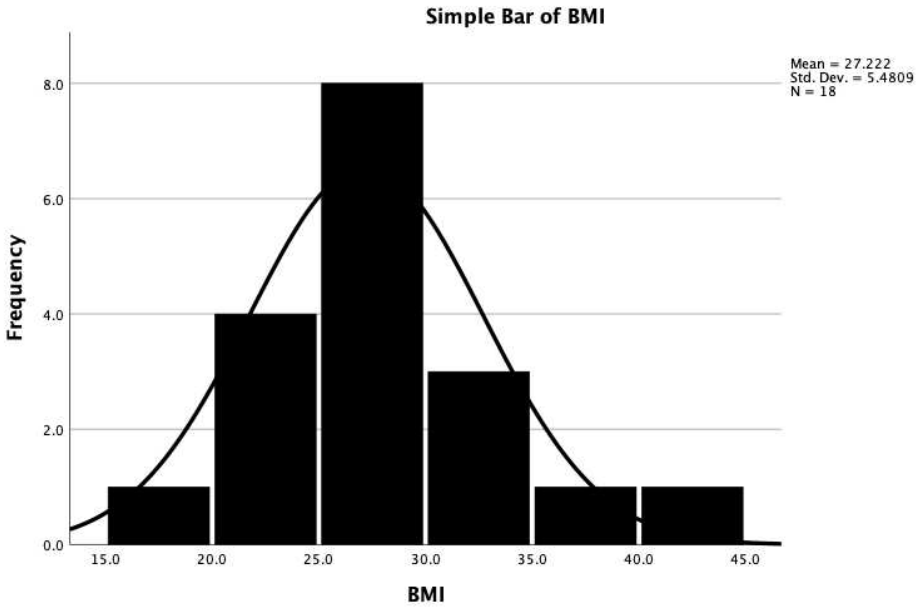


Figure 10. Simple bar of BMI PTU group

4.2 Description Thiamazole group

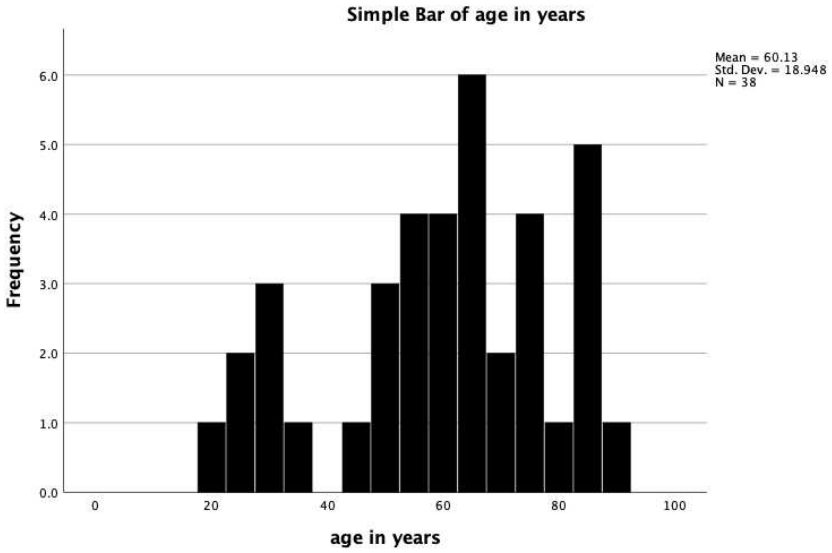


Figure 11. Simple bar of age in years Thiamazole group

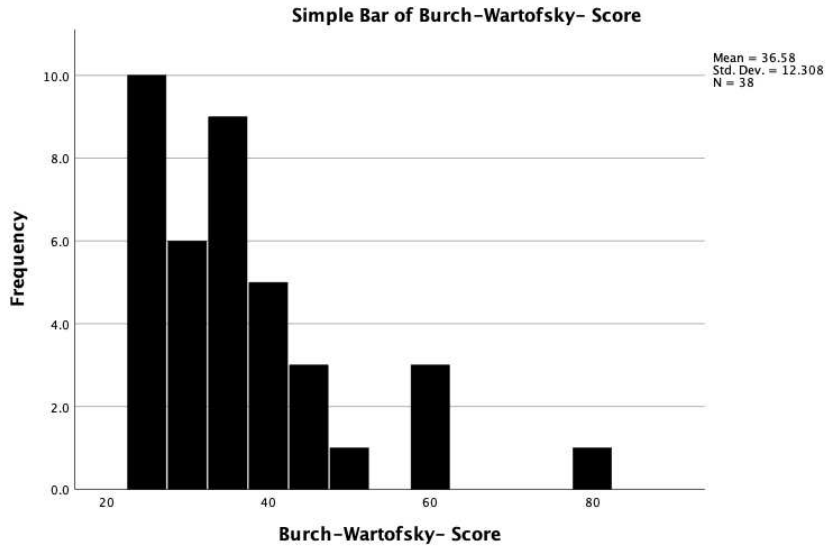


Figure 12. Simple bar of Burch- Warofsky- Score Thiamazole group

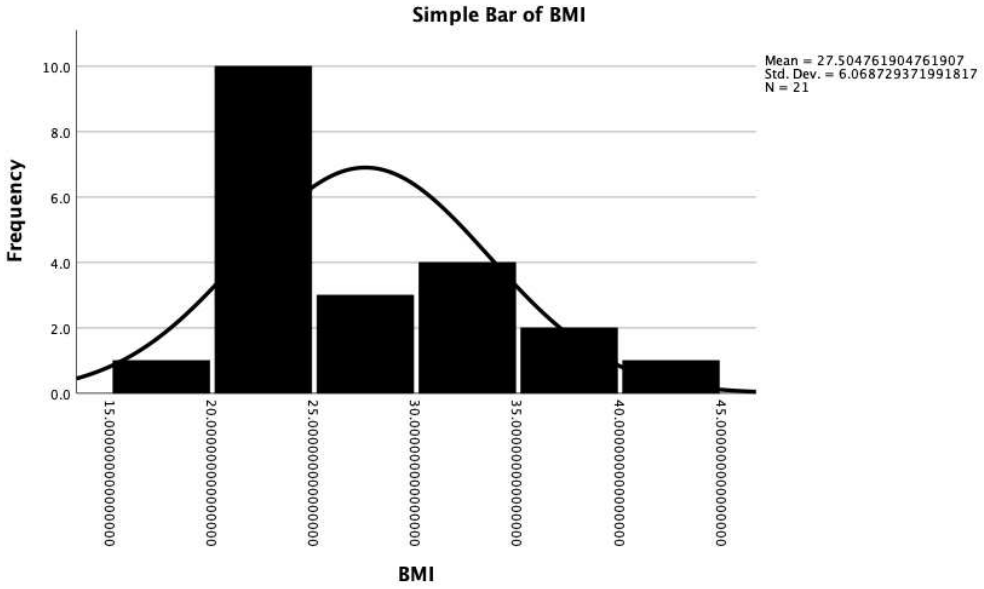


Figure 13. Simple bar of BMI Thiamazole group

4.3 Lifestyle habits: nicotine abuse

Smoking affects various aspects of hormone secretion, impacting the function of the pituitary, thyroid, adrenal glands, testes, and ovaries, along with calcium metabolism and insulin activity (51). The primary clinical consequences concerning the thyroid gland include an elevated risk and increased severity of Graves' hyperthyroidism and associated ophthalmopathy (52-54). Because this affects many of our study patients, we have placed a special emphasis on monitoring their smoking habits.

In the PTU-treated group, a total of 13 of the patients were identified as smokers. This corresponds to about 40.63% of the group.

There were 16 smokers in the thiamazole-treated group, accounting for approximately 42.11% of the group. There were 29 smokers in the total population, which is approximately 41.43% of the total group.

Since the most important thyroid disease that has been identified in the past in connection with smoking is Graves' disease (51-54), a particular focus was placed on this disease. In our study, we observed the following distribution of patients with Graves' disease. Of the total population of 70 patients, 37 patients had Graves' disease (n=37, 52.9%). Of these 37 patients with Graves' disease, 21 were identified as smokers (n=21, 56.8%).

In the PTU group, 18 of the 70 patients were treated with PTU (n=18, 25.7% of the total population). Of these 18 PTU-treated patients, 11 were smokers (n=11, 61.1%).

In the thiamazole group, 19 of the 70 patients were treated with thiamazole (n=19, 27.1% of the total population). Among these 19 thiamazole-treated patients, 10 were smokers (n=10, 52.6%).

4.4 Lifestyle habits: weight – BMI

In the PTU group, the patients were distributed across the BMI categories explained in 3.4.2 as follows: no patients were severely underweight (n=0, 0%), one patient was underweight (n=1, 5.56%), four patients were of normal weight (n=4, 22.22%), eight patients were overweight (n=8, 44.44%) and five patients were obese (n=5, 27.78%). The average BMI in the group was 27.22 kg/m², with a lowest BMI of 17.2 kg/m² and highest BMI 41.2 kg/m². In the thiamazole group, the patients were distributed among the BMI categories as follows: no patients were severely underweight (n=0, 0%), no patients were underweight (n=0, 0%), eleven patients were normal weight (n=11, 52.38%), three patients were overweight (n=3, 14.29%) and seven patients were obese (n=7, 33.33%). The average BMI was 27.50 kg/m², the lowest BMI was 19.9 kg/m² and the highest BMI was 44.0 kg/m². In the total population, the patients were distributed among the BMI categories as follows: no patients were severely underweight (n=0, 0%), one patient was underweight (n=1, 2.56%), fifteen patients were normal weight (n=15, 38.46%), eleven patients were overweight (n=11, 28.21%) and twelve patients were obese (n=12, 30.77%). The average BMI was 27.37 kg/m² with lowest BMI 17.2 kg/m² and highest BMI 44.0 kg/m². Overall, therefore, most patients in the entire population were either overweight or obese.

4.5 Thyroid related Pathologies

As shown in Figure 14 below the following can be seen: In the PTU-treated group, which comprised 32 patients, none of the patients had chronic hypothyroidism (n=0, 0%). Chronic hyperthyroidism was observed in 6 patients (n=6, 18.75%). Graves' disease was present in 18 patients (n=18, 56.25%). A goiter nodosa was observed in 9 patients (n=9, 28.13%), while a goiter multinodosa was found in 4 patients (n=4, 12.5%). Autonomous adenoma was diagnosed in 5 patients (n=5, 15.63%). TG carcinoma was detected in 1 patient (n=1, 3.13%) and Hashimoto's thyroiditis was not present in any of the patients (n=0, 0%).

In the thiamazole-treated group consisting of 38 patients, none of the patients had chronic hypothyroidism (n=0, 0%). Chronic hyperthyroidism was observed in 8 patients (n=8,

21.05%). Graves' disease was present in 19 patients (n=19, 50%). A goiter nodosa was observed in 6 patients (n=6, 15.79%), while a goiter multinodosa was observed in 1 patient (n=1, 2.63%). Autonomous adenoma was diagnosed in 2 patients (n=2, 5.26%). TG cancer was not detected in any of the patients (n=0, 0%), and Hashimoto's thyroiditis was present in 3 patients (n=3, 7.89%).

In the total population of 70 patients, none of the patients was chronically hypothyroid (n=0, 0%). Chronic hyperthyroidism was observed in 14 patients (n=14, 20%). Graves' disease was present in 37 patients (n=37, 52.86%). A goiter nodosa was observed in 15 patients (n=15, 21.43%), while a goiter multinodosa was observed in 5 patients (n=5, 7.14%). Autonomous adenoma was diagnosed in 7 patients (n=7, 10%). TG carcinoma was found in 1 patient (n=1, 1.43%) and Hashimoto's thyroiditis was present in 3 patients (n=3, 4.29%). The overall presence of elevated antibodies, in particular thyroid receptor antibodies (TSAb), thyroid peroxidase antibodies (TPOAb) and thyroglobulin antibodies (TGAb), was also investigated. In the group treated with propylthiouracil (PTU), 16 out of 32 patients (n=16, 50%) had elevated antibody levels. In the group treated with thiamazole, 20 out of 38 patients (n=20, 52.63%) showed elevated antibody levels. In total, 36 out of 70 patients (n=36, 51.43%) with elevated antibody levels were identified in the total population studied. These results emphasize the prevalence of underlying autoimmune reactions in patients with thyrotoxic crisis.

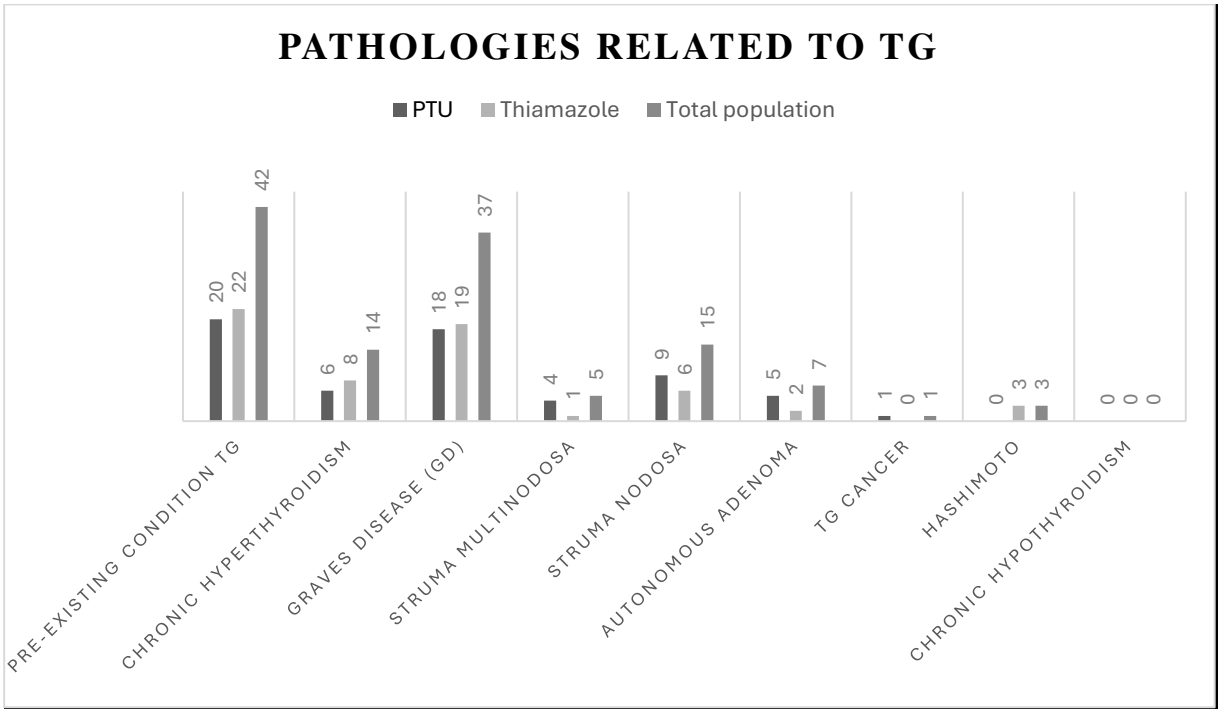


Figure 14. Main thyroid pathologies across the study group, Data are expressed as frequencies

4.6 Thyroid gland and tachycardia

The group treated with PTU 25 out of 32 patients (n=25, 78.1 %) presented with tachycardia. Of the group treated with thiamazole, 32 out of 38 patients (n=32, 84.2 %) had tachycardia. In the total population, 57 out of 70 patients (n=57, 81.4 %) suffered from tachycardia.

In the PTU-treated patient group, 8 patients with acute tachycardia already had premedication with beta-blockers (n=8, 32.0 %).

In the thiamazole-treated patient group, a total of 16 patients with tachycardia had also already received premedication with beta-blockers (n=16, 50.0%).

In the total population, 24 patients with tachycardia had already been premedicated with beta-blockers (n=24, 42.1%).

In the PTU-treated patient group, of the 25 patients with tachycardia, 22 patients (n=22, 88%) received acute beta-blockers in the hospital.

In the thiamazole-treated patient group, 31 of 32 patients with tachycardia received acute beta-blockers (n=31, 96.9%).

In the total population, 53 patients with tachycardia received acute beta-blockers (n=53, 93.0%).

4.7 Exitus in the inpatient course

No patient died in the PTU- treated group (n=0, 0.0%). In the Thiamazole- treated group 3 patients died (n=3, 7.9%). Thus, in the total population of 70 patients 3 patients died (n=3,4.3%)

4.8 Thyroid gland related characteristics

In the PTU-treated group, which comprised 32 patients, 20 patients had pre-existing thyroid disease (n=20, 62.5%). Regarding premedication, 10 patients received beta-blockers (n=10, 31.25%), 14 patients received premedication specifically for thyroid (n=14, 43.75%) and 6 patients received premedication with glucocorticoids (n=6, 18.75%).

In the thiamazole-treated group, which comprised 38 patients, 22 patients had pre-existing thyroid disease (n=22, 57.89%). Regarding premedication, 20 patients received beta-blockers (n=20, 52.63%), 16 patients received premedication specifically for thyroid (n=16, 42.11%) and 1 patient received premedication with glucocorticoids (n=1, 2.63%).

In the total population of 70 patients, 42 patients had pre-existing thyroid disease (n=42, 60.0%). In terms of premedication, 30 patients received beta-blockers (n=30, 42.86%), 30 patients received premedication specifically for thyroid (n=30, 42.86%) and 7 patients received glucocorticoids (n=7, 10.0%)

4.9 Differences in the induction of thyroid crisis

As already pointed out, there were patients whose thyrotoxic crisis was contrast-induced. In exact figures, this meant that in the PTU-treated group, 7 out of 32 crises were induced by contrast media (n=7, 21.88%). In the thiamazole-treated group, 11 of 38 patients were affected (n=11, 28.95%) and in the total population, 18 out of 70 patients were affected (n=18, 25.71%). Regarding the PTU-treated group, 1 out of 32 patients (n=1, 3.13%) had received contrast media immediately before the onset of symptoms, and 6 out of 32 patients (n=6, 18.75%) in the last 3 months before the onset of symptoms.

In patients treated with thiamazole, 4 of 38 patients (n=4, 10.53%) received contrast media immediately before the onset of symptoms, and 8 of 38 patients (n=8, 21.05%) in the last 3 months before the onset of symptoms.

Among the total population, 5 out of 70 patients (n=5, 7.14%) received contrast media immediately before the onset of symptoms and 14 out of 70 patients (n=14, 20.00%) in the last 3 months before the onset of symptoms.

Regarding the induction by amiodarone three out of 32 patients (n=3, 9.38%) in the PTU-treated group were amiodarone-induced thyrotoxic crises. Two out of 38 patients (n=2, 5.26%) in the thiamazole-treated group were amiodarone-induced. In the total population, 5 out of 70 patients (n=5, 7.14%) were amiodarone-induced.

Among the PTU-treated group, 1 of 32 patients (n=1, 3.13%) received amiodarone immediately before symptom onset and 2 of 32 patients (n=2, 6.25%) in the last 3 months before symptom onset.

The thiamazole-treated group had 2 of 38 patients (n=2, 5.26%) receiving amiodarone immediately prior to symptom onset and none (n=0, 0.00%) in the last 3 months prior to symptom onset.

Out of the total population, 3 out of 70 patients (n=3, 4.29%) received amiodarone immediately prior to symptom onset and 2 out of 70 patients (n=2, 2.86%) in the last 3 months prior to symptom onset.

4.10 Thyroid surgery during and after inpatient stay in different patient groups

Some patients had thyroidectomy during or after the inpatient course. In the PTU-treated group, 1 of 32 patients (n=1, 3.1%) had thyroid surgery during the inpatient stay. After the inpatient stay, 4 out of 32 patients (n=4, 12.5%) had thyroid surgery.

In the thiamazole-treated group, there were 1 of 38 patients (n=1, 2.6%) who had thyroid surgery during the inpatient stay. After the inpatient stay, 3 out of 38 patients (n=3, 7.9%) had thyroid surgery.

Thus, in the total population, 2 out of 70 patients (n=2, 2.9%) had thyroid surgery during the inpatient stay. After the inpatient stay, 7 out of 70 patients (n=7, 10%) had thyroid surgery.

4.11 Analysis of thyroid parameters

4.11.1 Normalization of thyroid hormones

In the PTU group, there were a total of 32 patients (n=32), of whom 26 patients (n=26, 81.25%) reached the reference range, while 6 patients (n=6, 18.75%) did not. For FT4, 16 patients (n=16, 50.0%) reached the reference range and 16 patients (n=16, 50.0%) did not reach it.

Of the 38 patients (n=38) in the thiamazole group, 33 patients (n=33, 86.84%) reached the reference range for FT3, while 5 patients (n=5, 13.16%) did not reach it before discharge. It should be noted that 3 patients in the thiamazole group also died. For FT4, 14 patients (n=14, 36.84%) reached the reference range, while 24 patients (n=24, 63.16%) did not reach the reference range.

For the overall population, of the 70 patients (n=70), 59 patients (n=59, 84.29%) reached the reference range for FT3, while 11 patients (n=11, 15.71%) did not. For FT4, 30 patients (n=30, 42.86%) reached the reference range, while 40 patients (n=40, 57.14%) did not reach the reference range. Many patients were just above the reference range before discharge, so the individual variance must of course be taken into account.

4.11.2 Days until normalization

PTU group

The mean number of days after which patients were in the reference range (3.1-6.8) for FT3 for the first time was 5.23 days. By contrast, the mean number of days after which patients were in the reference range (10.0-23.0) for FT4 for the first time was 7.38 days.

Thiamazole group

The mean number of days after which patients were in the reference range (3.1-6.8) for FT3 for the first time was 8.18 days whereas the mean number of days after which patients were in the reference range (10.0-23.0) for FT4 for the first time was 10.5 days.

Total population

It took a mean of 6.88 days for patients to be in the reference range (3.1-6.8) for FT3 for the first time. There was a mean of 8.83 days after which patients were in the reference range (10.0-23.0) for FT4 for the first time.

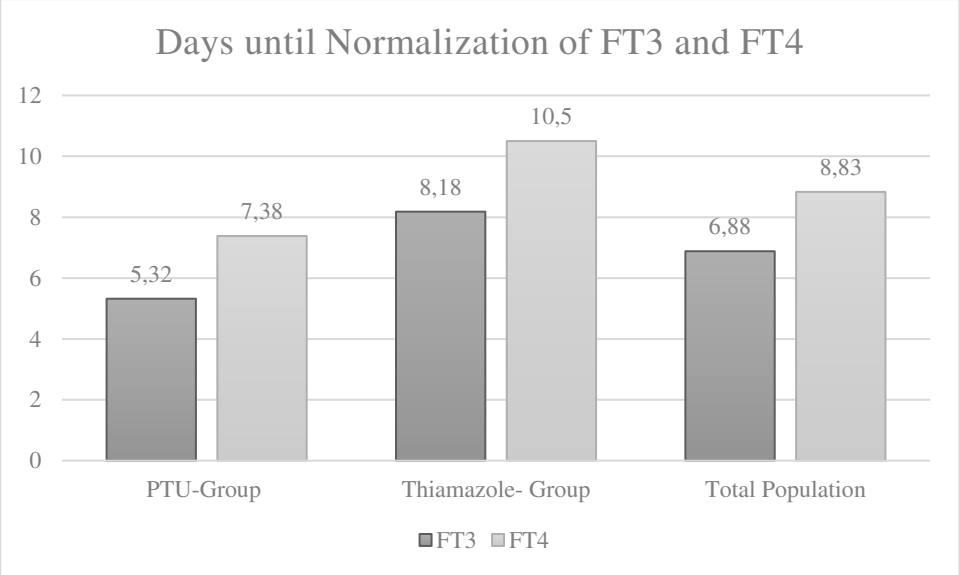


Figure 15. Progression of normalization of thyroid parameters in each group

The average time required for patients in each group to reach both the FT3 and FT4 reference ranges was 6.57 days in the PTU group, 11.0 days in the thiamazole group and 8.70 days in the total population. These results are based on the number of patients who reached the reference range for FT3 and FT4. There were 14 patients in the PTU group and 13 patients in the thiamazole group and thus 27 patients in the total population who were discharged within the defined reference range. Again, it should be noted that many patients were slightly above the reference range at discharge, and their individual variance and general stabilization throughout the study were sufficient for discharge. In this evaluation, such patients naturally had to be excluded.

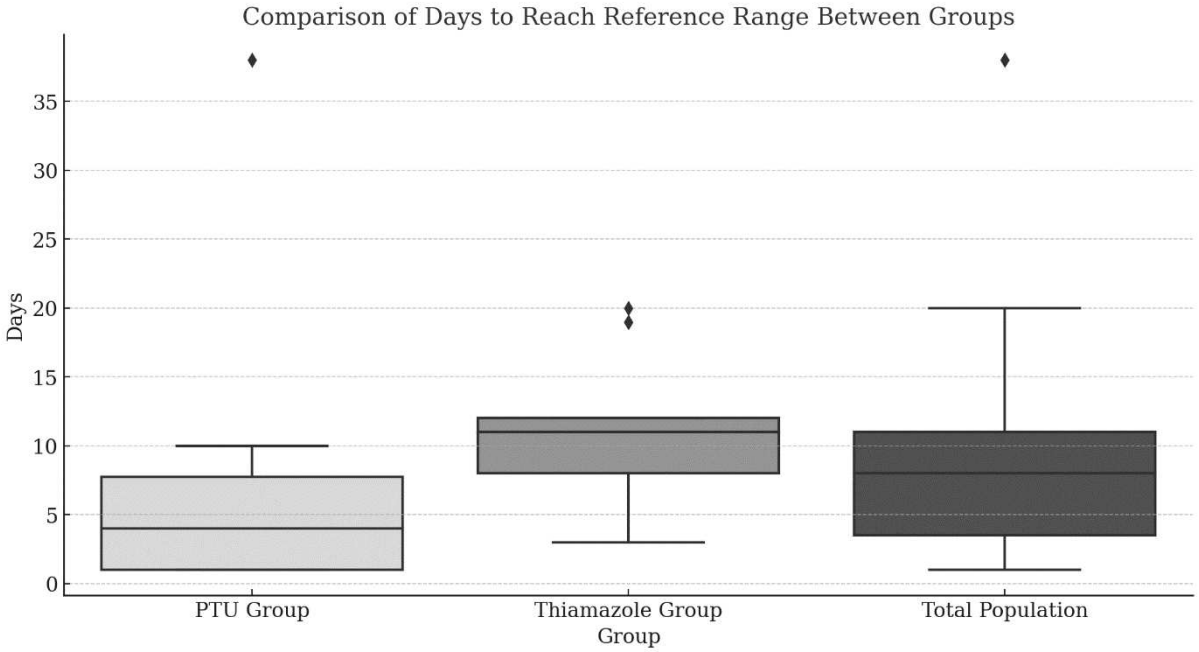


Figure 16. Boxplot chart of days to reach the Reference Range in each group

4.11.3 Comparison of Normalization of parameters in each group

In the PTU group, the average number of days to reach the reference range for FT3 was 5.23 days (95% confidence interval: 3.32; 7.14). For FT4, the average was 7.38 days (95% confidence interval: 2.45; 12.30). When both hormones reached the reference range at the same time, the average number of days was 7.71 (95% confidence interval: 2.45; 12.97).

In the thiamazole group, the average number of days to reach the reference range for FT3 was 8.18 days (95% confidence interval: 6.12; 10.25). For FT4, the average was 10.50 days (95% confidence interval: 7.33; 13.67). When both hormones reached the reference range at the same time, the average number of days was 11.15 (95% confidence interval: 8.04; 14.26).

The T-test and the Mann-Whitney U-test were used to compare the two groups. The T-test for FT3 resulted in a T-value of -2.10 (p-value: 0.04), indicating that the average days to reach the reference range for FT3 were significantly shorter in the PTU group than in the thiamazole group. For FT4, the T-value was -1.11 (p-value: 0.28), showing no significant difference between the groups. For both hormones together, the T-value was -1.19 (p-value: 0.24), which also shows no significant difference between the groups. The Mann-Whitney U-test for FT3 resulted in a U-value of 294.00 (p-value: 0.04), which confirms a significant difference between the groups. For FT4, the U-value was 61.00 (p-value: 0.03), which also shows a significant difference between the groups. For both hormones combined, the U-value was 36.00 (p-value: 0.01), confirming a significant difference between the groups.

In summary, the results show that patients in the PTU group reach the reference range for FT3 faster on average than patients in the thiamazole group. Although there are also differences for FT4, these are not statistically significant in the T-test, but significant in the Mann-Whitney U-test. When both hormones reach the reference range at the same time, the average times in the PTU group are also shorter and statistically significantly shorter in the Mann-Whitney U test, but not in the T test. These results could indicate a more effective or faster effect of PTU compared to thiamazole in regulating hormone levels.

Table 1. Comparison of Normalization of parameters in each group

Parameter	***U****	***p****	***p****	***t****	**PTU*** **	**Thiamazol*** **
fT3	294.0	0.038	0.041	-2.096	5.23 (3.32; 7.14)	8.18 (6.12; 10.25)
fT4	61.0	0.035	0.278	-1.105	7.38 (2.45; 12.30)	10.50 (7.33; 13.67)

*Man-Whitney-U Test
** t-Test
*** point estimate and confidence interval

4.11.4 Influencing variables in each group

Referring to Table 2. The average treatment duration and confidence intervals for the PTU, Thiamazole, and overall population groups by gender showed that men in the PTU group had an average treatment duration for FT3 of 6.5 days (95% CI: 1.76-11.24) and for FT4 of 4.2 days (95% CI: 0.14-8.26). In this group, 12 men were examined. Women in the PTU group had an average treatment duration for FT3 of 4.44 days (95% CI: 2.82-6.05) and for FT4 of 8.82 days (95% CI: 1.57-16.07) with 14 women examined.

In the Thiamazole group, the average treatment duration for FT3 in men was 7.0 days (95% CI: 2.39-11.61) and for FT4 10.33 days (95% CI: -8.96-29.63) with 8 men examined. Women in this group had an average treatment duration for FT3 of 8.63 days (95% CI: 6.17-11.08) and for FT4 of 10.55 days (95% CI: 7.05-14.04) with 10 women examined.

In the overall population, the average treatment duration for FT3 in men was 6.74 days (95% CI: 3.77-9.71) and for FT4 6.5 days (95% CI: 1.67-11.33) with 20 men examined. Women had an average treatment duration for FT3 of 6.95 days (95% CI: 5.26-8.64) and for FT4 of 9.68 days (95% CI: 6.00-13.37) with 24 women examined.

The analysis by BMI showed that patients with a BMI <25 in the PTU group had an

average treatment duration for FT3 of 4.5 days (95% CI: 0.29-8.71) and for FT4 of 7.67 days (95% CI: -4.59-19.92) with 10 patients examined. Patients with a BMI ≥25 had an average treatment duration for FT3 of 6.42 days (95% CI: 2.61-10.22) and for FT4 of 5.0 days (95% CI: 1.60-8.40) with 16 patients examined.

In the Thiamazole group, the average treatment duration for FT3 in patients with a BMI <25 was 7.52 days (95% CI: 5.28-9.77) and for FT4 9.11 days (95% CI: 5.58-12.64) with 12 patients examined. Patients with a BMI ≥25 had an average treatment duration for FT3 of 9.33 days (95% CI: 4.74-13.93) and for FT4 of 13.0 days (95% CI: 4.81-21.19) with 6 patients examined.

In the overall population, the average treatment duration for FT3 in patients with a BMI <25 was 6.35 days (95% CI: 4.58-8.13) and for FT4 8.35 days (95% CI: 4.42-12.28) with 18 patients examined. Patients with a BMI ≥25 had an average treatment duration for FT3 of 7.77 days (95% CI: 5.17-10.37) and for FT4 of 9.8 days (95% CI: 5.09-14.51) with 14 patients examined.

The age analysis in the PTU group showed that patients under 60 years had an average treatment duration for FT3 of 7.0 days (95% CI: 4.17-9.83) and for FT4 of 5.33 days (95% CI: 1.47-9.20) with 8 patients examined. Patients over 60 years had an average treatment duration for FT3 of 2.82 days (95% CI: 0.90-4.74) and for FT4 of 10.0 days (95% CI: -1.89-21.89) with 14 patients examined.

In the Thiamazole group, the average treatment duration for FT3 in patients under 60 years was 8.33 days (95% CI: -8.21-24.87) and for FT4 8.0 days (95% CI: 4.0-12.0) with 6 patients examined. Patients over 60 years had an average treatment duration for FT3 of 10.0 days (95% CI: -2.42-22.42) and for FT4 of 14.0 days (95% CI: -9.56-28.56) with 10 patients examined.

In the overall population, the average treatment duration for FT3 in patients under 60 years was 7.67 days (95% CI: 3.93-11.40) and for FT4 7.25 days (95% CI: 2.94-11.56) with 10 patients examined. Patients over 60 years had an average treatment duration for FT3 of 9.0 days (95% CI: 2.87-15.13) and for FT4 of 11.0 days (95% CI: -1.14-23.14) with 12 patients examined.

The analysis by nicotine abuse showed that non-smokers in the PTU group had an average treatment duration for FT3 of 4.81 days (95% CI: 1.83-7.79) and for FT4 of 7.73 days (95% CI: 0.48-14.97) with 10 non-smokers examined. Smokers had an average treatment duration for FT3 of 5.9 days (95% CI: 3.73-8.07) and for FT4 of 6.6 days (95% CI: -0.01-13.21)

with 10 smokers examined.

In the Thiamazole group, the average treatment duration for FT3 in non-smokers was 7.52 days (95% CI: 5.28-9.77) and for FT4 9.11 days (95% CI: 5.58-12.64) with 8 non-smokers examined. Smokers had an average treatment duration for FT3 of 9.33 days (95% CI: 4.74-13.93) and for FT4 of 13.0 days (95% CI: 4.81-21.19) with 6 smokers examined.

In the overall population, the average treatment duration for FT3 in non-smokers was 6.35 days (95% CI: 4.58-8.13) and for FT4 8.35 days (95% CI: 4.42-12.28) with 18 non-smokers examined. Smokers had an average treatment duration for FT3 of 7.77 days (95% CI: 5.17-10.37) and for FT4 of 9.8 days (95% CI: 5.09-14.51) with 14 smokers examined. The analysis of the time to euthyroid status, defined as both FT3 and FT4 within the reference ranges, showed the following results. In the PTU group, the average treatment duration to achieve euthyroid status in men was 10.2 days (95% CI: 4.3-16.1) and in women 12.1 days (95% CI: 5.4-18.8) with 10 men and 8 women examined. In the Thiamazole group, the average treatment duration for men was 11.3 days (95% CI: 5.2-17.4) and for women 13.5 days (95% CI: 6.6-20.4) with 6 men and 7 women examined. In the overall population, the average treatment duration for men was 9.8 days (95% CI: 5.5-14.1) and for women 11.7 days (95% CI: 6.2-17.2) with 18 men and 15 women examined.

Table 2. Influencing Variables in Groups 1

Category	***Group***	***Question***	**FT3 (days)**	**FT4(days)**	**FT3 U/p***	**FT4 Up***
Sex	PTU	Male	6,5 (1,76 - 11,24)	4,2 (0,14 - 8,26)	60.5 / 0.083	50.0 / 0.048
		Female	4,44 (2,82 - 6,05	8,82 (1,57 - 16,07)		
	Thiamazol	Male	7,0 (2,39 - 11,61)	10,33 (-8,96 - 29,63)	30-0 / 0.150	25.0 / 0.230
		Female	8,63 (6,17 - 11,08)	10,55 (7,05 - 14,04)		
	Overall	Male	6,74 (3,77 - 9,71)	6,5 (1,67 - 11,33)	180.0 / 0.090	170.5 / 0.054
		Female	6,95 (5,26 - 8,64)	9,68 (6,00 - 13,37)		
BMI	PTU	< 25	4,5 (0,29 - 8,71)	7,67 (-4,59 - 19,92)	50.0 / 0.062	45.0 / 0.042
		≥ 25	6,42 (2,61 - 10,22)	5,0 (1,60 - 8,40)		
	Thiamazol	< 25	7,52 (5,28 - 9,77)	9,11 (5,58 - 12,64)	40.5 / 0.200	30.0 / 0.150
		≥ 25	9,33 (4,74 - 13,93)	13,0 (4,81 - 21,19)		
	Overall	< 25	6,35 (4,58 - 8,13)	8,35 (4,42 - 12,28)	120.0 / 0.053	115.0 / 0.047
		≥ 25	7,77 (5,17 - 10,37)	9,8 (5,09 - 14,51)		
Age	PTU	<60	7,0 (4,17 - 9,83)	5,33 (1,47 - 9,20)	30.5 / 0.094	35.0 / 0.110
		≥ 60	2,82 (0,90 - 4,74)	10,0 (-1,89 - 21,89)		
	Thiamazol	<60	8,33 (-8,21 - 24,87)	8,0 (4,0 - 12,0)	25.0 / 0.180	20.0 / 0.210
		≥ 60	10,0 (-2,42 - 22,42)	14,0 (-9,56 - 28,56)		
	Overall	<60	7,67 (3,93 - 11,40)	7,25 (2,94 - 11,56)	110.0 / 0.066	105.0 / 0.049
		≥ 60	9,0 (2,87 - 15,13)	11,0 (-1,14 - 23,14)		

Table 3. Influencing Variab. in Groups 2 1

Category	***Group***	***Question***	**FT3 (days)**	**FT4(days)**	**FT3 U/p***	**FT4 Up***
Nicotineabusus	PTU	Nonsmoker	4,81 (1,83 - 7,79)	7,73 (0,48 - 14,97)	35.0 / 0.060	32.5 / 0.054
		Smoker	5,9 (3,73 - 8,07)	6,6 (-0,01 - 13,21)		
	Thiamazol	Nonsmoker	7,52 (5,28 - 9,77)	9,11 (5,58 - 12,64)	20.5 / 0.170	15.0 / 0.200
		Smoker	9,33 (4,74 - 13,93)	13,0 (4,81 - 21,19)		
	Overall	Nonsmoker	6,35 (4,58 - 8,13)	8,35 (4,42 - 12,28)	100.0 / 0.055	95.0 / 0.048
		Smoker	7,77 (5,17 - 10,37)	9,8 (5,09 - 14,51)		
Euthyreod (FT3+FT4)	PTU	Male	10,2 (4,3 - 16,1)		40.0 / 0.073	
		Female	12,1 (5,4 - 18,8)			
	Thiamazol	Male	11,3 (5,2 - 17,4)		22.0 / 0.160	
		Female	13,5 (6,6 - 20,4)			
	Overall	Male	9,8 (5,5 - 14,1)		90.0 / 0.068	
		Female	11,7 (6,2 - 17,2)			

5. DISCUSSION

Our study investigated the efficacy of different thyrostatic drugs in managing thyrotoxic crisis, specifically comparing Propylthiouracil (PTU) and Thiamazole (Methimazole, MMI). Additionally, we examined the influence of various independent variables such as age, BMI, smoking status, gender, and pre-existing conditions on treatment outcomes.

Independent variables had a significant influence on the duration of treatment in our study. When analyzed in depth, gender differences stood out, with men taking longer to reach normal thyroid hormone levels than women. In the PTU group, the average treatment duration for men was 6.5 days for FT3 and 4.2 days for FT4, while women needed 4.44 days for FT3 and 8.82 days for FT4. BMI also played a decisive role, as treatment took longer for patients with a higher BMI. Smokers also needed more time to normalize than non-smokers. Older patients generally needed more time to normalize FT4. Patients over 60 years of age in the PTU group required 10.0 days for FT4 normalization, compared to 5.33 days for younger patients.
These results underline the need for individualized treatment strategies for the management of thyrotoxic crises. Adjusting treatment plans for patient-specific factors such as gender, BMI, smoking status and age may optimize outcomes. Future research should further investigate the mechanisms underlying these differences and validate the results in larger, more diverse patient populations. This could lead to improved treatment protocols that reduce hospital length of stay and improve patient outcomes.

There is only one other relevant comparable study on this specific topic mentioned by Sun Y Lee (55), but it related exclusively to ICU and intermediate care patients and included 1383 patients. This study, which examined the outcomes of treatment with PTU and methimazole in patients with thyrotoxic crisis, showed that no significant differences in mortality or adverse events were observed between the two treatment groups in this study. Although this study is thematically along the same direction as ours, there are numerous differences such as these in the study conditions. In addition to the intensive care unit, our patients were also on the cardiology ward, internal medicine ward and pediatric ward. Moreover, we included more wide-ranging variables in a narrower population. Furthermore, our main inclusion criterion was determined by the level of the Burch- Wartosky score (>25).
In our study, 3 patients in the thiamazole group and none in the PTU group died. However, as the thiamazole group included more subjects, we cannot obtain a conclusion from this. Overall, both the results of Sun Y Lee (55) and our study suggest that the current guidelines favoring PTU over methimazole in the treatment of thyrotoxic crisis may need to be reconsidered. Our results support the need for further studies to determine the optimal treatment for thyrotoxic

crisis.

Overall, our study provides valuable insights into the treatment of thyrotoxic crises and emphasizes the need for personalized therapeutic approaches. By considering individual patient characteristics and responses to therapy, treatment strategies can be optimized and the overall management and outcomes of patients with thyrotoxic crises can be improved.

This study, while providing valuable insights into the management of thyrotoxic crisis, has several limitations that must be acknowledged. Firstly, the sample size was relatively small, encompassing only 70 patients, which may limit the generalizability of the findings to a broader population. Additionally, the study's retrospective design, relying on previously recorded data, could introduce inconsistencies or missing information, potentially affecting the accuracy of the results.

Being a single-center study, the findings are specific to the practices and patient population of one hospital, which may not be representative of other settings. Furthermore, the influence of confounding variables, such as other medical conditions or concurrent treatments not accounted for in the analysis, could have impacted the outcomes observed.

The generalizability of the results to all patients with thyrotoxic crisis is also limited, particularly when considering different demographic groups or those with varying comorbidities. Lastly, the small number of observed deaths within the study cohort may not provide a comprehensive understanding of the mortality risk associated with the different treatment modalities examined.

The study also underlines the importance of additional therapies in the treatment of thyrotoxic crises. The administration of beta-blockers, glucocorticoids and iodine supplements contributed significantly to symptom control and stabilization of patients. In particular, 93% of patients with tachycardia received acute beta-blockers, which effectively supported symptom control. In the PTU group, 88% of patients with tachycardia received beta-blockers, compared to 96.9% in the thiamazole group.

These results underline the need for individualized treatment strategies for the management of thyrotoxic crises. Adjusting treatment plans to patient-specific factors such as gender, BMI, smoking status and age may optimize outcomes. The results of the study suggest that future research should further explore the mechanisms underlying these differences and validate the results in larger, more diverse patient populations. This could lead to improved treatment protocols, potentially reducing the length of hospital stay and improving patient outcomes.

6. CONCLUSION

This study provides a holistic assessment of the response rates of different thyrostatic drugs, in particular PTU and thiamazole, in the treatment of thyrotoxic crisis. It also highlights the influence of several independent variables such as age, BMI, smoking status, gender and pre-existing conditions on treatment outcomes.

The efficacy of the thyrostatic drugs was evident, with PTU resulting in faster normalization of thyroid hormone levels compared to thiamazole. The study population consisted of 70 patients divided into two groups: 32 were treated with PTU and 38 with thiamazole. The mean time to achieve FT3 normalization was 5.23 days for PTU and 8.18 days for thiamazole. Similarly, the mean time to FT4 normalization was 7.38 days for PTU and 10.5 days for thiamazole. These results suggest that PTU may provide more rapid biochemical control in thyrotoxic crises.

Independent variables significantly influenced the duration of treatment. Gender differences were striking, with men taking longer to normalize thyroid hormone levels than women. In the PTU group, men had an average treatment duration of 6.5 days for FT3 and 4.2 days for FT4, while women needed 4.44 days for FT3 and 8.82 days for FT4. BMI also played a decisive role, as treatment took longer for patients with a higher BMI. In the PTU group, patients with a BMI $\geq$25 required 6.42 days for FT3 normalization and 5.0 days for FT4 normalization. Smoking status also had an effect on treatment duration, with smokers requiring more time for normalization compared to non-smokers. Specifically, smokers in the PTU group required 5.9 days to achieve FT3 normalization, while non-smokers required 4.81 days. Age was another significant factor, with older patients generally requiring more time for FT4 normalization. Patients over 60 years of age in the PTU group required 10.0 days for FT4 normalization, compared to 5.33 days for younger patients.

In summary, this study provides valuable insights into the treatment of thyrotoxic crises and highlights the need for personalized therapeutic approaches. By considering individual patient characteristics and responses to therapy, healthcare providers can optimize treatment strategies to improve the overall management and outcomes of patients with thyrotoxic crises.

These results can help improve the individualization of thyroid disorder treatments and provide more specific patient care. Further studies are needed to better understand the underlying mechanisms of these differences and to verify these observations in larger and more diverse patient groups.

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8. SUMMARY

Purpose of the thesis

The primary aim of this thesis was to investigate the efficacy of different thyrostatic drugs, in particular propylthiouracil (PTU) and thiamazole, in the treatment of thyrotoxic crisis. The objective of the study was to find out which drug responds most quickly and to investigate how factors such as age, BMI, smoking status, gender and previous illnesses for example Graves' disease influence the treatment results. The study examined how additional therapies, including glucocorticoids, beta blockers and iodine supplements, affected the effectiveness of these treatments.

Methods

The methology of this thesis included a study of a retrospective analysis of 70 patients treated for thyrotoxic crisis at the Bezirkskrankenhaus Oberfranken/Südthüringen Klinikum Coburg from 2018 to 2022. The patients were divided into two groups: those treated with PTU (32 patients) and those treated with thiamazole (38 patients). Data collection included thyroid function tests (TSH, FT3, FT4), heart rate, weight, height, smoking habits and medical history. The severity of the crisis was assessed using the Burch-Wartofsky score and statistical analyses were performed to compare the treatment outcomes of the two drug groups.

Results

The study showed that PTU led to a faster normalization of thyroid hormone levels compared to thiamazole. Patients in the PTU group achieved normalization of FT3 in an average of 5.23 days and FT4 in 7.38 days. In contrast, patients in the thiamazole group required 8.18 days for FT3 normalization and 10.5 days for FT4 normalization. Independent variables were found to have a significant impact on treatment duration, with men, older patients and smokers requiring more time for hormone normalization. The study also found that 60% of the total population had pre-existing thyroid conditions.

Furthermore, the study concludes that PTU causes a faster normalization of thyroid hormone levels in patients with a thyrotoxic crisis than thiamazole. The results underline the importance of individualized treatment strategies, taking into account factors such as gender, BMI, smoking status and age, to optimize patient outcomes. The study advocates for further research to understand the mechanisms behind these differences and to validate the results in larger, more diverse populations.

9. CROATIAN SUMMARY

Svrha rada

Primarni cilj ovog rada bio je istražiti učinkovitost različitih tireostatskih lijekova, posebno propiltiouracila (PTU) i tiamazola, u liječenju tireotoksične krize. Cilj studije bio je otkriti koji lijek najbrže djeluje te istražiti kako faktori poput dobi, BMI, statusa pušenja, spola i prethodnih bolesti poput Gravesove bolesti utječu na rezultate liječenja. Također je proučeno kako dodatne terapije, uključujući glukokortikoide, beta blokatore i dodatke joda, utječu na učinkovitost ovih tretmana.

Metode

Studija je uključivala retrospektivnu analizu 70 pacijenata liječenih zbog tireotoksične krize u Bezirkskrankenhaus Oberfranken/Südthüringen Klinikum Coburg od 2018. do 2022. godine. Pacijenti su podijeljeni u dvije skupine: oni liječeni s PTU (32 pacijenta) i oni liječeni s tiamazolom (38 pacijenata). Prikupljanje podataka uključivalo je testove funkcije štitnjače (TSH, FT3, FT4), srčani ritam, težinu, visinu, navike pušenja i medicinsku povijest. Ozbiljnost krize procijenjena je korištenjem Burch-Wartofsky skora, a statističke analize su provedene kako bi se usporedili rezultati liječenja dviju skupina lijekova.

Rezultati

Studija je pokazala da PTU dovodi do brže normalizacije razine hormona štitnjače u usporedbi s tiamazolom. Pacijenti u PTU skupini postigli su normalizaciju FT3 u prosjeku za 5,23 dana, a FT4 za 7,38 dana. Nasuprot tome, pacijentima u tiamazol skupini bilo je potrebno 8,18 dana za normalizaciju FT3 i 10,5 dana za normalizaciju FT4. Nezavisne varijable imale su značajan utjecaj na trajanje liječenja, pri čemu su muškarci, stariji pacijenti i pušači zahtijevali više vremena za normalizaciju hormona. Studija je također utvrdila da je 60% ukupne populacije imalo prethodne bolesti štitnjače.

Studija zaključuje da PTU uzrokuje bržu normalizaciju razine hormona štitnjače kod pacijenata s tireotoksičnom krizom u usporedbi s tiamazolom. Rezultati naglašavaju važnost individualiziranih strategija liječenja, uzimajući u obzir faktore poput spola, BMI, statusa pušenja i dobi, kako bi se optimizirali ishodi pacijenata. Studija zagovara daljnja istraživanja kako bi se razumjeli mehanizmi iza ovih razlika i potvrdili rezultati na većim, raznovrsnijim populacijama.