Incidence of hypothyroidism in Coburg Hospital 2018-2023

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INCIDENCE OF HYPOTHYROIDISM IN COBURG HOSPITAL 2018-2023

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LIST OF ABBREVIATIONS

ECLIA	–	electrochemiluminescence immunoassay
ERCP	–	endoscopic retrograde cholangiopancreatography
FT3	–	triiodothyronine
FT4	–	thyroxine
ICU	–	intensive care unit
IQR	–	interquartile range
NHANES III	–	the National Health and Nutrition Examination Survey
PD-1-agent	–	anti-programmed cell death protein-1
PNR	–	patient number
Q-Q plot	–	Quantile-Quantile plot
SD	–	standard deviation
TSH	–	thyroid stimulating hormone/ thyrotropin
T3	–	triiodothyronine
T4	–	thyroxine

1. INTRODUCTION

Hypothyroidism is a common non-communicable disease of the thyroid gland, characterized by thyroid hormone deficiency at the respective target tissues. The iodine-containing thyroid hormones, triiodothyronine (T3) and thyroxine (T4) are essential for all organ systems throughout the human body (1). The thyroid hormone thyroxine is produced in the thyroid gland exclusively, whereas the thyroid hormone triiodothyronine derives to 20% from the thyroid gland itself and the other 80% are converted in peripheral, nonthyroidal tissues by the enzyme 5'-deiodinase from T4 (2). The thyroid hormones are essential for pathways in virtually all nucleated cells, therefore inevitable for several body functions, such as growth, neuronal migration and differentiation, reproduction and stimulation of the energy metabolism (3).

The secretion of thyroid hormones is closely regulated by the pituitary gland and the hypothalamus via a negative feedback mechanism. As a response to low blood levels of the thyroid hormones, the hypothalamus releases thyrotropin releasing hormone (TRH), which stimulates the production and secretion of thyroid stimulation hormone, or thyrotropin, (TSH) from the anterior pituitary gland. TSH acts on thyroid tissue as stimulant for the production of the thyroid hormones, T3 and T4 (4). In contrast, high levels of thyroid hormones lead to negative feedback and inhibition of this mechanism and will result in reduced production and secretion of the beforementioned hormones.

Thyroid hormone production can be disturbed at several levels. It can be disrupted at the level of hypothalamus and pituitary gland, secretion from the thyroid gland itself and metabolism in the peripheral tissues (5). Most often pathologies of the thyroid arise in the gland itself, in case of hypothyroidism being characterized by deficient hormone production of the thyroid gland, being referred to as primary hypothyroidism (3). Secondary hypothyroidism is classified by the deficiency of thyroid stimulating hormone and tertiary hypothyroidism by the lack of thyrotropin releasing hormone (6).

1.1. Causes of Hypothyroidism

Since iodine is an essential constituent of the thyroid hormones, in most cases an environmental iodine deficiency is the cause of primary hypothyroidism. To avoid the most severe consequence of such, cretinism, a severely impaired abnormal mental and physical development due to the lack of thyroid hormones, iodine fortification programs have been introduced in the past to prevent this disease (6,7). In areas where iodine supply is adequate,

spontaneous occurrences of the disease are mostly attributed to autoimmune thyroiditis, also referred to as Hashimoto's Disease (6,7), but are also observed to happen postpartum (7).

Iatrogenic causes, such as the therapy with drugs interfering with thyroid function or medical procedures, such as radioiodine treatment, (hemi)thyroidectomy and neck radiation are also well known to cause the disease (6,7). Especially iatrogenic causes became more attention with the introduction of immunotherapies (4,7).

Congenital hypothyroidism occurs at a rate of one in 3500-4000 newborns and is in iodine-replete areas mostly due to thyroid dysgenesis, developmental failure of the thyroid gland, or complete absence of thyroid tissue (athyreosis). Newborn babies are most often minimally symptomatic, but at high risk of permanently developing growth failure, severe mental retardation and other neuropsychological impairments. Congenital hypothyroidism is known to be an easily treatable cause of mental retardation (8). The European Society for Pediatric Endocrinology recommends worldwide neonatal screening for hypothyroidism in order to initiate treatment as early as possible if necessary (9). In Germany, it is part of the routinely performed newborn screening for various congenital metabolic disorders, endocrinopathies and cystic fibrosis. The TSH screening test is carried out by a blood test within the first 36-72 hours of life (10).

1.1.1. Iatrogenic Causes of Hypothyroidism

It is known that iodine-containing drugs, as amiodarone is one, can lead to iodine overload consequently resulting in sudden blockage of thyroid hormone synthesis, known as the Wolff-Chaikoff effect, a mechanism that is still not fully understood. Estimations show that around 14% of patients receiving amiodarone develop hypothyroidism as a consequence of such treatment (6,11). Amiodarone induced thyrotoxicosis occurs less frequent in iodine sufficient areas (3).

One of the most important agents frequently used in the targeted tumor therapy and known to be responsible for development of hypothyroidism are anti-cytotoxic T-lymphocyte antigen 4 (CTLA-4) agents, anti-programmed cell death protein-1 (PD-1) agents and anti-PD-1 ligand molecules (PD-L1 and PD-L2). Most probably they act due to their reactivating mechanism on the immune system not only against the cancer cells, but also stimulate an autoimmune reaction against the thyroid axis (3).

Follow-up of patients who were treated with radioiodine due to Grave's Disease and toxic nodular goiter showed, that around 50-80% of patients will develop hypothyroidism as a consequence of treatment. Around 8% developed hypothyroidism when the cause of treatment was solitary toxic nodules. After undergoing hemithyroidectomy, 20% of patients needed treatment with thyroid hormone replacement (6).

1.2. Symptoms of Hypothyroidism

There is consensus in the literature that the symptoms of hypothyroidism are, as most organ systems of the body are involved, often highly non-specific and commonly complaints that can be found in both hypothyroid and euthyroid populations (6,7,12). Also, clinical presentation differs in presentation due to age, sex and ethnicity and is further dependent on the time between onset and diagnosis of the disease. Usually, symptoms become more prominent with decreasing thyroid hormone levels within the body, which usually takes some time (6,7). Approaches in research to develop appropriate scores or to identify an overall applicable clinical picture of a hypothyroid patient, failed (13).

Still, some symptoms are mentioned multiple times, as "weight gain, fatigue, poor concentration, depression, diffuse muscle pain, menstrual irregularities, and constipation" (Chiovato et al.), being generally non-specific presentations. Symptoms appearing to be more specific for the hypothyroid state are "constipation, dry skin, hair loss and proximal weakness" (Chiovato et al.), as research showed (7).

Especially patients with severely pronounced hypothyroidism are described with having presenting symptoms such as "altered mental status, hypothermia, progressive lethargy and bradycardia and can eventually result in multiple organ dysfunction syndrome and death" (Chaker et al.), a condition being referred to as myxedema coma (6).

Canaris et al. investigated for correlation between symptoms of hypothyroidism and biochemical disease severity and concluded that symptoms alone cannot be used to identify a patient with hypothyroidism with such precision as sensitive biochemical measurements can. However, some combinations of signs and symptoms can indicate a high likelihood of the presence of the disease but cannot replace biochemical testing. They also stated that while "the presence of symptoms is suggestive of disease, […] their absence fails to exclude disease"

(Canaris et al.), meaning that clinicians should use laboratory methods to evaluate for thyroid function at a low threshold (13).

Symptoms occurring with thyroid hormone deficiency are likely to be confused with symptoms occurring due to other natural processes such as ageing or pregnancy (14). Most likely do changed or newly reported symptoms indicate a hypothyroid state in a patient (13).

1.3. Diagnostic Workflow and Limitations

Given that the presence of symptoms cannot identify patients with hypothyroidism reliable, it becomes clear, why biochemical laboratory thyroid function tests are inevitable for diagnosis of thyroid dysfunction (1,13).

Laboratory analysis of serum TSH level is the most reliable and sensitive method to identify patients with abnormal thyroid status. Abnormal TSH values, in the case of hypothyroidism elevated levels, indicate thyroid dysfunction early. Such findings can, and should be followed, by further diagnostical methods, such as measurement of thyroid hormones, thyroid related antibodies or ultrasonographic imaging of the tissue of the thyroid gland, to confirm or reject the suspicion of a disease (1). It is important to note that there are different laboratory parameters that can be determined, as there are differences between the amount of free hormones and total hormones, including the amount of hormones bound to transport proteins (15).

The diagnosis of manifest primary hypothyroidism is to be confirmed, if an elevated serum TSH level together with reduced levels of circulating thyroid hormones, triiodothyronine and thyroxine, is detected. Sometimes, only the thyroid hormone thyroxine is designated as enough to define thyroid hormone deficiency (4,14). The condition, in which TSH levels are elevated, but thyroid hormone levels are within reference ranges, is known as subclinical hypothyroidism, indicating possible early failure of the thyroid gland and potential development of overt hypothyroidism (14).

Whether or not those patients with subclinical hypothyroidism should be treated with levothyroxine remains controversial, since studies in the past could not clearly show evidence for improved outcomes in case of early initiation of therapy. This remains to be a case-by-case decision based on the patients' personal risk factors, clinical symptoms and in the knowledge that therapy becomes increasingly useful with increasing TSH (literature: >10µU/mL) (16).

The standardized definition for thyroid disease only by reference ranges of the thyroid function tests is however under discussion, since reference ranges are statistical results derived from an apparently healthy population. Without consideration to differences in age, sex and ethnicity, which are factors known to affect reference ranges for thyroid function, it might be too simplistic and not fully applicable in clinical practice (4,6). Attempts in Australia and the UK, where age-specific reference ranges were used for patients, oftentimes changes the categorization from abnormal to normal thyroid function, especially in the elderly population (17,18).

Screening the general population for hypothyroidism or thyroid diseases in general is currently not recommended, as there is at this time insufficient evidence that clinical outcomes would be significantly improved by earlier detection and initiation of treatment (1,6). Still, some researchers came to the conclusion that more widespread screening programs would be useful to prevent delayed diagnosis with harmful consequences of the disease and ask for initiation of routine screening programs, at least for specifically identified risk groups (4,19).

1.4. Treatment of Hypothyroidism

With clinical presentation and biochemical confirmation of manifest hypothyroidism, there is indication for initiation of, usually lifelong, treatment with thyroid hormone replacement with a synthetic thyroxine. Levothyroxine monotherapy, taken orally on an empty stomach, ideally 30-60 minutes before breakfast, is currently the treatment of choice (1,6). Due to the long half-life of one week it allows to be given only once daily and generates a stable level of triiodothyronine in the peripheral tissues by conversion of T4 into T3. In contrast, liothyronine, a synthetic T3, has a short half-life of only one day, so treatment with liothyronine would be taken more than once daily and could result in unsteady levels of T3 throughout the day (2).

The daily dose of levothyroxine is calculated by the body weight of the patient and should be gradually increased to the target dosage when initiating the therapy (1,6). The dosage is titrated until the patient's clinical symptoms improve and an euthyroid level is reached. TSH levels should be again checked four to six weeks after therapy initiation, if reaching a level within the reference range, follow up should be done every 12 months and dosage adjustments should be initiated accordingly. Due to levothyroxine treatment the symptoms of thyroid hormone deficiency should be disappeared and associated long-term complications prevented

(2,7). Patients with signs of malabsorption, e.g., after bariatric surgery or due to gastrointestinal disorders, could benefit from liquid thyroxine formulations as a substitute for tablets (1).

For patients where the treatment goal cannot be achieved by levothyroxine monotherapy, additional treatment with synthetic T3 can be necessary. The 2012 European Thyroid Association guidelines define this as an experimental approach that should only be attempted by experts, such as internists and endocrinologists, closely monitored and evaluated and should be discontinued if there is no improvement after three months of treatment (2).

Undertreatment of hypothyroidism is associated with several adverse long-term effects. Poor growth and development in children and adolescents need to be prevented by adequate treatment. In the population of adults, poorly treated hypothyroidism is associated with several other diseases, such as obesity, hypertension, increased cardiovascular risk and reduced quality of life. In women, hypothyroidism is oftentimes a preventable and treatable reason for infertility, miscarriages, preeclampsia and impaired fetal growth (4,12).

1.5. Myxedema Coma

The most pronounced form and clinically severe complication of hypothyroidism is the myxedema coma. If it is not recognized early and treated immediately, it can be lethal with a mortality rate of 50-60%. This condition might present spontaneously, but more often, occurs in patients with known hypothyroidism which is aggravated by other causes, such as drugs, trauma and several other systemic illnesses. It is characterized by multiple organ dysfunctions and severe mental deterioration. Despite the altered mental status of such a patient, a classical myxedematous face, with characteristics such as “general puffiness, macroglossia, ptosis, periorbital edema and coarse, sparse hair” (Wall), can be recognized. Severe findings of the cardiovascular, gastrointestinal system and neurological findings are frequently present, but these are not specifically attributable to the thyroid gland and the severity oftentimes depends on the time of diagnosis. Other signs, as hypothermia, hyponatremia, hypercarbia and hypoxemia, should raise suspicion to test severely, but unspecific, symptomatic patients for thyroid dysfunction. Patients with suspected myxedema coma should be treated with intravenous levothyroxine at an intensive care unit setting, where also other necessary supportive measures, like mechanical ventilation, warming or therapy with vasopressor agents, with close monitoring of the vital functions can be initiated (1,20).

1.6. Incidence of Hypothyroidism – Research Background

Generally, there is variation of probability of developing hypothyroidism according to the iodine supply of the respective area. Hypothyroidism commonly occurs in areas of severe iodine deficiency, but also in areas with excessive iodine intake. Surprisingly, mild iodine deficiency sometimes leads to thyroid nodularity and autonomy, resulting in the opposite thyroid dysfunction – hyperthyroidism. Therefore, the iodine intake should be closely regulated to be sufficient, but excessive intake should be avoided (21).

Information about the frequency of hypothyroidism differs strongly according to region, literature and study designs and usually does not analyze for and distinguish between causes of primary hypothyroidism (1,19). To the best of our knowledge, a 2014 meta-analysis (Garmendia et al.) was the first one aimed at estimating epidemiologic data on thyroid dysfunction, both hyper- and hypothyroidism, among the European population. It assessed seven studies with a resulting mean prevalence of 4.94% (4.75-5.13%) for undiagnosed hypothyroidism with clear female predominance. Further, nine studies were analyzed aiming at a prevalence for both previously diagnosed and undiagnosed hypothyroidism, with a mean result of 3.05% (3.01-3.09%), ranging from 0.37% for overt to 3.8% for subclinical hypothyroidism. Female preponderance was again found, with a prevalence of hypothyroidism of 5.1% for females and 0.92% for males. Analyzing seven studies regarding the incidence rate of hypothyroidism resulted in a mean of 226.2 (222.26-230.17) per 100'000 per year. Again, a female domination could be shown, with an incidence rate of 396.96 per 100'000 and 72.48 per 100’000 for females and males, respectively (19). This meta-analysis specifically excluded studies aimed at prevalence of hypothyroidism only.

A more recent systematic review and meta-analysis from the year 2019 (Mendes et al.) considered more studies and was aimed at identifying a prevalence of undiagnosed hypothyroidism among the European population. They excluded patients with previously known thyroid disease and came to the result that the prevalence of undiagnosed hypothyroidism was 4.7%, with 4.11% being subclinical and 0.65% being clinical hypothyroidism. Another finding was that hypothyroidism more commonly occurs in females, among patients aged 65 years and older and in studies with low sample sizes (22).

The Whickham survey, published in 1977 in the UK, recorded elevated TSH levels (threshold 6.0 mu/L) in 7.5% of their female and 2.8% of their male population. Prevalence of overt hypothyroidism was between 14 and 19 per 1000 females and 1 per 1000 males (23).

A reference for the prevalence of hypothyroidism in the United States population was given by the National Health and Nutrition Examination Survey (NHANES III), according to which 4.6% of their population were affected by overt and subclinical hypothyroidism (24). Another American prevalence study, from Colorado from the year 2000, found a prevalence of 9.5% for elevated TSH levels (threshold 5.1 mIU/L) in a population comprised of visitors of a statewide health fair. They also noticed that among patients already receiving thyroid hormone replacement therapy, only 60% had TSH values within the reference range (25).

Information about epidemiology of hypothyroidism in Asia is limited. For Japanese adults, a prevalence of almost 10% is reported for abnormal thyroid function in general (26).

We found that the criteria are always relative to the respective reference range, which is unfortunately not always disclosed and probably different among the various studies. Comparing the results from the literature, the impression appears that hypothyroidism is slightly more common among the European than the American population. When looking at the prevalence of finding elevated TSH levels among a population, the American appear to show higher likelihood compared to the Europeans.

2. OBJECTIVES

2.1. Aims of the Study

The main goal is to observe and analyze the overall incidence of subclinical and overt hypothyroidism in the Coburg Hospital during the timespan 2018-2023 using the laboratory thyroid parameters TSH, FT3 and FT4. We are particularly interested in any differences of occurrence within the group of patients with severe clinical hypothyroidism, first characterized by extremely elevated serum TSH levels and second additionally reduced values of the thyroid hormones, FT3 and FT4.

This study aims to provide a statistical analysis of the patient data of 2018-2023 to gain an objective and data driven view on these criteria and investigate for trends between the years.

Furthermore, based on the statistical analysis, it is our goal to discuss potential reasons, inside the corresponding patient groups, for exceptional, statistically deviating occurrences of extreme cases of hypothyroidism.

2.2. Hypothesis

- This thesis is motivated by empirical observations by the medical staff that there was a perceived change of frequency of cases of extreme hypothyroidism in the recent past, with an increase of cases with severely elevated TSH levels in the year 2023, compared to previous years. This constitutes the main hypothesis for this work.

3. MATERIALS AND METHODS

3.1. Study Design and Ethical Approval

This retrospective, observational cross-sectional study was conducted using anonymized data from patients treated at the hospital in Coburg, Regiomed Klinikum Coburg, between January 1st, 2018, and December 31st, 2023. The hospital in Coburg is a specialized care hospital (care level II) with around 510 beds and 22 specialist departments in the region of Upper Franconia, Northern Bavaria, Germany. The area covered extends across the city and district of Coburg and beyond, for specific specialist departments (27).

On February 15th, 2024, the internal review board of the Medical School Regiomed, Coburg, decided, that there were no objections to the implementation of this research project and granted ethical approval.

3.2. Inclusion and Exclusion Criteria

Our study included all patients who were registered at the Department of Laboratory Medicine at Coburg Hospital with available results for their serum TSH levels, as well as all patients with additionally measured values for the thyroid hormones FT3 and FT4. Patients with all thyroid function levels, patients who were currently being or have ever been treated with thyroid hormones or thyreostatic drugs, patients who have undergone thyroid surgery or ablation therapy, and patients with a history of thyroid malignancy were included. We enrolled all patients despite their current or previous comorbidities and malignancies. We accepted patients of all ages and genders in this study.

We excluded patients who were only treated in another hospital of the Regiomed group but not in Coburg.

A total of 216'240 data points, representing individual laboratory test results, were included in this study.

3.3. Data Source and Characteristics

In this work, we rely on analyses of two datasets. The first one will be used to provide a statistically validated, data driven view. The second one will be used for explanation of potential reasons for the observations seen on the first. Details will be explained in the following section.

3.3.1. Dataset 1

For this study we obtained already collected data from the patients' electronic medical records. This data was used in anonymized form, it is impossible to trace the individual patient identities via this dataset. All patients who underwent biochemical evaluation of their serum TSH level were used to create the data foundation for this study.

The data obtained from the laboratory of the hospital in Coburg contained the following information about the patient:

Data Point ID ("Auftragsnummer") and Patient Number (PNR): Each of the 216'240 data points has a unique identifier, representing one measurement which was performed during clinical stay. These data point ids are related via the case number ("Fallnummer"), also referenced as patient number (PNR), which refers to an individual patient during one stay in the hospital. (Note: An individual person may receive multiple PNR if this person has multiple disjointed hospital stays. A PNR alone cannot be used to identify an individual person over multiple stays.) This means that one PNR can have multiple related data point ids characterizing the measurements taken, and each data point id is related to exactly one PNR (patient stay).

Gender: The gender of the patients, classified according to the characteristics M=male, F=female, U=non-binary, NA=not available. In the following, those patients with unavailable information regarding their gender will be represented together with the non-binary patients as characteristic "U" (Figure 1).

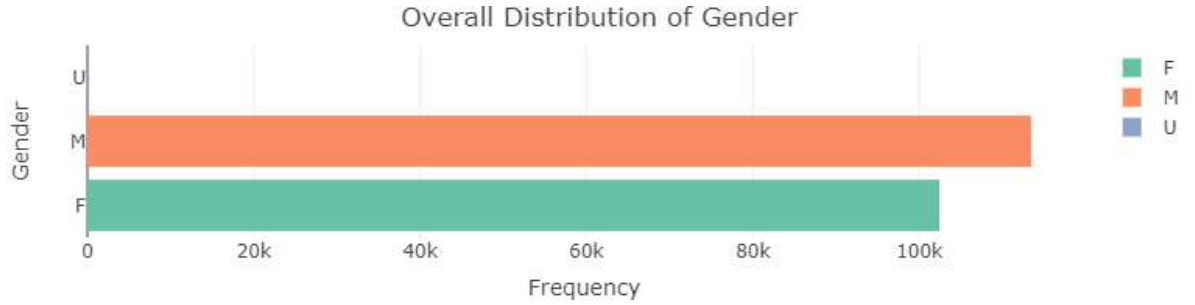

Figure 1. The distribution of gender with the characteristics female (F), male (M) and non-binary or undisclosed (U) for the overall population of dataset 1. Data presented as frequencies. *N=216'240.*

Date of Birth and Age: The date of birth of the patients. The age was derived as an additional factor based on fully completed years of age from the birth date in comparison with December 31st of the respective year the measurement was taken. An example: A patient who was born on September 13th, 1991, and was treated in the year 2021 is therefore considered to

be 30 years old, regardless of whether he was treated in the months before or after his birthday. The minimum age is 0 years for newborn patients.

TSH, FT3, FT4: Laboratory values of thyroid parameters obtained during the measurements. Not all values are taken with each data point, depending on clinical standard and individual decision about medical necessity by the clinic staff during the stay of the patient. TSH values were measured in unit μU/mL. FT3 and FT4 levels were given in unit pmol/L. For details see Section 3.6.

Date and Time of Measurement: The date and exact time when the measurement was carried out.

3.3.2. Dataset 2

At a later stage (see 4.5), an additional dataset is introduced. This second dataset 2 is a result of analyses made on the overall dataset, which will be described later. It contains a smaller number of patients, but extended information about those patients' clinical stay.

Dataset 2 is the result of a manual review of all patients with TSH >100 μU/mL and thyroid hormone levels below the respective reference ranges. This dataset was collected pseudonymously so that individual patient identities cannot be traced. This second dataset will include the following information in addition to that already mentioned:

Symptoms and Diagnoses at Time of Admission to the Hospital: All symptoms registered at the time of admission at the hospital, usually emergency ward, with special interest, if the patient complained about signs and symptoms of severe hypothyroidism/ myxedema coma (see 1.5). It was checked whether hypothyroidism was suspected at time of first presentation in the emergency ward of the hospital.

Previous Diagnoses and Drug Therapies: All previously diagnosed conditions, with particular interest of any thyroid disorder and diagnoses of tumorous diseases. Previous and current drug therapies, specifically antithyroid and thyroid hormone replacement therapies as well as drugs that may interfere with the thyroid function, in particular amiodarone and antitumor therapy with monoclonal antibodies, were noticed.

The Treatment during Clinical Stay: The necessary treatment initiated during hospitalization, whether the patients had to be admitted to the intensive care unit (ICU) and

whether an intravenous treatment with levothyroxine was required. We were also interested in whether the patients of dataset 2 received additional consultation with an endocrinology specialist during their clinical stay.

3.4. Data Anomalies and Missing Values

In the following section we will briefly describe anomalies and missing values of our data, that should be recognized before handling the data. As our datasets rely only on data that has already been collected, we were unable to supplement the missing criteria.

3.4.1. Dataset 1

Missing PNR: In 1510 of the data points, 0.73% of the overall dataset, the PNR is not given. These data points are not removed as the missing PNR is not interfering with the interpretation of the laboratory results in question. However, all these measurements are part of the total analyses taken over the years and might be relevant in placing certain results in context.

Missing Gender / Gender Non-Binary / Gender Not Available: For 351 (0.16%) of values, the gender was either not specified, non-binary or not available, which is why they are referred to as category U in the analyses.

Missing Date of Birth: For 383 of the data points, 0.18% of the overall dataset, the respective date of birth is not provided. Therefore, no age of the patients can be derived. These data points were retained so as not to change the overall measurements and, if necessary, manually checked or excluded in individual cases. If this should be the case, it will be mentioned at an appropriate point in the course of this work.

Missing FT3 / FT4 Value: 170'304 of the data points, 78.86% of the overall population; and 170'205 of the data points, 78.81% of the overall population, have missing values for the thyroid hormones FT3 and FT4, respectively. These data points are not removed from the dataset because the determination of thyroid hormone levels is often only a secondary measure – usually just requested when TSH is elevated – and non-existing values are to be expected in daily clinical practice.

Non-Numeric Values: Due to the transfer from the laboratory software, some results were non-numeric, e.g. “>100”. These were checked and corrected manually using clinic’s documentation software Orbis.

All characteristics not mentioned here (but in 3.3) can be treated as completely available over all data points.

3.4.2. Dataset 2

The 43 measurements that meet the inclusion criteria for this dataset (see 3.3.2) are attributable to 27 PNR/clinical stays of patients. It was possible to obtain the abovementioned extended information on 26 of these patients, as one case was affected by non-disclosure. This case, with its two associated measured values, was therefore excluded from further analyses and the following analyses on dataset 2 are made with 41 measurements of 26 corresponding patients.

Past Medical History: For some patients, anamnestic data was not, or not completely, obtained. Therefore, some specific statements about their medical history, including current intake of medication and current and pre-existing diagnoses and conditions could not be made in these cases. In the corresponding analyses (see 4.5), reference is made to the incompleteness of the data.

3.5. General Limitations of the Datasets

As already mentioned before, a central limitation is the fact that the datasets contain past laboratory measurements and already obtained anamnestic data about our patients. We have no control over the number of measurements taken, nor over the quality of data collection and documentation with regards to the medical conditions, examination findings and past medical history of our study population. We can only rely on the relevant, existing documentation but can no longer complete the missing data. This certainly represents a limitation of our study, but this is to be expected in a retrospective study that works with data that was collected in everyday clinical practice and was not explicitly designed for participation in a study.

Theoretically, the datasets represent patients, but through the relation of those data points to a case id (see 3.3.1), it is possible that several measurements are registered for one case id. It is possible to summarize those values, but it is necessary to select one way for the whole analysis. One method would be to take only all maximal values into account and reject all others. In that case, we would operate with higher values in general. An alternative method would be to use statistical means in case of more measurements per patient. In this case, we would lose the maximal values, which could possibly lead to loss of clinical significance in some cases, due to our special interest in high values of TSH. All methods of aggregation (from data point to PNR/patient per stay) have the severe downside that we have no control when a new PNR is generated. A person leaving the hospital and returning three times will be continued as three PNR/patients, while a patient with the same number of measurements staying in the clinic will only count as one patient/PNR in the data.

We conclude that this is a structural limitation of the dataset which cannot be overcome, and this is why our analysis is carried out on the basis of data points/measurements. We accept double mentions of patients, due to our specific interest in extreme values. In individual cases, the measurements per patient should provide a conclusive medical picture.

Due to the pseudonymization of the data, it was not possible to exclude that the same patient was not registered as different PNR due to several clinical stays. This must be accepted in this type of anonymized analysis in order to protect the patients' identities but may need to be taken into account when integrating the results, especially in the individual case analyses.

The limitations mentioned above relate to the characteristics of the datasets themselves, as they influence the further handling of the data. Limitations about the validity of our results will be discussed again later in Section 5.

3.6. Laboratory Analysis and Reference Values

As already mentioned in Section 1.3 there are different laboratory parameters for the thyroid hormones that can be determined. In this work, we will refer to the laboratory parameters of unbound hormones, free triiodothyronine (FT3) and free thyroxine (FT4).

Laboratory analyses of the thyroid parameters TSH, FT3 and FT4 were carried out in the Regiomed Klinikum Coburg's own laboratory. Until December 2022, the analyses were conducted on a Cobas e601 system (ROCHE Diagnostics, Mannheim, Germany) using the

ECLIA methodology. In December 2022, the laboratory became part of the Synlab Holding Deutschland GmbH (Augsburg, Germany). From then on, blood analyses were performed using an Alinity system (Abbott, Wiesbaden, Germany).

The reference range given for TSH was 0.27-4.20 µU/mL in all observed years. For the thyroid hormones FT3 and FT4, it changed over the years. From 2018-2022, the reference ranges for FT3 were 3.1-6.8 pmol/L and for FT4 12.0-22.0 pmol/L. For 2023, the reference ranges were 2.43-6.0 pmol/L for FT3 and 9.1-19.1 pmol/L for FT4. These reference ranges are not to be confused with the technically possible observation limits which are in general larger than the reference range and depending on methods used by the laboratory.

As already mentioned above (see 3.5), TSH is a laboratory parameter that is used to initially assess thyroid function. In everyday clinical practice, it may be sufficient if the resulting value is within the reference range. If abnormal results occur, indicating thyroid dysfunction, a secondary measurement of the thyroid hormones FT3 and FT4 is automatically taken (1).

As this study is focused on those patients suffering from severe, clinically manifest hypothyroidism, in some analyses we did not only consider an elevated TSH level but added the criteria of abnormally reduced thyroid hormone levels, FT3 and FT4, to further differentiate between patients with subclinical and clinical hypothyroidism (see 1.3).

3.7. Statistical Analysis

For processing, analysis and presentation of our dataset, R in version 4.3.1, (R Foundation for Statistical Computing, Vienna, Austria) was used. Additionally, the online tools SankeyMATIC.com and FreeWordCloudGenerator.com were used for the creation of Figure 13, Figure 14 and Figure 15.

For normality testing of dataset 1 we had to choose between several statistical tests. We reject using the Shapiro-Wilk test, which can be only used for smaller datasets, with data points smaller than 50. The Kolmogorov-Smirnov test is suitable for larger datasets, but was not applicable for our dataset, as there should be no bindings between the values of the dataset. In our work we use the Anderson-Darling test since our datasets under analyses contained more than 10'000 data points. It tests with the null hypothesis that the data is normally distributed. The rejection of the null hypothesis, in our case with P value <0.05, indicates non-normality.

We realized the problem with statistical tests for normality with large sample sizes. With increase in sample size, the tests get highly sensitive, because the power of the test increases with sample size, leading to rejection of the null hypothesis due to small variations from normality that might be practically not significant (28). We took this into consideration when interpretating our statistical analysis and complemented the testing by using graphical methods. We use Q-Q plots (Quantile-Quantile Plots) to provide an intuitive and visual way to understand the distribution characteristics of our dataset. Q-Q plots compare the data's quantiles to theoretical quantiles of a normal distribution. If the data follows normal distribution, the plot follows exactly a straight line at 45° angle. Deviations from the straight line indicate non-normality.

Even though the Q-Q plots gave the appearance of some kind of normality of our dataset (see 4.3), we relied on the result of the Anderson-Darling test and decided to continue for further statistical analyses with non-parametric tests.

In the following, groups were formed (for further information see 4.2), which were compared and tested for statistical significance by using the Mann-Whitney U test. The Mann-Whitney U test is a non-parametric test to test for significant difference between the distributions of two independent groups. It works with the null hypothesis, that the distribution of the two groups is equal. The test works by ranking the values of both groups. If the ranks of those groups significantly differ from one another, the null hypothesis is rejected, and we can assume that those two groups distributions are structurally different.

For reasons of better readability and clear data presentation, the group size with which the corresponding tests were carried out is indicated below in the caption of the respective table or figure as *N=number*.

Numerical variables are described using descriptive statistics, such as mean with standard deviation (SD), median, minimum and maximum values.

For all tests, if not stated otherwise, the statistical significance was set to $P<0.05$. To improve the readability of the results, the different levels of significance are flagged with stars (*) as follows: *P*-value <0.05 (*), <0.01 (**), <0.001 (***).

4. RESULTS

4.1. Baseline Characteristics of the Study Population

In total, 216'240 data points were included in our study. Our study population consists of 102'424 (47.4%) female, 113'465 (52.5%) male and 351 (0.0016%) patients for whom the gender is non-binary or not specified. On average, patients were 66 years old ± 18.5 years, with a median age of 70 years. The youngest patient was newborn, and the oldest patient was 107 years old.

The distribution of the entire study population by age and gender is visualized in Figure 2. As expected, we see characteristics that are typical for clinical populations, with many elderly people and a steady proportion of newborns.

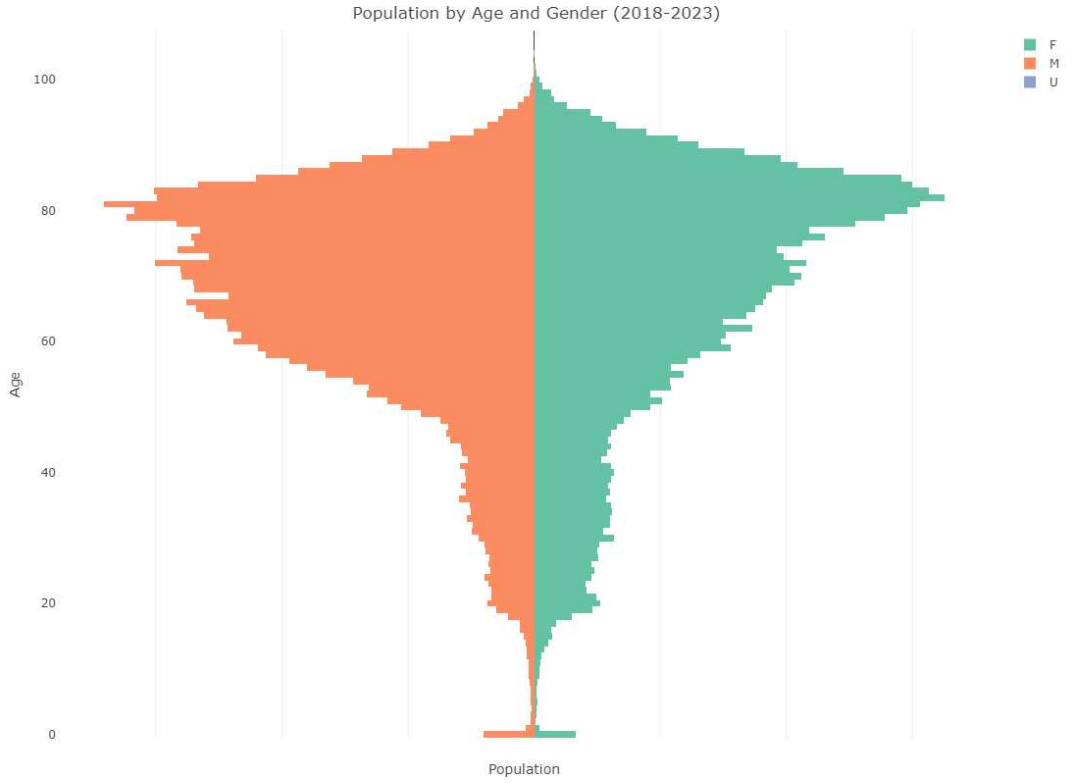

Figure 2. Distribution of the entire study population of dataset 1 by age and gender of the patients. Age is expressed in years. Data presented as frequencies. *N=216'240.*

On average, over all measurements the mean TSH value was 2.15 µU/mL ± 4.92, with a median value of 1.46 µU/mL, with a minimum value of 0 and a maximum value of 830.3 µU/mL. For FT3 levels, the mean was 3.96 pmol/L ± 1.97, the median 3.81 pmol/L, with minimum and maximum values of 0 and 92.63 pmol/L, respectively. For FT4 values, the mean was 17.45 pmol/L ± 6.4, the median 16.54 pmol/L, with a minimum value of 0 and a maximum value of 99.2 pmol/L.

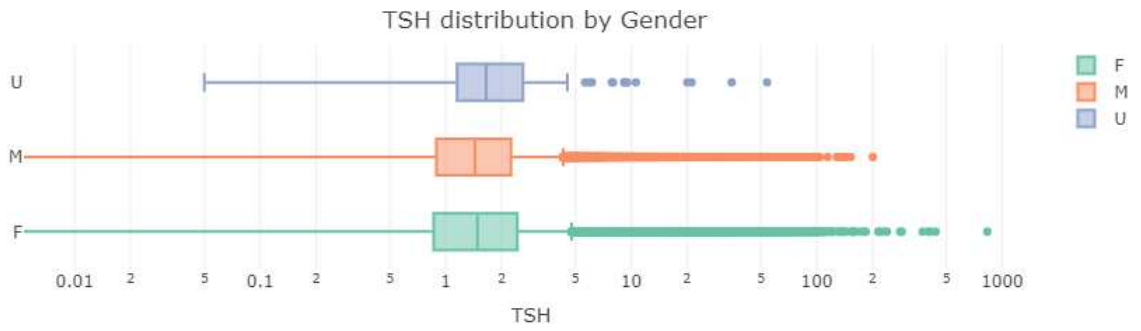

Figure 3. Distribution of all measured TSH values for the entire population of dataset 1 across the different genders on a logarithmic scale. Data presented as boxplots with median and IQR. *N=216'240.*

Looking at the distribution of all TSH values measured across the different gender categories (Figure 3), it becomes clear that around 75% of the population across all genders has values below a level of 5 µU/mL. Measurements with values above 5 µU/mL represent the outliers in this population. The boxes show that most of the measured values are within the reference range, reflecting results of an apparently healthy population, but the many outliers towards the higher values of TSH indicate that there is considerable variation of TSH levels among the entire population of dataset 1.

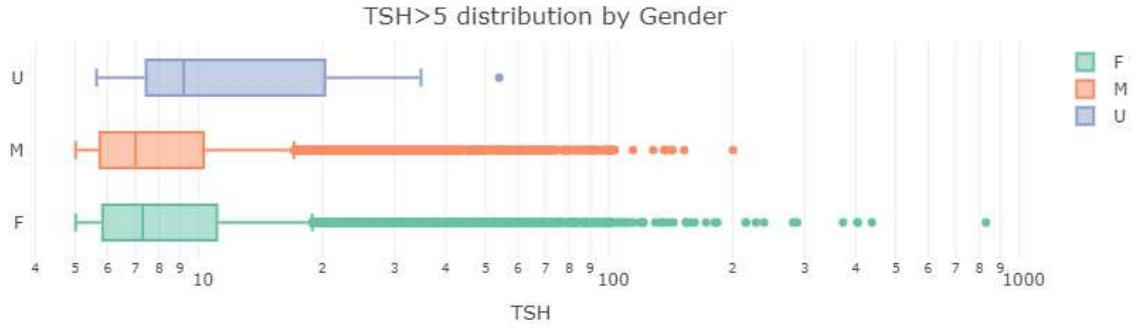

Figure 4. Distribution of all measured TSH values >5 µU/mL for the entire population of dataset 1 across the different genders on a logarithmic scale. Data presented as boxplots with median and IQR. *N=11'576.*

The outlying values from the previous diagrams, TSH values above 5 µU/mL, represented in Figure 4, show a distribution comparable to that of all measurements. Around 75% of the results in these plots are distributed between 5 and 10 µU/mL for females and males with the whiskers ranging up to a value of about 20 µU/mL. The values of non-binary patients are somewhat more widespread at a range up to 20 µU/mL and whiskers up to about 35 µU/mL. Extreme values are still numerous and again reflect outliers, although a selection for the "higher" values has already been made, prompting to a further narrowing down towards even higher values, represented in Figure 5.

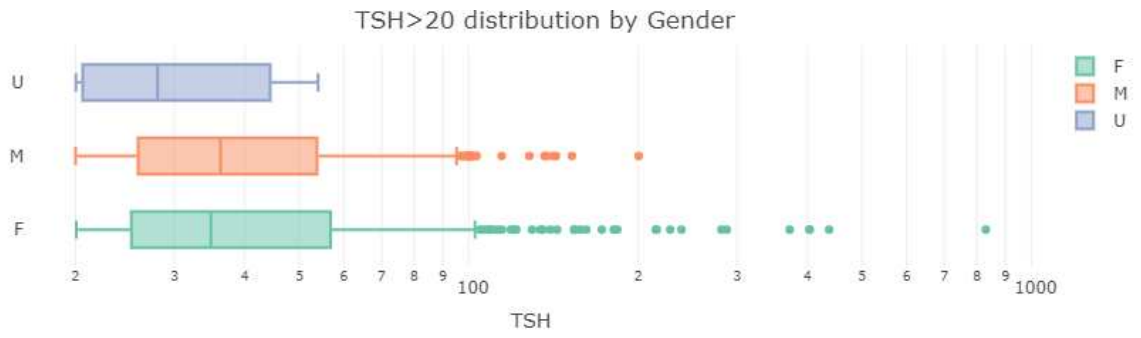

Figure 5. Distribution of all measured TSH values >20 µU/mL for the entire population of dataset 1 across the different genders on a logarithmic scale. Data presented as boxplots with median and IQR. *N=1121.*

With focus on the distribution of "very high" TSH levels, greater than 20 µU/mL, again, the distribution of majority of measurements remains concentrated towards "lower" levels of TSH. Results at levels of around 100 µU/mL and higher appear to be the outliers of this narrowed population.

In all figures, half of the results of the TSH measurements (shown as a box) for women are distributed over a slightly larger range. Another finding is that a larger proportion of deviating, extremely elevated TSH values were measured in women.

In 16'584 cases, corresponding to 7.67% of the overall study population, the TSH level was >4.2 µU/mL and thus above the reference range. For 2918 data points, 1.35% of all data points, TSH values were in a range between 10 and 50 µU/mL, 287 data points, 0.13%, had results between 50 and 100 µU/mL and 57 data points, 0.03%, had extremely elevated TSH values >100µU/mL.

For 1499 measurements, accounting for 0.69% of the total data points, not only elevated TSH values, but also thyroid hormone levels below the respective reference ranges, were registered, so that the criteria for clinical hypothyroidism were met. The remaining 15'085 data points with elevated TSH, 6.98% of all measurements, therefore meet the criteria of subclinical hypothyroidism.

4.2. Group Creation

In this section we will derive groups from dataset 1 to determine factors correlating with clinical hypothyroidism. To analyze potential differences between the years we will introduce a grouping by treatment years. Additionally, we will use the TSH values to categorize by clinical relevance.

4.2.1. Grouping by Treatment Years

We grouped all measurements according to the year they were carried out and got the following data points:

Table 1. Absolute numbers of measurements of TSH levels and respective numbers of patients for the corresponding treatment years

	Data points / Measurements	PNR / Patients	Factor
2018	39'169	27'602	0.70
2019	39'574	28'135	0.71
2020	34'738	23'329	0.67
2021	35'098	23'961	0.68
2022	34'186	23'065	0.67
2023	33'475	23'117	0.69

Data is presented as frequency. Factor is derived from data points x factor = PNR. *N=216'240.*

This grouping is relevant when checking if there are any temporal effects in the underlying population, which is one of our goals of this study (see 2.1).

Over the years, we can observe some differences in the number of measurements and patients. The first two years of our observation had relatively steady counts, with the highest number of measurements and patients in 2019. In the following years, the number of measurements and patients has declined, reaching its lowest level in 2023, with around 6000 measurements and 5000 patients less than in 2019. The measurements and numbers of patients seem to correlate similarly for the different year groups, since the factor which is derived from number of measurements and patients is relatively steady, as Table 1 shows. Although it is not clear whether people get one or more PNR, due to several hospital stays, as discussed in Section 3.3, the underlying mechanism seems to be comparable over time, as the resulting factor is always close to ~0.69.

After splitting our dataset by treatment years, we want to provide insight into the distribution of our grouped dataset again before starting our analyses. Detailed information about the years can be obtained from Table 2.

Table 2. Statistical measures for age and gender distribution of all patients of the corresponding treatment years among the entire dataset 1

	Age				**Gender Distribution**		
	Min (years)	Max (years)	Mean ± SD (years)	Median (years)	Female (%)	Male (%)	Non-Binary (%)
2018	0	102	65.58 ± 18.87	69	47.7	52.1	0.0015
2019	0	103	65.83 ± 18.73	70	48.2	51.7	0.0012
2020	0	106	66.35 ± 18.31	70	48.4	51.4	0.0018
2021	0	107	66.07 ± 18.65	70	46.3	53.5	0.0018
2022	0	104	65.98 ± 18.41	70	45.7	54.0	0.002
2023	0	102	66.56 ± 18.06	70	47.7	52.3	0.00033
Overall	0	107	66.0 ± 18.5	70	47.4	52.5	0.0016

Age data presented as minimum and maximum values, mean ± standard deviation (SD) and median. Gender data presented as proportion (%). Min= minimum value, Max= maximum value.
N_{2018}= 39'169; N_{2019}= 39'574; N_{2020}= 34'738; N_{2021}= 35'098; N_{2022}= 34'186; N_{2023}= 33'475.

Due to our grouping the age distribution did not change, since the mean ages of the groups ranged between 65.56 and 66.56 years ± 18.06-18.87. All groups included newborn patients and patients up to the ages of 102-107 years (Figure 6). The distribution of genders was nearly equal during all observed years, with proportion of females of 45.7-48.4% and males of 51.4-54.0% and around 0.0014% patients with non-binary gender per year.

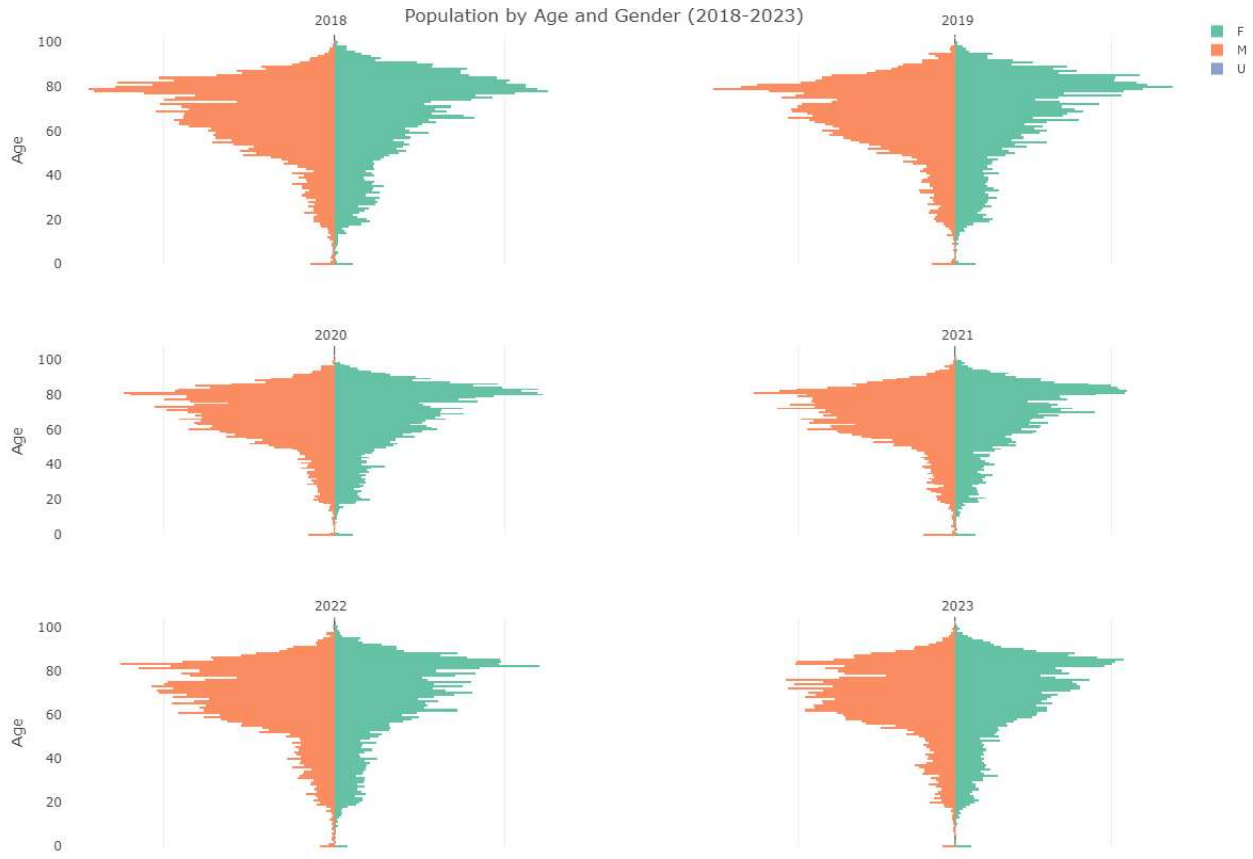

Figure 6. Distribution of the population of dataset 1 by age and gender of the patients for the corresponding treatment years 2018-2023. Age is expressed in years. Data represented as frequencies.
N_{2018}= 39'169; N_{2019}= 39'574; N_{2020}= 34'738; N_{2021}= 35'098; N_{2022}= 34'186; N_{2023}= 33'475.

Results of the statistical analysis of the laboratory values TSH, FT3 and FT4 are provided in Table 3. Across all years, the mean TSH levels were between 2.03-2.21 µU/mL ± 3.75-6.22, with median values between 1.30-1.53 µU/mL, with the lowest median in 2023. The means for FT3 values ranged between 3.43 and 4.28 pmol/L ± 1.49-2.46, with the highest mean in 2018 and the lowest mean in 2023. The medians for FT3 ranged between 3.35 and 4.12 pmol/L. The FT4 values were quite similar for the years 2018-2022, with mean values ranging from 17.31-18.27 pmol/L ± 5.97-7.05 and median values in a range of 16.67-17.31 pmol/L. Noticeable are the low mean and median values for FT4 of 13.67 pmol/L ± 4.25 and 13.21 pmol/L, respectively, of the year 2023, which might be indicating that there were generally lower values or more measurements with low values for the thyroid hormone thyroxine collected.

Table 3. Statistical measures for all measured values of TSH, FT3 and FT4 of the corresponding treatment years for the overall dataset 1

	TSH				FT3				FT4			
	Min	Max	Mean ± SD	Med	Min	Max	Mean ± SD	Med	Min	Max	Mean ± SD	Med
2018	0.00	101.00	2.15 ± 3.98	1.49	0.40	92.63	4.28 ± 2.46	4.12	0.68	99.20	18.25 ± 7.05	17.18
2019	0.00	830.30	2.20 ± 6.05	1.53	0.00	50.00	4.19 ± 2.13	4.04	0.00	99.20	18.10 ± 6.72	17.05
2020	0.00	403.40	2.09 ± 4.87	1.41	0.00	38.54	3.90 ± 1.80	3.78	0.00	84.74	18.27 ± 6.30	17.31
2021	0.00	141.00	2.19 ± 3.98	1.50	0.00	36.99	3.94 ± 1.76	3.84	0.00	99.20	17.78 ± 6.09	17.05
2022	0.00	98.87	2.21 ± 3.75	1.52	0.60	43.70	3.80 ± 1.78	3.66	0.50	99.20	17.31 ± 5.97	16.67
2023	0.01	437.24	2.03 ± 6.22	1.30	1.64	30.72	3.43 ± 1.49	3.35	5.15	63.72	13.67 ± 4.25	13.21
Overall	0.00	830.30	2.15 ± 4.92	1.46	0.00	92.63	3.96 ± 1.97	3.81	0.00	99.20	17.45± 6.4	16.54

Data presented as minimum and maximum values, mean ± standard deviation (SD) and median. TSH values are meant in µU/mL, FT3 and FT4 values are meant in pmol/L; for reasons of readability the unit has been omitted. N_{2018}= 39'169; N_{2019}= 39'574; N_{2020}= 34'738; N_{2021}= 35'098; N_{2022}= 34'186; N_{2023}= 33'475.

Due to this short analysis, we can assume that the grouping by years did not artificially produce extreme bias for the categories age and gender and that we can use the grouped dataset for further analyses. Possible differences in TSH and thyroid hormone levels are part of further assessments and are in some way expected.

4.2.2. Grouping by Clinical Relevance

In addition to the grouping by treatment years, we additionally introduce the dimension "clinical relevance" as another criterion for grouping.

Patients with TSH values higher than the threshold of 4.20 µU/mL were assigned to the group HYPO, representing the population of both subclinical and, potentially, clinical hypothyroidism. They were further subdivided into groups of TSH values of 10-50 µU/mL, 50.1-100 µU/mL and >100 µU/mL.

In the following, this grouping is represented by the groups TSH 10, with data points with TSH values of 10-50 µU/mL, TSH 50, with data points with TSH values of 50.1-100 µU/mL, and TSH 100, with data points of TSH levels >100 µU/mL.

Additionally, the corresponding reference ranges for FT3 and FT4 (see 3.6) were used to differentiate between patients with subclinical and clinical hypothyroidism. Whenever we refer to the group of data points with TSH values >4.20 µU/mL together with thyroid hormone levels below the reference ranges, representing the patients with thyroid hormone deficiency and clinically manifested hypothyroidism, the group name CLINICAL HYPO is used for ease of reference. The change in reference values for FT3 and FT4 over the years was considered when grouping the results.

Based on the criteria explained above, the groupings were further subdivided into subgroups. The proportions of test results with elevated TSH values were sorted according to their severities and the respective treatments years, as can be seen in Table 4. To ensure that possible differences between the subgroups or years are not due to an in- or decrease in measurements per patient (as we discussed already in Section 3.5, we have no control over the number of measurements taken and therefore have to handle the data accordingly), Table 5 provides the numbers of patients belonging to the respective measurement results.

Table 4. Absolute and relative numbers of measurements of TSH levels belonging to the respective groups HYPO, TSH10, TSH50, TSH100 and CLINICAL HYPO of the corresponding treatment years in relation to the number of measurements of the entire dataset 1

	HYPO	**TSH 10**	**TSH 50**	**TSH 100**	**CLINICAL HYPO**
	N_{HYPO}	N_{TSH10}	N_{TSH50}	N_{TSH100}	$N_{CLINICAL\ HYPO}$
	$\%_{HYPO}$	$\%_{TSH10}$	$\%_{TSH50}$	$\%_{TSH100}$	$\%_{CLINICAL\ HYPO}$
2018	3050	511	56	10	277
	7.8%	1.3%	0.143%	0.026%	0.71%
2019	3178	502	46	13	237
	8.0%	1.3%	0.11%	0.033%	0.6%
2020	2595	449	37	6	225
	7.5%	1.3%	0.11%	0.017%	0.6%
2021	2890	501	52	3	257
	8.2%	1.4%	0.15%	0.0086%	0.73%
2022	2869	526	48	0	348
	8.4%	1.5%	0.14%	0%	1.02%
2023	2002	424	39	25	155
	6.0%	1.3%	0.12%	0.075%	0.46%

Data presented as frequencies. N_X= number of patients in group X; $\%_X$= percentage of patients in group X. N_{2018}= 39'169; N_{2019}= 39'574; N_{2020}= 34'738; N_{2021}= 35'098; N_{2022}= 34'186; N_{2023}= 33'475.

If the number of measurements within the HYPO group is set in relation to the number of patients in the same year, it can be seen that, as with the overall population, there is constant correlation between the two values, as the resulting factor is always close to ~0.7. However, this factor is different for the group CLINICAL HYPO and unsteady over the different treatment years. For the years 2018-2020, a factor always close to 0.62 can be derived and for the years 2022 and 2023, the factors derived from the number of measurements and patients have a mean value of 0.5. This in turn means that in the years 2022-2023, patients with clinical hypothyroidism had more often higher measurement results than those in the other years (in the latter years one patient had on average 2 test results belonging to the subgroup, whereas patients of the other treatment years had on average 1.6 test results per patient fulfilling the criteria to be assorted into the subgroup CLINICAL HYPO). This may be due to the selected interval between the various tests, most probably a shortening, or to the persistently clinically poor condition of these patients of the years 2022 and 2023.

Table 5. Absolute and relative numbers of patients with results of TSH levels belonging to the respective groups HYPO, TSH10, TSH50, TSH100 and CLINICAL HYPO of the corresponding treatment years in relation to number of patients of the entire dataset 1

	HYPO	**TSH 10**	**TSH 50**	**TSH 100**	**CLINICAL HYPO**
	N_{HYPO}	N_{TSH10}	N_{TSH50}	N_{TSH100}	$N_{CLINICAL\ HYPO}$
	$\%_{HYPO}$	$\%_{TSH10}$	$\%_{TSH50}$	$\%_{TSH100}$	$\%_{CLINICAL\ HYPO}$
2018	2185	320	35	9	165
	7.9%	1.2%	0.12%	0.033%	0.60%
2019	2371	345	32	10	149
	8.4%	1.2%	0.11%	0.036%	0.53%
2020	1736	282	24	3	141
	7.4%	1.3%	0.10%	0.013%	0.6%
2021	2054	324	28	3	159
	8.6%	1.4%	0.12%	0.013%	0.66%
2022	1966	314	22	0	175
	8.5%	1.4%	0.095%	0%	0.76%
2023	1352	236	17	8	73
	5.8%	1.0%	0.074%	0.035%	0.32%

Data presented as frequencies. N_X= number of patients in group X; $\%_X$= percentage of patients in group X. N_{2018}= 27'602; N_{2019}= 28'135; N_{2020}= 23'329; N_{2021}= 23'961; N_{2022}= 23'065; N_{2023}= 23'117.

The proportion of measurements with laboratory results for TSH >4.2 µU/mL were comparable over the years 2018-2022. This is similar for the other subgroups, except for 2022, in which there were no results >100 µU/mL for TSH, but at the same time the proportion of TSH results with concomitant too low results for the thyroid hormones was more than 1.5-fold higher than in any other year. In 2023, only 6% of all measurements, around 2% less than in all other years, generated values of >4.2 µU/mL, but the proportion of results of >100 µU/mL was 0.075%, as high as in no other year. However, the proportion of measurements that met the criteria for clinically relevant hypothyroidism was 0.46%, as low as in no other year (Figure 7).

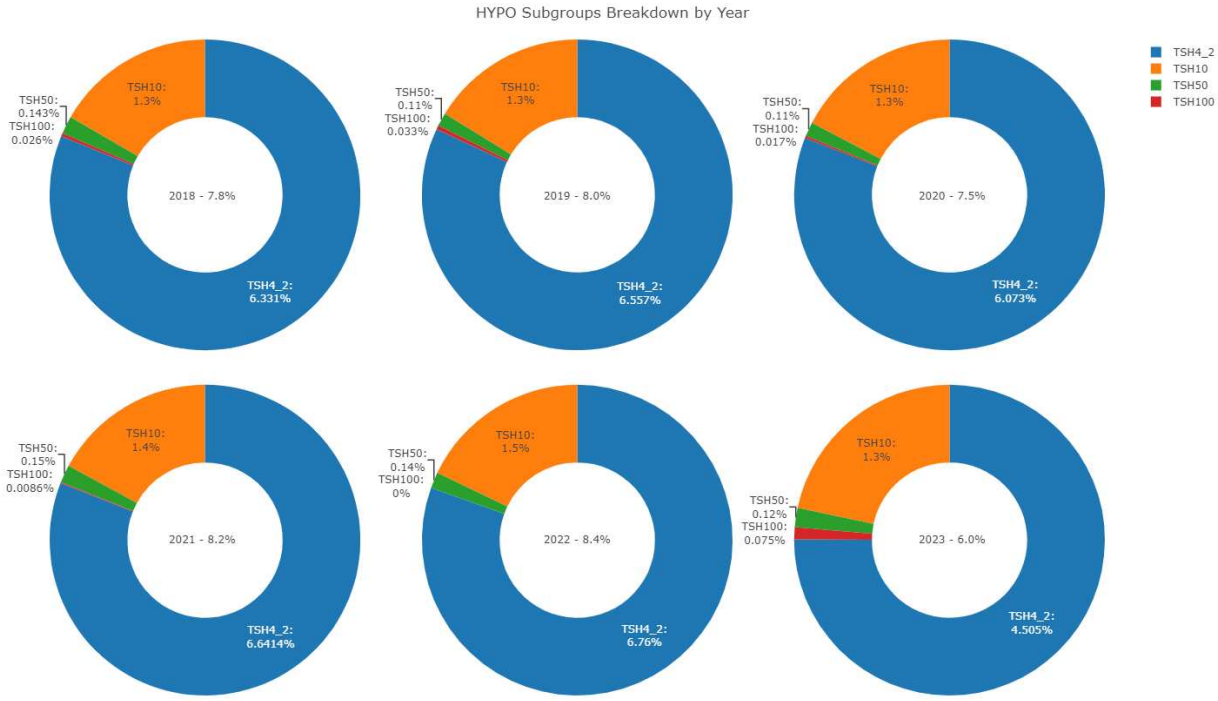

Figure 7. Breakdown of measurements in the TSH4_2-group (TSH >4.2 µU/mL) by year and severity of increase, i.e. TSH10 (>10 µU/mL), TSH50 (>50 µU/mL), TSH100 (>100 µU/mL), presented as frequencies (%). Total proportion of HYPO is presented in the center of each donut.
N_{2018}= 3050, N_{2019}= 3178, N_{2020}= 2595, N_{2021}= 2890, N_{2022}= 2869, N_{2023}= 2002.

It appears that the year 2023 is exceptional, with the lowest number of total measurements and patients as well as individual patients belonging to the HYPO group, but concomitantly a comparably high proportion of patients with TSH levels >100 µU/mL, as in the years 2018 and 2019. This results in a relative increase of the number of measurements meeting the criteria for severe clinical hypothyroidism, when putting the grouped data into the context of our overall dataset.

Also, the year 2022 seems to be exceptional, with no patients with results for TSH levels >100 µU/mL, but still the greatest number of patients and measurements belonging to the group CLINICAL HYPO.

4.3. Test for Normality

For a better understanding of the differences between the years, we will first focus on the TSH values. As discussed in Section 3.7, we test for normality of the TSH values using the Anderson-Darling test. Based on our dataset grouped by treatment years, the tests resulted in *P* values of <0.001 (even smaller than the initially set significance level <0.05), which leads to rejection of normality of TSH values for all years (see Table 6 below). Since measurements of blood values are naturally limited by zero, we applied a data transformation using log (TSH) as a representative and tested again for normality, which also led to rejection of null hypothesis (see also Table 6).

Table 6. Results of normality testing for all TSH and log (TSH+0.01) values of the corresponding treatment years

	TSH *P*†	**Log (TSH) *P*†**
2018	<0.001***	<0.001***
2019	<0.001***	<0.001***
2020	<0.001***	<0.001***
2021	<0.001***	<0.001***
2022	<0.001***	<0.001***
2023	<0.001***	<0.001***

† Anderson-Darling test. Significance levels indicated by *P* <0.05(*), *P* <0.01(**) and *P* <0.001(***).
N_{2018}= 39'169, N_{2019}= 39'574, N_{2020}= 34'738, N_{2021}= 35'098, N_{2022}= 34'186, N_{2023}= 33'475.

Additional graphical analysis of our grouped datasets, such as Q-Q plots, support this result for the whole dataset, as Figure 8 shows, for the individual treatment years. Especially the extreme, high values dominate the plots, and the reference line (red) appears horizontal. This could lead to the assumption that the tail of the distribution is problematic for normality. For the year 2023, this tail seems to be most pronounced.

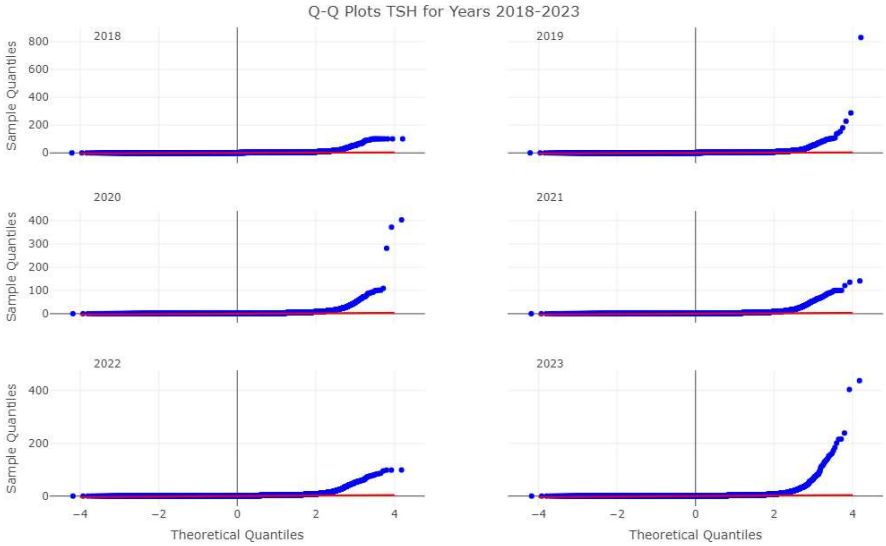

Figure 8. Q-Q plots for all measurements of TSH of dataset 1 of the corresponding treatment years 2018-2023. *N=216'240.*

Limiting the scope to TSH values to a range of 0.1-20 µU/mL, to eliminate the extreme values, changes the Q-Q plots, but the non-linear shape is still not matching the criteria for normal distribution (Figure 9).

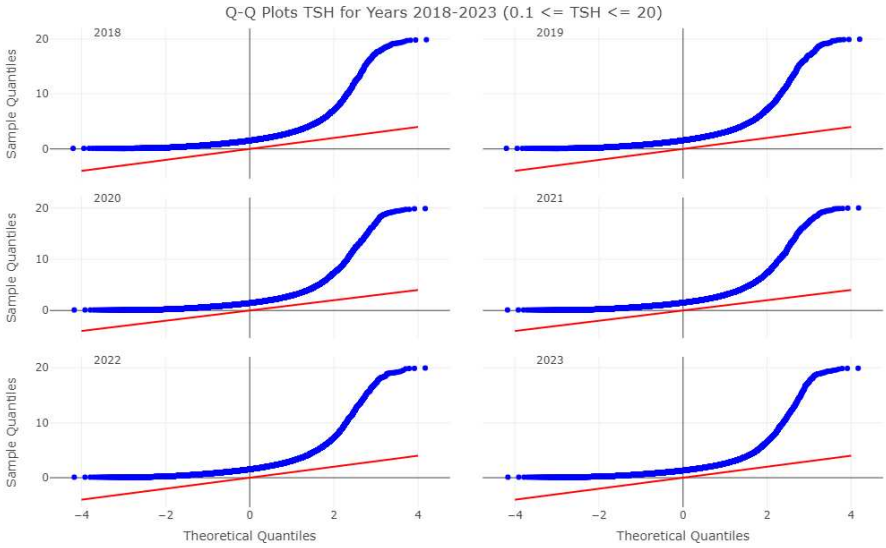

Figure 9. Q-Q plots for all measurements of TSH with values from 0.1-20 µU/mL of dataset 1 of the corresponding treatment years 2018-2023. *N= 208'310.*

The attempt to find normality when looking at log (TSH) is only moderately successful. This approach improves the appearance of the Q-Q plots considerably; however, extremely small or large values remain to appear problematic (Figure 10).

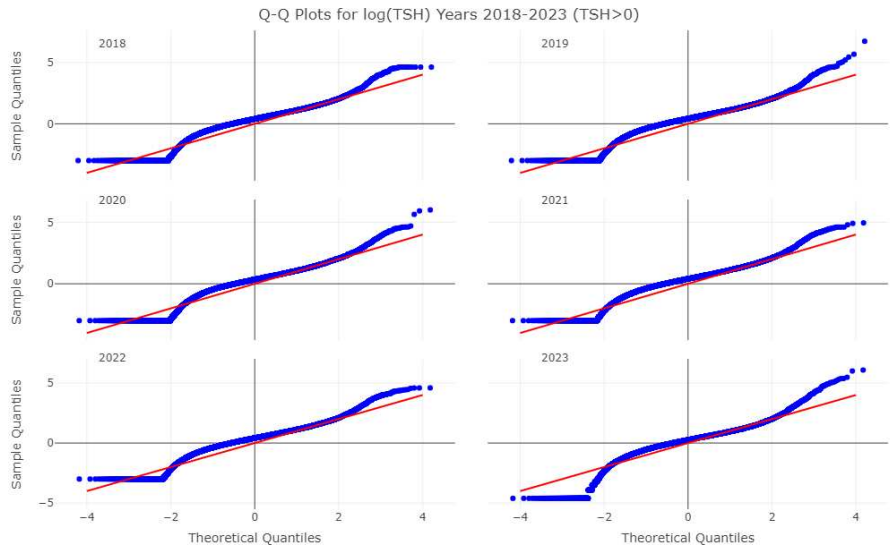

Figure 10. Q-Q plots with logarithmic values for all TSH measurements of dataset 1 of the corresponding treatment years 2018-2023. *N=216'240.*

The closest resemblance to normality is reached when looking at log (TSH) for TSH values at a range of 0.1-20 µU/mL (Figure 11).

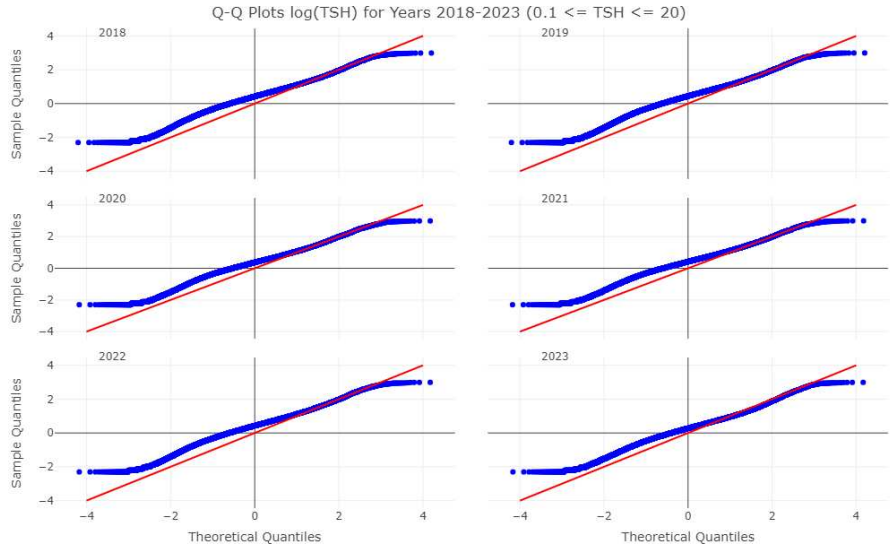

Figure 11. Q-Q plots with logarithmic values of all TSH measurements in a range of 0.1-20 µU/mL of dataset 1 of the corresponding treatment years 2018-2023. *N=208'310.*

This graphical analysis might lead to the conclusion that there might be some sort of normality under the right selection criteria. However, since we are especially interested in high values of TSH in our statistical analysis, as this is characteristic for the disease under investigation, hypothyroidism, this approach to normality in the center of distribution is not helpful to further investigation. As there is not enough statistical evidence to assume normal distribution of TSH values, especially in context of the results presented in Table 6, for our significance level of <0.05, we will proceed with non-parametric statistical tests.

4.4. Statistical Analysis of Clinical Relevance between the Years 2018-2023

Since normality assumption was rejected in the previous section, we focused on non-parametric Mann-Whitney U tests to determine if the distribution of TSH values is comparable between the different treatment years or if structural differences can be identified (see 3.7). In the following tables the resulting *P*-values of the Mann-Whitney U tests in pairwise comparison between the years will be presented.

Table 7. Results of pairwise testing for structural differences with all measurements of TSH of dataset 1 of the corresponding treatment years

	2018†	**2019**†	**2020**†	**2021**†	**2022**†	**2023**†
2018†		<0.001***	<0.001***	0.049*	<0.001***	<0.001***
2019†	<0.001***		<0.001***	0.044*	0.901	<0.001***
2020†	<0.001***	<0.001***		<0.001***	<0.001***	<0.001***
2021†	0.049*	0.044*	<0.001***		0.068	<0.001***
2022†	<0.001***	0.901	<0.001***	0.068		<0.001***
2023†	<0.001***	<0.001***	<0.001***	<0.001***	<0.001***	

† Mann-Whitney U test. Significance levels indicated by P <0.05(*), P <0.01(**) and P <0.001(***).
N_{2018}= 39'169, N_{2019}= 39'574, N_{2020}= 34'738, N_{2021}= 35'098, N_{2022}= 34'186, N_{2023}= 33'475.

When the Mann-Whitney U test is used to compare the different treatment years regarding all measured TSH values, oftentimes it resulted in P values <0.05, showing that there is significant difference between different years in pairwise comparison. This picture appears to be unspecific for the years 2018, 2019, 2021, 2022 (some significant deviations and some similarities to other years). At the same time, the years 2020 and 2023 show to be significantly different from all other years in pairwise comparison, including the comparison 2020 vs. 2023 (Table 7).

Following our initial hypothesis that especially high values of TSH appeared in 2023 which might cause this finding we performed the same tests focusing on data points with TSH values >50 µU/mL (as one example) to analyze if there is a significant difference in distribution for increased TSH values (Table 8).

Table 8. Results of pairwise testing for structural differences with all measurements of TSH with results >50 µU/mL of dataset 1 of the corresponding treatment years

	2018†	**2019**†	**2020**†	**2021**†	**2022**†	**2023**†
2018†		0.056	0.481	0.593	0.144	<0.001***
2019†	0.056		0.480	0.031*	0.002**	0.101
2020†	0.481	0.480		0.208	0.026*	0.028*
2021†	0.593	0.031*	0.208		0.262	<0.001***
2022†	0.144	0.002**	0.026*	0.262		<0.001***
2023†	<0.001***	0.101	0.028*	<0.001***	<0.001***	

† Mann-Whitney U test. Significance levels indicated by P <0.05(*), P <0.01(**) and P <0.001(***).
N_{2018}= 56, N_{2019}= 46, N_{2020}= 37, N_{2021}= 52, N_{2022}= 48, N_{2023}= 39.

The tests for the group TSH 50 no longer show 2020 as a structurally different year in pairwise comparison. Overall, the years 2018 to 2022 appear to not structurally differ as much as before, while 2023 remains to show the most pronounced statistically significant differences (significance level <0.001***) to almost all other years, excluding only 2019.

In the group TSH 100, as an intermediate step to the CLINICAL HYPO group, there were no values reported for the year 2022, so a complete pairwise comparison could not be performed. Therefore, we proceed with analyses of clinical cases.

Table 9. Results of pairwise testing for structural differences with all measurements for TSH of the group CLINICAL HYPO of the corresponding treatment years

	2018†	**2019**†	**2020**†	**2021**†	**2022**†	**2023**†
2018†		0.245	0.276	0.297	0.165	0.004**
2019†	0.245		0.986	0.979	0.854	<0.001***
2020†	0.276	0.986		0.922	0.875	<0.001***
2021†	0.297	0.979	0.922		0.752	<0.001***
2022†	0.165	0.854	0.875	0.752		<0.001***
2023†	0.004**	<0.001***	<0.001***	<0.001***	<0.001***	

† Mann-Whitney U test. Significance levels indicated by P <0.05(*), P <0.01(**) and P <0.001(***).
N_{2018}= 165, N_{2019}= 149, N_{2020}= 141, N_{2021}= 159, N_{2022}= 175, N_{2023}= 73.

When testing within the group of clinical relevance, CLINICAL HYPO, (see 4.2.2), the year 2023 is the only year which shows an overall statistically significant deviation in comparison with every other year from 2018 to 2022 in pairwise comparison. Four of five pairwise comparisons show a significance level of <0.001*** and the remainder a level of <0.01** which is both far below the initially set threshold of P<0.05 (see 3.7). Additionally, there is no other pairwise comparison between any of the years from 2018-2022 which results

in a difference to any reasonable significance level, which additionally showcases the uniqueness of 2023 (Table 9).

Since in general the Mann-Whitney U test only tells us that there is a difference, which could mean both structurally higher or lower values for TSH, a last analysis step is required before we can confirm the initial hypothesis.

Looking at the average TSH value in the CLINICAL HYPO groups of the different years (see Table 10) we conclude that the statistical deviation is due to a significant increase in values of TSH, since the mean TSH is around 1.5 to 2 times higher compared to all other years in the CLINICAL HYPO group. Looking at the overall population, provided for comparison, the number of extreme cases might not be high enough to show an increase in top TSH values when measuring the mean value alone (~35'000 overall measurements vs. ~250 extreme cases per year).

Table 10. Comparison of mean TSH values between the group CLINICAL HYPO and the overall population of dataset 1

	CLINICAL HYPO	**Overall Population**
	Mean TSH ± SD (µU/mL)	Mean TSH ± SD (µU/mL)
2018	24.82 ± 26.13	2.15 ± 3.98
2019	26.84 ± 59.82	2.20 ± 6.05
2020	23.97 ± 33.67	2.09 ± 4.87
2021	23.42 ± 25.95	2.19 ± 3.98
2022	20.57 ± 20.17	2.21 ± 3.75
2023	41.12 ± 48.24	2.03 ± 6.22

Data presented as mean ± standard deviation (SD).
CLINICAL HYPO: N_{2018}= 277, N_{2019}= 237, N_{2020}= 225, N_{2021}= 257, N_{2022}= 348, N_{2023}= 155.
Overall population: N_{2018}= 39'169, N_{2019}= 39'574, N_{2020}= 34'738, N_{2021}= 35'098, N_{2022}= 34'186, N_{2023}= 33'475.

This thesis' central hypothesis – that there were more cases of clinically pronounced hypothyroidism with significantly increased TSH values in 2023 – which was initially based on clinical observations, is now statistically significantly supported.

4.5. Individual Case Analyses of Patients with Severe Clinical Hypothyroidism

Those patients of our overall dataset, who fulfilled the criteria of severe clinical hypothyroidism with TSH values >100 µU/mL and reduced thyroid hormone levels, were used to create the second dataset mentioned in Section 3.3.2, which serves as the basis for further individual case analyses. This dataset contains more comprehensive information and is aimed at a better understanding of potential reasons for such a high occurrence of severe forms of hypothyroidism, as discussed in Section 4.4. As already mentioned in Section 3.4.2, the one case affected by non-disclosure was, together with its two corresponding measurements, excluded from further analyses. The contained cases were analyzed based on patient ids, not measurements anymore. The patients were analyzed regarding their symptoms, their premedical history and treatment during their hospital stay.

4.5.1. Baseline Characteristics of the Second Dataset

Dataset 2 comprises 41 measurements, belonging to 26 patients, that fulfill the abovementioned criteria of severe, clinically relevant hypothyroidism. Since in the year 2022 no measurements of TSH levels >100 µU/mL were registered, it contains only measurements from the years 2018-2021 and 2023. Of the included 26 patients, 20 were females and six males, resulting in a gender ratio of 76.92%/23.08%, which is significantly different from that of the overall dataset, with a clear female predominance. For the years 2019 and 2020, no male patient was listed with measurements matching our criteria.

The newly formed subpopulation had a mean age of 56.16 years ± 28.19, with a median of 65 years. The youngest patient was newborn, the oldest affected patient 88 years old. The following Figure 12 shows the distribution of the patients' age in context of the measured maximum TSH value and gender.

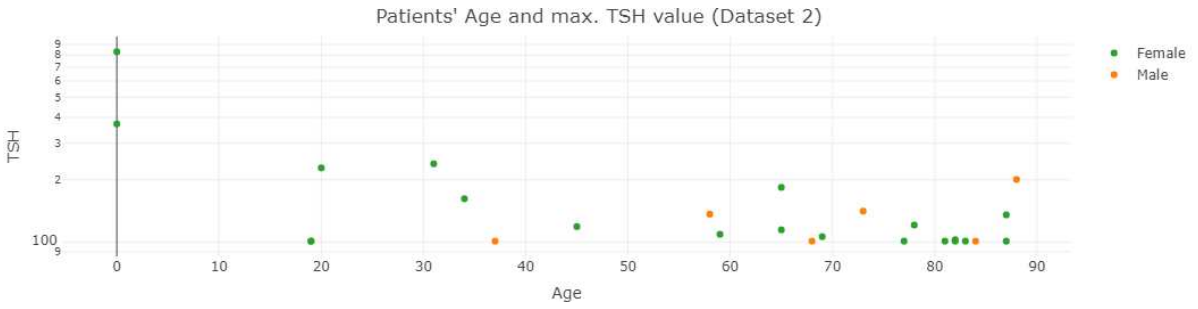

Figure 12. Distribution of patients' age and maximum measured TSH value (log-scale) in dataset 2. Age expressed in years, TSH in µU/mL. Patient data presented as points. *N= 26*.

Compared to the overall population, the population affected by severe clinical hypothyroidism appears to be younger, which could be influenced by the two newborn patients. In our small dataset of patients in the CLINICAL HYPO group with TSH >100 µU/mL, female patients can be observed in any age group, while male patients are mostly part of the elderly.

The maximum TSH values of this population are between 101-830.3 µU/mL. The measurements of this dataset have a mean TSH level of 165.78 ± 149.25 µU/mL and a median for TSH of 111.78 µU/mL. The mean FT3 level is 1.67 ± 0.59 pmol/L and the median of all FT3 values is 1.64 pmol/L. The mean of all FT4 values is 4.95 ± 2.31 pmol/L, the median for FT4 is 5.15 pmol/L. These values are outside the respective reference ranges and deviate from our overall population, but this was to be expected as this was our criterion for sampling for this dataset.

Three patients in our second dataset died during the respective hospital stay we are analyzing, and another one was transferred to the palliative care unit. It is not possible to determine from the documentation whether the severe hypothyroidism is, or is related to, the cause of death.

4.5.1.1. Previously diagnosed Thyroid Diseases

Of all patients, nine patients had no previously diagnosed thyroid disease and the other 16 patients had one or more thyroid-related diseases.

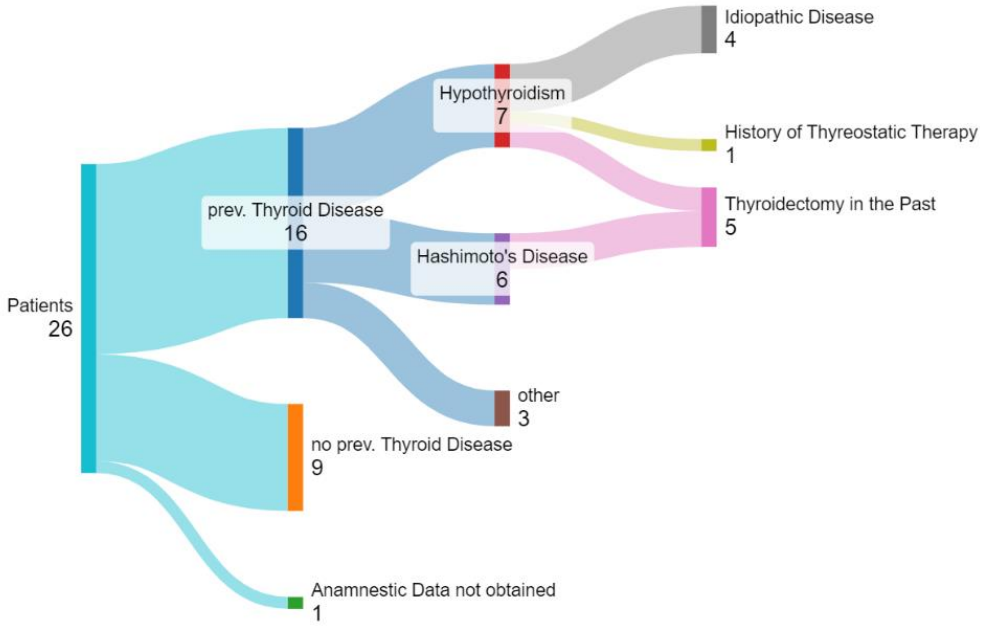

Figure 13. Analysis of all patients of dataset 2 regarding previous thyroid diseases and past thyroid interventions. Data presented as frequencies. *N=26*.

As Figure 13 shows, of these 16 previously diagnosed patients, seven patients had been diagnosed with hypothyroidism in the past, two of them had underwent thyroidectomy in the past and one patient had a history of thyreostatic treatment. Six patients had previously been diagnosed with Hashimoto's Disease, and three of them had additionally had thyroidectomy. There was also one patient each with a history of thyroid follicular carcinoma, Graves' Disease and nodular goiter. One patient's medical history was not obtained.

4.5.2. Potential Causes for the Severe Clinical Hypothyroidism

The two newborn patients of our second dataset, suffering from congenital hypothyroidism, had abnormal newborn screening values, one was also affected by icterus gravis. They were therefore admitted, by their pediatrician, to hospital for further diagnosis and initiation of treatment. For one of the patients, it is known that the cause for severe hypothyroidism was thyroid agenesis, as no thyroid tissue could be identified on ultrasound.

In several cases of hypothyroidism of this dataset 2, iatrogenic causes could be held responsible for the severe clinical hypothyroidism. One patient without previous diagnoses of the thyroid gland was receiving the thyreostatic drug thiamazole at time of admission and another was prescribed with amiodarone due to cardiac arrythmias. One patient already receiving thyroid hormone replacement was concurrently under therapy with amiodarone, too (see Figure 14, p. 43). These patients, most probably, developed hypothyroidism as a result of that treatment. Their clinical situations improved rapidly after changing the cardiologic therapy and initiating or adjusting thyroid hormone substitution. Another patient, who received thiamazole for Graves' Disease, showed clinical improvement after thyreostatic treatment was reduced and low-dose therapy with levothyroxine was initiated.

Of the patients already diagnosed with hypothyroidism, three had a history of invasive thyroid treatment. Two of them had already underwent thyroidectomy in the past, and one patient had previously been treated with thyreostatics. However, it is unclear whether these treatments caused or exacerbated the hypothyroidism. To be able to examine causality, chronology of events needs to be explained in more detail, but there is a certain probability that there might be a connection. The same applies to the patients with Hashimoto's disease who have also underwent thyroidectomy in the past. It is very likely that this was the surgical attempt to treat the underlying disease, but it could also be that this has caused or further worsened the thyroid hormone deficiency.

Of all patients of our dataset, 20 patients did not have any history of cancer. Five patients had a history of one or more tumorous diseases. One patient had received the substance pembrolizumab, a monoclonal antibody against the PD1-receptor, used in treatment of breast cancer, and the other four patients were treated without the use of immunotherapy. At the time of admission, no patient was currently under the treatment of targeted tumor therapy. For one patient the past medical history was not obtained. It cannot be ruled out that this PD-1 agent has interfered with the finely regulated thyroid axis, but here, too, no statement can be made about causal relationships.

4.5.2.1. Non-Adherence of Patients as a Potential Cause for the Severe Clinical Hypothyroidism

Of the 26 patients, 14 patients had already received a diagnosis of a thyroid disease leading to hypothyroid state and therefore the need of hormone replacement therapy. Seven of

them, half of this group, were taking their thyroid medication regularly, as prescribed. Six patients were receiving monotherapy with levothyroxine, one patient was treated with a combination of levothyroxine and liothyronine. The other seven patients, the other half of those needing thyroid hormone substitution, were taking none or not regularly taking the prescribed medication at the time of their hospital admission.

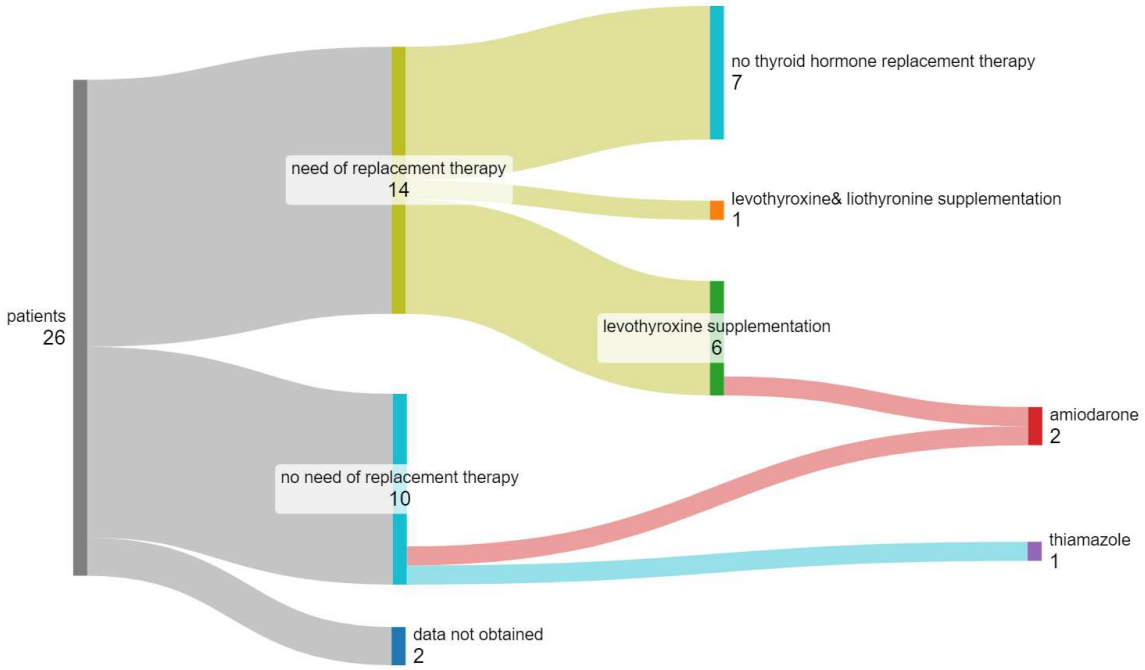

Figure 14. Analysis of all patients of dataset 2 regarding the need of thyroid hormone replacement therapy, due to already diagnosed thyroid disease, and concomitant therapy with amiodarone and thiamazole. Data presented as frequencies. *N=26.*

The ten patients without thyroid related disorders were all not taking any thyroid hormones (no need of replacement therapy). For two of our patients of dataset 2 the anamnestic data was not completely obtained and information about current medication is unavailable (Figure 14).

Of all patients who refused to take their thyroid hormones as prescribed, four of them were registered in the year 2018, the three other patients in the year 2023. Six of the patients did not follow their therapy at all, one patient was not adhering to the therapy regularly, and refused to be treated with intravenous levothyroxine therapy during hospitalization.

4.5.3. Symptoms of the Patients with Severe Clinical Hypothyroidism

The patients of dataset 2 presented with a great variety of different signs and symptoms, which are presented in Figure 15. It is important to emphasize, as already mentioned in Section 3.5, that the anamnestic data was obtained in a setting of an emergency department and most often patients present only with the symptoms of their subjective importance. Not always there is enough time to evaluate for any other symptoms, especially if one does not follow a specific working diagnosis, or documentation is incomplete. This should be kept in mind as a limitation of our data, when interpreting the findings.

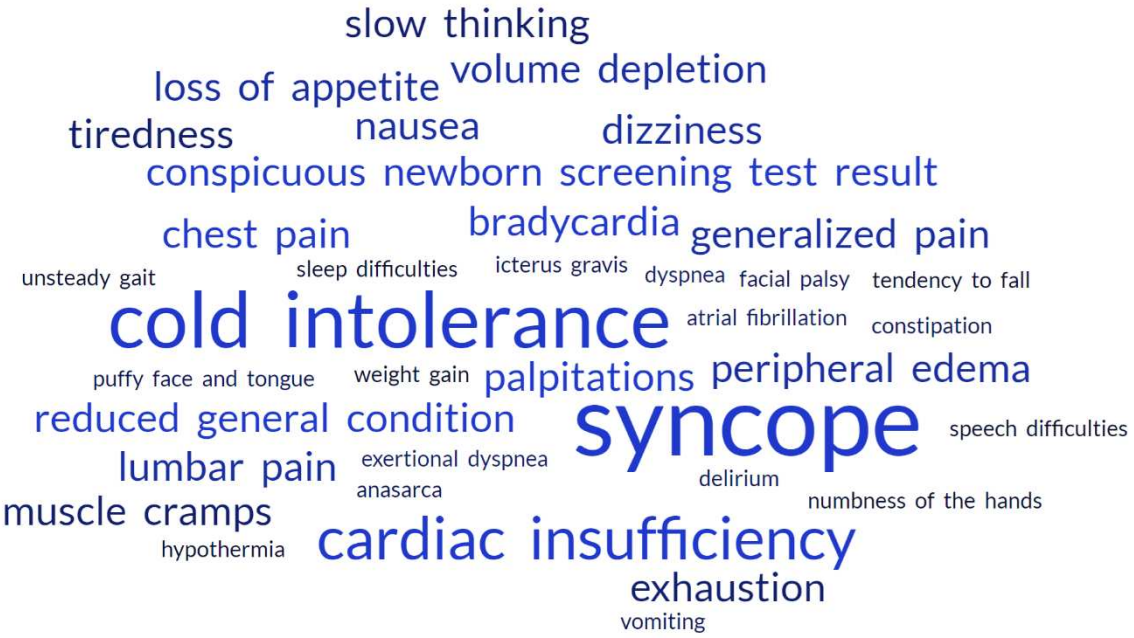

Figure 15. Signs and symptoms of the patients with severe clinical hypothyroidism of dataset 2. The font size indicates the frequency of occurrence, with small font size indicating less frequent occurrence and bigger font sizes indicating more frequent occurrence. *N=26 patients with multiple symptoms each.*

Of all patients, only 20 presented to the hospital emergency department with clinical signs and symptoms that could be attributed, at least retrospectively, to hypothyroidism. Six of the patients were admitted to hospital with symptoms that were clearly not attributable to hypothyroidism. They presented with upper gastrointestinal bleeding due to duodenal ulcer, ulnar epicondylitis, hydronephrosis with suspected ureteral stenosis after radiation therapy, macrohematuria of unknown origin and in preparation for a planned ERCP examination for cholelithiasis. In these patients, the finding of extremely deranged thyroid values is highly likely to be an incidental finding. To improve readability, those symptoms are not mentioned in Figure 15.

In five cases, the combination and severity of clinical signs and symptoms, at least retrospectively, could lead to the suspicion of the most severe form of hypothyroidism, myxedema coma. One patient presented with chest pain, bradycardia, dizziness, nausea, fatigue and muscle cramps. During hospitalization, Hoffmann Syndrome, a highly uncommon complication of hypothyroidism presenting with painful muscle pseudohypertrophy (29), was suspected. The patient, who was hospitalized because of syncope, palpitations and cold intolerance, was diagnosed with severely manifest hypothyroidism during clinical stay. Another patient was brought to the hospital by the emergency services due to severe end-stage heart failure (with known mitral valve insufficiency II-III°), dyspnea, bradycardia, hypothermia (32.9°C), anasarca, peripheral edema, generalized pain and impaired consciousness. The clinical condition of this patient deteriorated dramatically, and the patient died on the same day. The main cause of death could not be fully determined from the available documentation. The patient, who complained about fatigue, numbness of hands, cold intolerance, dizziness, nausea, impaired concentration, speech and sleep, weight gain, generalized pain, puffy face and tongue, peripheral edema and muscle cramps, exhibited may of the signs and symptoms that can occur with myxedema coma. This initial working diagnosis was proven after further diagnostics and the appropriate treatment was initiated. Another patient with the diagnosis of severe hypothyroidism “only” complained of tiredness despite adequate sleep. This patient had previously seen her general practitioner, who detected the abnormal TSH level and therefore admitted her to the hospital.

We find that these cases only occurred in the years 2018, 2020 and 2023, which confirms the impression, at least partially, that there were cases of clinically pronounced hypothyroidism again in 2023 after a long period of time.

4.5.4. Treatment of Patients with Severe Hypothyroidism during Hospitalization

Of all 26 patients, 17 patients received an endocrinological consultation during their hospital stay. Nine patients were treated by their attending physician only. It is noticeable that in the year 2018 all patients except one did receive a specialist’s consultation and also in the year 2023 every patient was additionally seen by an endocrinological specialist. In comparison, during both years 2020 and 2021 one patient each was additionally examined by a secondary, consulting physician. In 2019 no additional specialist consultation took place.

In almost all cases, oral levothyroxine monotherapy was initiated or the current hormone replacement therapy was adjusted. The patients' long-term medication was examined for drugs that could interfere with thyroid function and, if necessary, the relevant substances were discontinued, changed or reduced in dosage after consultation with a respective specialist.

In addition, five patients had to be treated with acute short-term intravenous replacement therapy with levothyroxine under the controlled conditions of an intensive care unit. These cases were only documented for the year 2023. Whether the reason for this is the "more severe" clinical manifestation or raised awareness of this treatment option, remains unclear.

5. DISCUSSION

Of this study population, 7.67% have TSH levels greater than 4.2 µU/mL, pointing towards the possibility of hypothyroidism. 0.69% of all measurements in this dataset meet the criteria for clinical hypothyroidism, with TSH values above and thyroid hormone values below the respective reference ranges. The remaining 6.98% of the study population with elevated TSH levels therefore meet the criteria of subclinical hypothyroidism.

Our values exceed the findings of the meta-analysis of Garmendia et al. for the European population, which gives a prevalence of 0.37% for overt and 3.8% for subclinical hypothyroidism (19). Since 7.67% of population with possible hypothyroidism might seem an unusually high portion for a completely random sample, we must consider that we are dealing with a dataset consisting of laboratory values of hospital patients for whom the corresponding value was requested by medical personnel. Hence, a general bias towards a higher proportion of increased values is to be expected. Due to this circumstance, our study population already contains a certain sampling bias and is therefore not without restriction transferable to an overall population with equally diseased and healthy patients. Against this background, a higher incidence of the disease in an anticipated "sicker" population is not surprising and consistent with our results. The results of the 2019 meta-analysis of Mendes are aimed at finding a prevalence for undiagnosed hypothyroidism and are therefore with an overall prevalence of 4.70% (22) lower than our results, as we are including both previously and newly diagnosed hypothyroidism in our analysis. The Colorado prevalence study from the year 2000, evaluating the prevalence of elevated TSH levels, in their case with a threshold of 5.1 mIU/L, found those in 9.5% of their population (25) and the Wickham survey, published in 1977 in the UK, found that 7.5% of their female and 2.8% of their male study population had elevated TSH levels, their threshold was set at 6.0 mu/L (23). As these studies were each conducted using different criteria, these values can only be compared to a limited extent, but still, the results can be used to get an idea of approximate frequencies of the disease hypothyroidism.

The proportion of measurements and patients with test results for TSH >4.2 µU/mL are comparable between the respective treatment years 2018-2023. The subgroups formed according to increasing TSH values show the same tendency, except for the year 2022, in which there are no results for TSH >100 µU/mL.

For the year 2023, around 2% fewer measurements than in all other years, approximately 6% of all, with test results for TSH >4.2 µU/mL are documented. However, at 0.075%, the proportion of results of >100 µU/mL is higher than in any other year. The

proportion of clinically relevant hypothyroidism is the lowest of all treatment years in comparison, accounting for 0.46% of all measurements taken, whereas the highest proportion, 1.02%, is documented for the year 2022.

Pairwise carried out Mann-Whitney U tests for TSH show a picture of highly unspecific statistically significant differences between the different treatment years when looking at the complete range of TSH measurements. The analyses of laboratory results belonging to the group of clinical hypothyroidism show an overall statistically significant deviation of the years 2023 in comparison with every year from 2018 to 2022 in pairwise comparison, to significance levels of <0.001*** and <0.01**. The mean TSH value for the group of clinical hypothyroidism of the year 2023 significantly differs from that of all other observed treatment years (41.12 ± 48.24 µU/mL for 2023 vs. 20.57-26.84 ± 20.17-59.82 µU/mL for 2018-2022). The extreme values do not seem to derange the mean TSH value of the overall population of 2023 (probably due to the small number of severe cases in comparison to the entire population), since statistical measures for the laboratory parameters TSH, FT3 and FT4 carried out over all measurements of the whole dataset show no significant differences in temporal analysis.

This thesis' central hypothesis – that there were more cases of clinically pronounced hypothyroidism with significantly increased TSH values in 2023 – is statistically significantly supported.

This thesis' second dataset, consisting of 26 patients with TSH results >100µU/mL and thyroid hormone levels below the reference range, representing the population of severe clinical hypothyroidism of our total study population, show a gender ratio of 76.92% female and 23.08% male patients, suggesting that in our study population, severe clinical hypothyroidism occurs about 3.33 times more frequently in females than in males. This female predominance is somewhat consistent with findings in the literature, although a comparable result for our particular sampling criteria could not be found. From the literature, it was found that hypothyroidism is generally 10 times more common in women than in men (8).

In general, as already discussed in Section 3.5, our dataset has some limitations due to the characteristics of data and the nature of collection, as we are analyzing data collected in daily clinical practice and not for inclusion in a study. Therefore, we have to accept some uncertainties, such as when data is not available, and that due to pseudonymization of data, there is a possibility that the same patient could be registered as multiple PNRs due to several clinical stays, which could potentially lead to a biased result. The analysis of the baseline

characteristics of the second dataset, see 4.5.1, also aims to make the risk of bias assessable in this way detailing the data again, but is also limited due to anonymity of data. This must be considered when evaluating the results and should be seen as a general limitation of this study.

In many of the cases analyzed, it is suspected that the occurrence of hypothyroidism can be attributed to (or is at least exacerbated by) medical therapies, undertaken for different reasons. Of the 26 patients in our dataset, five had undergone thyroidectomy and one had been treated with thyreostatic drugs. Three patients were concurrently treated with drugs such as amiodarone or thiamazole, which can potentially impair thyroid function. One patient was treated with pembrolizumab due to a tumor diagnosis. All these therapies are known to be potential reasons for the occurrence of iatrogenic hypothyroidism, in some cases to a not inconsiderable extent (6). It is not the nature of a retrospective observational study to specify causalities, but certainly these findings highlight the need of clinicians to be aware of possible interactions. They must regularly observe and monitor patients with their respective diseases and treatments in order to react to and treat potential adverse effects in a timely manner.

In 20 of our patients, the symptoms with which they presented to the emergency department could be attributed to hypothyroidism, although they were often non-specific and involved several distinct organ systems. In the retrospective analysis, the combination and severity of clinical signs and symptoms in five cases seems to suggest a possible suspicion of myxedema coma.

However, it is important to emphasize at this point that the focus of this analysis was clearly, and above all exclusively, on hypothyroidism with its possible clinical presentation. In everyday clinical practice, it is much more important to assess the patient, recognize and prevent vital threats and find the cause of the clinical condition as quickly as possible from a variety of possible differential diagnoses. It must be borne in mind that patients often suffer from not only one disease at the same time, that drug interactions and adverse effects may be involved and, above all, that a thorough medical history and physical examination may reveal symptoms and signs that may be of lesser importance to the patient but of high clinical relevance.

It was striking that 50% of patients who had to adhere to substitution therapy with thyroid hormones due to a corresponding diagnosis refused or discontinued the treatment autonomously and subsequently developed a pronounced clinical picture of severe thyroid hormone deficiency. As these were not only findings in 2023, but occurred most frequently in 2018 and 2023, the patients' non-adherence to therapy cannot be exclusively responsible for

the increase in severe hypothyroidism in the latter year, but further pronounces the subjective impression that these occurrences are exceptional in 2023 (after 4 years without this observation). It is hardly understandable why patients would reject the relatively simple and non-invasive, though lifelong, treatment of a curable disease they have already been diagnosed with.

We cannot ask about the individual patient's reason for this decision, but the 2012 ETA Guidelines briefly addressed this issue, pointing out that awareness of hypothyroidism as a chronic disease needs to be raised and that patients often feel unwell and unhappy due to the lifelong dependence on hormone replacement therapy (2). Lack of patient adherence to therapy has been raised in research as a possible reason for not reaching therapeutic goal, along with "prescription or intake of inadequate doses, interaction with supplements or medications, concurrent medical conditions" (Chaker et al., 2017), with some of them being already addressed in this section (6).

This study provided a brief insight into the incidence of elevated TSH levels and severe clinical hypothyroidism in a German population of hospitalized patients. The inclusion in the general context is rather limited. There is a need for further scientific research to gain a better understanding of the prevalence of hypothyroidism among the European population.

There is also a need to raise awareness of thyroid disorders to prevent cases of hypothyroidism going unrecognized and patients suffering from a variety of symptoms that do not improve without appropriate treatment. There is a great responsibility on physicians to recognize patients who are at risk of developing or have recently developed thyroid disease and to consider hypothyroidism even, or especially in the presence of nonspecific signs and symptoms.

As TSH is a laboratory parameter that is relatively inexpensive and easy to determine, further research could aim at defining specific patient groups at higher risk of developing hypothyroidism and implementing screening programs. Especially today, at a time where medicine is increasingly focusing on the prevention of diseases rather than treating them, more attention should be paid to thyroid diseases.

However, all research and new findings are only of limited use if patients are not adequately informed about their illness and involved in their treatment. The high number of patients in our study population who did not adhere to the prescribed therapy and subsequently suffered a clinical deterioration is alarming. What ultimately led these patients to make this

decision will remain unclear, but it is possible that dissatisfaction with the therapy and its success, frustration about this lifelong “commitment” to therapy or lack of understanding led to this decision. Overall, it is the obligation of every healthcare professional to help ensure that patients are educated about their disease to facilitate an understanding of the risks of severe hypothyroidism and the absolute necessity of adherence to therapy. Adherence to life-long therapy reduces the incidence of severe, preventable hypothyroidism for patients with already established diagnosis.

6. CONCLUSIONS

- The results of this study have shown that our main hypothesis, specifically the perception of an increase in extreme cases of hypothyroidism with severely elevated TSH levels in 2023 compared to previous years, can be statistically significant supported. For the year 2023, fewer measurements overall, but controversially more results with severely elevated TSH levels >100 µU/mL, were recorded compared to any previous year analyzed.

- We further found that the incidence of elevated TSH values of more than 4.2 µU/mL in our study population, patients from a German hospital observed over the years 2018-2023, was 7.67%. Of all measurements analyzed during this time span, 0.69% meet the criteria for clinical hypothyroidism, 6.98% reflect results indicating subclinical hypothyroidism.

- Within our group of clinical severe hypothyroidism, the disease occurs about 3.33 times more frequently in women than in men. In 38.46% of all severe cases of hypothyroidism, we could suspect that medical treatments were involved in the initiation or exacerbation of the hypothyroidism and that these are iatrogenic cases of hypothyroidism. Of all patients in our severe clinical subpopulation, 50% of patients requiring hormone replacement therapy did not adhere to the prescribed therapy. The signs and symptoms of six patients of the filtered dataset were not relatable to the deterioration of thyroid function. The other 20 patients presented, at least in retrospective analysis, with a great variety of symptoms leading to the suspicion of hypothyroidism.

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8. SUMMARY

Objectives: Hypothyroidism is a worldwide non-communicable disease with incidence among the European population of 4.7-7.5% with a potentially high number of undetected cases and a higher occurrence among females. It was the impression of healthcare workers of a German hospital, in the region of Upper Franconia, Bavaria, that there was an increase of frequency of cases of extreme hypothyroidism in the year 2023 compared to previous years. It is our goal to validate this impression with statistical methods, comparing 2023 with the other observed years 2018-2022.

Materials and methods: 216'240 data points, representing laboratory results of patients during a hospital stay, are included in the dataset for statistical analysis. This dataset is grouped by treatment years and clinical relevance using the respective measurements for the parameters TSH, FT3 and FT4, if available. TSH value was used for statistical significance testing of structural differences in distributions between the years. – Extreme cases were identified and a case study was performed on a smaller dataset, but with more extended information.

Results: In our study population, 7.67% of all measurements taken resulted in TSH values >4.2 µU/mL and are therefore above the reference range. Of all measurements, 0.69% meet the criteria for clinical hypothyroidism, with additionally low thyroid hormone levels. We can confirm literature results that hypothyroidism occurs more often in female population.

Statistically significant evidence is provided that indeed cases in 2023 show structurally higher TSH values, supporting the observed increased severity in cases. The case analysis showed that surprisingly 50% of these patients were non-adherent to therapy, although being previously diagnosed with hypothyroidism.

Conclusion: Looking at the average TSH values for the different treatment years 2018-2023, the values show resemblance. However, in an analysis of cases with increased severity the year 2023 was established as outstanding. Further analysis showed that for some cases, based on our available dataset, the reasons could not be clearly determined. Other cases could be attributed to medical therapies directed for other conditions, and about half of the cases are coinciding with probably causal non-compliance with already prescribed therapy for hypothyroidism.

9. CROATIAN SUMMARY

Naslov: Incidencija hipotireoze u bolnici Coburg 2018-2023

Ciljevi: Hipotireoza je nezarazna bolest rasprostranjena diljem svijeta, s incidencijom među europskom populacijom od 4,7-7,5%, te potencijalno velikim brojem neotkrivenih slučajeva. Bolest se češće javlja kod žena. Zdravstveni djelatnici jedne njemačke bolnice u regiji Gornja Frankonija, Bavarska, imali su dojam da je u 2023. godini došlo do povećanja učestalosti slučajeva ekstremne hipotireoze u usporedbi s prethodnim godinama. Naš cilj je potvrditi ovaj dojam statističkim metodama, uspoređujući 2023. godinu s ostalim promatranim godinama od 2018. do 2022.

Materijali i metode: Za statističku analizu korišten je skup podataka koji sadrži 216.240 mjerenja laboratorijskih rezultata pacijenata tijekom boravka u bolnici. Ovaj skup podataka grupiran je prema godinama liječenja i kliničkoj relevantnosti koristeći odgovarajuće mjerenja za parametre TSH (tireotropni hormon), FT3 (slobodni trijodtironin) i FT4 (slobodni tiroksin), ukoliko su dostupni. Vrijednosti TSH korištene su za testiranje statističke značajnosti strukturnih razlika u distribucijama između godina. Ekstremni slučajevi su identificirani, a studija slučaja provedena je na manjem skupu podataka s više detaljnih informacija.

Rezultati: U populaciji naše studije, 7,67% svih mjerenja rezultiralo je vrijednostima TSH >4,2 μU/mL, što je iznad referentnog raspona. Od svih mjerenja, 0,69% ispunjava kriterije za klinički hipotireoidizam, s dodatno niskim razinama hormona štitnjače. Potvrđujemo rezultate iz literature da se hipotireoza češće javlja kod ženske populacije. Statistički značajni dokazi pokazuju da slučajevi u 2023. godini zaista imaju strukturno više vrijednosti TSH, podržavajući opaženu povećanu težinu slučajeva. Analiza slučajeva pokazala je da je iznenađujuće 50% pacijenata bilo neadherentno terapiji, iako su prethodno dijagnosticirani s hipotireozom.

Zaključak: Promatrajući prosječne vrijednosti TSH za različite godine liječenja od 2018. do 2023., vrijednosti pokazuju sličnost. Međutim, analiza slučajeva s povećanom težinom u 2023. godini istaknula je ovu godinu kao značajno drugačiju. Daljnja analiza pokazala je da se za neke slučajeve, na temelju dostupnog skupa podataka, uzroci nisu mogli jasno utvrditi. Drugi slučajevi mogli bi biti povezani s medicinskim terapijama usmjerenim na liječenje drugih stanja. Otprilike polovica slučajeva vjerojatno je bila posljedica nepoštivanja već propisane terapije za hipotireozu.