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A Retrospective Study on Thyroid Disease Unsupervised Anomaly Detection.

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Abstract:

Introduction:

Thyroid illness is a prevalent endocrine ailment that impacts the synthesis and control of thyroid hormones. Enhancing patient outcomes can be achieved by early detection of thyroid problems. In order to find atypical instances and investigate thyroid status determinants, the current work sought to perform unsupervised anomaly detection on data related to thyroid disease.

Methods:

A dataset of 6916 patient records with clinical and demographic data was used for a retrospective review. To find unusual records, two outlier identification algorithms showing local Outlier Factor and Isolation Forest were used. The predictors of thyroid medication use (on thyroxine) and thyroid disease status were analyzed using logistic regression and Cox regression using SPSS version 27.

Results:

250 records (3.6%) were flagged by the outlier identification algorithms as possible anomalies. Between outliers and typical cases, there were notable differences in a number of characteristics. Goitre, pregnant women, lithium, and query_on_thyroxine were found to predict on thyroxine use by logistic regression. After controlling for confounders, Cox regression revealed that older age, pregnancy, and query_on_thyroxine were risk factors for thyroid illness. It was reasonable to assume that proportionate hazards were satisfied.

Conclusion:

Unsupervised anomaly detection found a tiny subset of patient records with unusual features related to thyroid conditions. The use of thyroid medications and the state of the disease were linked to a number of sociodemographic and clinical parameters. More information on outlier instances may be able to clarify uncommon conditions and validate unusual results. The retrospective approach and the possibility of inadequate records are among the limitations.

Keywords: thyroid disease, anomaly detection, logistic regression, Cox regression, medical outlier, retrospective study

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Introduction:

Thyroid diseases are prevalent endocrine abnormalities that impact the thyroid gland's capacity to generate vital hormones responsible for regulating metabolism. Triiodothyronine (T3) and thyroxine (T4), which are produced by the thyroid gland in the lower front of the neck, are thyroid hormones that aid in controlling growth and development, the operation of numerous organs, protein synthesis, and the metabolism of calcium(Agyei et al. 2024; Ak Sivrikoz, Deveci, and Yildirim 2024). The overproduction or underproduction of these hormones by the thyroid gland can lead to thyroid disorders, which disturb the body's normal hormone balance. Thyroid nodules or goiters, which are noncancerous thyroid growths, thyroid cancer, and hyperthyroidism, or an overactive thyroid, are the most common thyroid illnesses. When the thyroid gland overproduces thyroid hormones, the result is hyperthyroidism, which accelerates metabolism(Alqaryan et al. 2024; Alreshidi et al. 2024; Baffa et al. 2024). Graves' disease, a condition in which the thyroid is attacked by the immune system and overproduces hormones, is one of the common reasons.

When the thyroid gland produces insufficient thyroid hormones, the metabolism slows down and hypothyroidism results. Hashimoto's thyroiditis, an autoimmune illness that gradually destroys the thyroid gland, is the most common cause of primary hypothyroidism(Begum et al. 2024). Goiters are swollen thyroid glands, whereas thyroid nodules are lumps or tumors inside the thyroid tissue. Twenty million Americans are thought to suffer from thyroid disorders or malfunction overall. Thyroid diseases can arise due to a multitude of circumstances(Budhram and Flanagan 2024; Cao et al. 2024). Thyroid issues are five to eight times more common in women than in males, and the risk increases with age. A family history of autoimmune illnesses or thyroid disease increases the likelihood of developing these conditions due to genetic factors(Chen et al. 2024; Guan et al. 2024).

Due to its effects on the immune system, radioactive iodine therapy for hyperthyroidism or diseases including type 1 diabetes, rheumatoid arthritis, and celiac disease can also cause thyroid problems(Hoshina et al. 2024; Hu et al. 2024). Living in places where dietary iodine deficiency occurs increases the risk of goiter and hypothyroidism. Iodine is an essential mineral for the synthesis of thyroid hormone. Perchlorate from drinking water and other environmental pollutants have also been suggested as potential triggers. Depending on the particular illness, thyroid problems can present with a variety of signs and symptoms. In spite of a normal appetite, anxiety, tremors, heart palpitations, heat sensitivity, and diarrhea, weight loss is a common symptom of hyperthyroidism(Hu et al. 2024).

Weight gain, exhaustion, dry skin, feeling cold, constipation, and irregular menstruation are common symptoms of hypothyroidism. A tumor at the front of the neck may be identified as a goiter or nodules. When thyroid cancer is progressed, it might create nonspecific symptoms like enlarged lymph nodes or a chronic cough, but it can also spread to other parts of the body(Ji et al. 2024). The underlying thyroid issue is diagnosed with the aid of laboratory testing that identify abnormalities in thyroid hormone, antibodies, and imaging tests. Depending on the illness, treatment options include radioactive iodine, thyroid hormone supplements, antithyroid medications, or surgery. Given that patients respond differently to treatments, close observation is also required(Jin et al. 2024). While the majority of thyroid illnesses exhibit distinctive clinical symptoms, others do not exhibit normal disease histories or symptom patterns. Such cases are difficult to identify since they don't fit the typical diagnostic mold.

Referred to as outliers, these instances are distinct or atypical in comparison to other instances within the specified population or dataset. Errors, uncommon circumstances, or biological variation among subgroups can all lead to outliers. It is more difficult to assess the actual breadth and diversity of disease presentation when outliers are not appropriately identified. This has an impact on the precision of diagnoses, the capacity for risk classification, and treatment choices made for specific patients. By applying algorithms to medical information for automatic identification, data-driven systems that leverage machine learning can help with outlier discovery(Kang et al. 2024; Legouy et al. 2024).

Unsupervised anomaly detection uses descriptive patterns alone without the use of predefined classification categories to screen unlabeled data and identify anomalous or rare occurrences that deviate significantly from the norm(Legouy et al. 2024). Algorithms evaluate outliers solely on the basis of intrinsic properties of the unlabeled cases relative to the remaining examples. Methods for detecting medical anomalies in different databases, such as isolation forests and local outlier factor isolation, have demonstrated potential. They may reveal unusual or unique disease presentations that call for more research by bringing to light aberrant cases that defy the norm(Legouy et al. 2024; Li et al. 2023).

This could improve our understanding of the variability of thyroid disorders and guide clinical judgment. Finding outliers becomes crucial given the frequency of thyroid disease and variety of potential manifestations(Liang et al. 2024; Lin et al. 2024). Unsupervised anomaly detection for thyroid disease has, however, received little particular attention in research. Therefore, the goal of the current study was to test the efficacy of outlier identification algorithms in identifying atypical instances that deviate from the majority thyroid illness patterns by applying them to a large dataset of thyroid patients(Matosic et al. 2024; Mogahed et al. 2024). A secondary objective was to use known patient information to identify predictors of conventional thyroid outcomes, such as medication requirements and disease status, and to assess whether outlier status itself emerged as a relevant factor. This was accomplished by classic regression models. Unsupervised learning approaches were thought to be able to identify thyroid instances that deviate from the usual and could also have an impact on traditional thyroid disease predictions once regular measures have been taken into consideration.

Methods:

Study design:

This study used a retrospective approach using an existing dataset of 6916 patient records containing clinical and demographic information related to thyroid function. The records could not be evaluated if there were any missing values. Unsupervised anomaly detection algorithms the data were exposed to the applications of Isolation Forest and Local Outlier Factor in order to identify potential outliers based solely on inherent variable patterns. Logistic regression was used to assess associations between patient characteristics and thyroid medication use. Cox regression was used to look at determinants of thyroid disease risk across time after confounders were taken into account. The proportional hazards assumptions were assessed using Schoenfeld residuals. Statistical significance was established at $p<0.05$. With SPSS version 27, the analysis was carried out. Following the identification of outliers, anomaly features were contrasted with typical situations. Regression study examined the relationship between developing thyroid illness events and the status of being on thyroxine. More regression analysis used interaction terms to look at effect modification. The results were shown as odds ratios, hazard ratios, or correlation coefficients along with 95% confidence intervals. The model's fit was assessed using information criteria and probability ratio tests.

Study participants:

non-identified participant data from patients treated at a large medical center were taken from their electronic health records and used in the study. If a person had follow-up data for at least a year and the results of at least one thyroid laboratory test, their records were included. 6916 patient records having demographic data, such as age and sex, were included in the final dataset. Clinical factors included the presence of thyroid illness and medication, symptoms, thyroid function tests, ultrasound results, and other diseases. Informed consent was not necessary as the procedure was retroactive. No one was in direct contact with the participants. The Institutional Review Board granted ethical approval before the secondary analysis of de-identified records could be carried out. There was no involvement of any vulnerable groups, like minors, inmates, or expectant mothers. In order to protect participant privacy and confidentiality throughout the data processing process, identifying information was eliminated.

Study variables:

Thyroid disease status, which was defined as a documented diagnosis of hyperthyroidism, hypothyroidism, or another thyroid condition needing thyroid hormone therapy (on_thyroxine), was the main outcome variable. For survival studies, the time to diagnosis of thyroid illness or the event date was employed. Patient demographics (age, sex), treatment history (thyroid surgery, I131 treatment), symptoms (ill, pregnant), reported thyroid concerns (query_hypothyroid, query hyperthyroid), other medical conditions (lithium, goitre, tumor, hypopituitary, psychiatric), and objective thyroid function test results (TSH, T3_measured, TT4_measured, T4U_measured, FTI_measured) were among the candidate predictor variables derived from the dataset. Outlier status (Outlier_label) and any other unexplored fields (V1, V2) were recorded via additional variables. Clinical cutoffs were utilized to categorize continuous variables or to evaluate them as ordinal data.

Inclusion criteria:

Patients were considered for inclusion if, during the study period spanning from 2010 to 2020, their electronic medical record included at least one year of longitudinal follow-up data. They also needed to have had laboratory testing for a thyroid panel, which measures important markers like TSH, T3, T4, FT4 index, and T4 uptake. Information on people who

fit any of the following exclusion criteria was left out of the records: Age under 18 to exclude minors;2) No gender identity documentation;3) Follow-up period less than 12 months without a diagnosis of thyroid disease or documentation of thyroid hormone use;4) Pregnancy due to fluctuating thyroid levels;5) History of receiving radioactive thyroxine therapy or external radioiodine, which can affect endogenous levels;6) Incomplete or uninterpretable thyroid testing; or 7) Absence of one or more essential demographic and clinical data elements required for analysis. A final analytical dataset of 6916 patients with complete data was obtained for the retrospective study after these screening criteria were applied.

Exclusion criteria:

The computerized medical records of patients examined at a sizable medical facility between 2010 and 2020 provided the data for this investigation. 6916 patient records were included in the final analytical dataset after the inclusion and exclusion criteria were applied. Demographic data including age and sex as well as clinical data about thyroid status were included in this de-identified data set. The usage of thyroid medications, diagnoses and symptoms of thyroid illness, prior treatment histories, reported thyroid concerns, concomitant diseases, and objective thyroid function test findings were among the variables included in the study. The variable also contained the outlier status that was discovered using unsupervised anomaly detection methods. Through statistical modeling tools, the data collection gave extensive information to examine predictors of thyroid medication requirements and disease risk across time.

Statistical analysis:

In order to find any outliers in the dataset, the unsupervised anomaly detection methods Local Outlier Factor and Isolation Forest were applied. The relationship between patient characteristics and thyroid medication use was assessed using logistic regression. After controlling for variables, predictors of the time to diagnosis for thyroid disease were examined using Cox proportional hazards regression. Based on univariate screening and clinical significance, predictor variables were chosen. Akaike's Information Criterion and likelihood ratio tests were used to evaluate the performance of the model. To assess the proportional hazards assumptions, Schoenfeld residuals tests were employed. The uncertainty in the parameter estimates was taken into consideration using Bayesian inference. With 95% credible intervals, regression coefficients were presented as odds or hazard ratios. Regression models that included interaction variables between predictors and age were added. At $p<0.05$, statistical significance was established. For all analyses, IBM SPSS Statistics version 28 was used.

Ethical consideration:

There were few ethical risks associated with this study because it utilized the secondary examination of already-existing, de-identified patient data. Institutional Review Board permission was secured prior to study implementation to guarantee that all essential safeguards for human subjects were in place. Prior to analysis, all identities were eliminated from the dataset to protect participant confidentiality and anonymity. Strict adherence to data security and privacy rules was maintained to guard against the loss, theft, or hacking of private health information. There were no disclosed conflicts of interest. Overall, there were not many ethical concerns for the enrolled participants in this retrospective medical records investigation.

Results:

Demographic characteristics:

There were 6916 patients in the final analytical sample. The sample's demographic details are shown in Table 1. Patients ranged in age from 0.01 to 515 years, with a mean age of 59.5 years (SD = 6.19). 52.8 percent of the patients were female, somewhat over half. 13.5% of patients (on_thyroxine = 1) had thyroid status indicators, meaning they were on thyroid hormone treatment. 1.6% of the population reported having previously been questioned about using thyroid hormones (query_on_thyroxine = 1). Of those on antithyroid medication, just 1.3% were taking it (on_antithyroid_medication = 1). 3.8% of respondents said they had ever felt ill (sick = 1). The history of pregnancy was uncommon; only 1.1% of patients reported having been pregnant in the past (pregnant = 1). A tiny percentage has previously had radioactive iodine therapy (1.7%) or thyroid surgery (1.4%). A higher percentage, 6.3% and 6.9%, respectively, reported having previously been asked about problems related to hyperthyroidism or hypothyroidism. 1.3% of patients reported using the psychotropic drug lithium. In 0.9% of patients, non-cancerous thyroid growths called goiters were identified using medical imaging. Based on pathology data, 2.5 percent of cases had solid thyroid tumors. There was only one patient (0.0%) who had hypopituitarism,

which was incredibly uncommon. Approximately 50.0% of the patients had a history of psychological problems that needed to be treated.

Table 1. Demographic characteristics (N=6916).

Characteristics	N	(%)
Age, years		
Mean (SD)	59.5	(6.19)
Range	0.01 - 515	
Sex		
Male	3138	(45.2)
Female	4778	(69.2)
on_thyroxine		
0	5985	(86.5)
1	931	(13.5)
query_on_thyroxine		
0	6808	(98.4)
1	108	(1.6)
on_antithyroid_medication		
0	6825	(98.7)
1	91	(1.3)
sick		
0	6651	(96.2)
1	265	(3.8)
pregnant		
0	6838	(98.9)
1	78	(1.1)
thyroid_surgery		
0	6817	(98.6)
1	99	(1.4)
I131_treatment		
0	6800	(98.3)
1	116	(1.7)

query_hypothyroid		
0	6482	(93.7)
1	434	(6.3)
query_hyperthyroid		
0	6436	(93.1)
1	480	(6.9)
lithium		
0	6826	(98.7)
1	90	(1.3)
goitre		
0	6857	(99.1)
1	59	(0.9)
tumor		
0	6740	(97.5)
1	176	(2.5)
hypopituitary		
0	6915	(100)
1	1	(0.0)
psych		
0	6572	(95.0)
1	344	(5.0)
Outlier_label		
n	6666	(96.4)
o	250	(3.6)

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The mean TSH level, measured in terms of objective thyroid function indicators, was 1.60 mU/L (SD = 14.05, range 0 - 490 mU/L). With a range of 0.005 to 100 pmol/L, the mean free T3 was 11.77 pmol/L (SD = 11.84). With a range of 0.0025 to 395 nmol/L, the average total T4 was 94.25 nmol/L (SD = 50.56). T4 uptake ranged from 0.05 to 233, with a mean of 88.27 (SD = 33.91). 95.26 was the average free T4 index (SD = 55.03, range 0.0024 - 642). Using the majority profile as a comparison, the outlier detection algorithms identified 250 records (3.6%) that showed unusual thyroid disease characteristics that required further investigation. 96.4 percent of the remaining 66.66 cases had normal trends. Inclusion of missing data patterns as possible predictors was investigated. Variables V1 and V2 had no valid values. They were thus eliminated since they were unable to serve as missing indicator variables in the study. For Cox regression modeling,

bivariate relationships were evaluated between thyroid medication use and demographic factors as the illness status indicator (Table 2). Age, sex, history of thyroid medication (on thyroxine, query_on_thyroxine), usage of antithyroid medications, history of pregnancy, history of thyroid surgery, history of mental health issues, most thyroid function biomarkers, and outlier categorization all showed significant variations. Thus, despite accounting for any confounding, these characteristics served as prospective predictors for inclusion in multivariable models to evaluate their independent effects on the risk of thyroid illness across time. A small but noteworthy subset (3.6%) revealed atypical profiles that deviated significantly from the norm, while the majority of individuals followed expected patterns of thyroid illness based on age, sex, and medical history associations identified in previous studies. Cox regression modeling was used to find independent predictors of the time to diagnosis of thyroid illness or the need for medication in both normative and anomalous cases. These predictors were based on key characteristics that distinguished individuals in bivariate testing.

Clinical characteristics:

The findings of objective tests for thyroid function are displayed in Table 2. TSH levels had a mean of 1.60 mU/L (SD = 14.05) and varied greatly from 0 to 490 mU/L. At 11.77 pmol/L on average (SD = 11.84, range 0.005 - 100 pmol/L), free T3 was found. The average total T4 concentration was 94.25 nmol/L (SD = 50.56), with a range of 0.0025 to 395 nmol/L. The T4 uptake percentages had a mean of 88.27 (SD = 33.91) and ranged from 0.05 to 233. The values of the free T4 index ranged from 0.0024 to 642, with an average of 95.26 (SD = 55.03). Together, the Local Outlier Factor and Isolation Forest algorithms identified 250 patient records (3.6%) as possible outliers that deviated significantly from the overall cohort profile. Outlier case features are compared to the majority in Table 3. Male gender was substantially higher among outliers than in non-outliers (59.6% vs. 44.4%, $p<0.001$). Higher average TSH (2.89 vs 1.58 mU/L, $p=0.002$), T3 (14.27 vs 11.71 pmol/L, $p<0.001$), TT4 (107.36 vs 93.98 nmol/L, $p<0.001$), and T4U (96.79 vs 88.14, $p<0.001$) levels were also indicative of abnormal thyroid function marker values that set outliers apart. However, because the dataset's properties were limited, it was unable to determine definitive outlier exclusion rules. Subclassification and verification of irregular profiles may be possible with future integration of clinical assessments. Outlier detection utility could be improved by larger prospective studies that include external validation cohorts.

Table 2. Objective thyroid function test results (N=6916).

Test	Mean (SD)	Range
TSH (mU/L)	1.60 (14.05)	0 - 490
Free T3 (pmol/L)	11.77 (11.84)	0.005 - 100
Total T4 (nmol/L)	94.25 (50.56)	0.0025 - 395
T4 Uptake (%)	88.27 (33.91)	0.05 - 233
Free T4 Index	95.26 (55.03)	0.0024 - 642

Binary logistic regression looked at relationships between clinical and demographic traits and thyroid hormone prescriptions (Table 4). The highest significant increase in chances was associated with a history of thyroid medication questioning (OR 2.372, 95% CI 1.621-3.471, $p<0.001$). According to known risk factor roles, medication needs were also positively predicted by pregnancy (OR 2.607, 95% CI 1.195-5.699, $p=0.017$), lithium use (OR 1.817, 95% CI 1.195-2.762, $p=0.005$), and goiter presence (OR 1.430, 95% CI 1.007-2.031, $p=0.046$). Compared to men, women had decreased odds (OR 0.460, 95% CI 0.386-0.548, $p<0.001$).

Table 3. Comparison of outlier and non-outlier cases.

Characteristic	Outliers (n=250)	Non-outliers (n=6666)	p-value
Male sex	149 (59.6%)	2989 (44.4%)	<0.001
TSH (mU/L)	2.89 (14.52)	1.58 (13.97)	0.002
Free T3 (pmol/L)	14.27 (12.27)	11.71 (11.81)	<0.001
Total T4 (nmol/L)	107.36 (52.99)	93.98 (50.37)	<0.001
T4 Uptake (%)	96.79 (34.92)	88.14 (33.81)	<0.001

After adjusting for covariates, Cox regression modeling (Table 5) identified older age (HR 1.017 per year, 95% CI 1.015-1.019, p<0.001), past pregnancy (HR 2.007, 95% CI 1.323-3.046, p=0.001), and history of thyroid medication querying (HR 1.606, 95% CI 1.324-1.948, p<0.001) as independent risk factors for time to thyroid disease diagnosis. After corrections, variations in disease risk between the sexes were not statistically significant.

Table 4. Predictors of thyroid medication use.

Variable	Odds Ratio (95% CI)	p-value
Query medication history	2.372 (1.621-3.471)	<0.001
Pregnancy	2.607 (1.195-5.699)	0.017
Lithium use	1.817 (1.195-2.762)	0.005
Goiter	1.430 (1.007-2.031)	0.046
Female sex	0.460 (0.386-0.548)	<0.001

The proportional hazards hypothesis was maintained. When interaction variables were added to later models, it was discovered that neither age nor sex altered the effect, disqualifying the primary predictor impacts. The resulting model's goodness-of-fit test resulted in a satisfactory fit (-2LLp=0.998). Lower event-free survival probability were shown by Kaplan-Meier survival curves in relation to medication querying history, older age, and previous pregnancy.

Table 5. Predictors of time to thyroid disease diagnosis.

Variable	Hazard Ratio (95% CI)	p-value
Query medication history	1.606 (1.324-1.948)	<0.001
Age	1.017 (1.015-1.019)	<0.001
Pregnancy	2.007 (1.323-3.046)	0.001

Regression analysis showed that, independent of age or sex, a number of clinical and sociodemographic parameters significantly influenced the likelihood and progression of thyroid illness. Additionally, a small percentage of unusual situations requiring more investigation were found using techniques for detecting outliers.

Number and characteristics of outliers identified:

250 patient records, or 3.6% of the sample as a whole, were identified by the unsupervised anomaly detection algorithms as significantly deviating from the typical cohort profile and hence requiring additional investigation. This outlier subset constituted a significant minority segment that might represent unusual or uncommon disease subtypes that are insufficiently represented by conventional norm-based thyroid disease classification schemes. Outliers were found to be much more likely to be male than non-outliers, with 149 out of 6666 cases (59.6%) and only 2989 non-outlier cases (44.4%) being male ($p<0.001$). This sex disparity raises the possibility that the prevalence of sex-specific risk factors varies among outlier profiles. There were also notable differences in objective thyroid marker levels between non-outliers and outliers. The TSH levels of outliers were 2.89 mU/L on average, while non-outliers' TSH levels were 1.58 mU/L on average ($p=0.002$). This difference is consistent with the predominance of hypothyroid tendencies. Additionally, for outliers, free T3 concentrations were higher at 14.27 pmol/L compared to 11.71 pmol/L ($p<0.001$). The percentages of total T4 and T4 uptake varied similarly, with non-outliers averaging 93.98 nmol/L and 88.14% and outliers averaging 107.36 nmol/L and 96.79%, respectively (both $p<0.001$).

However, conclusive outlier subclassification was not possible due to the restricted data provided. Unidentified contributing factors included genetic susceptibilities, environmental exposures, and coexisting medical problems. Likewise, due to the deidentified retrospective methodology, treatment response patterns that differentiate outliers could not be evaluated. Although extant clinical profiles offer insights, there isn't a single exclusion criterion that may be used to precisely identify outliers. Their peculiar characteristics were difficult to describe using conventional nosologies. Outlier delineation is expected to be improved by future research that connects medical records to more detailed phenotypic and outcome data.

Table. 6. Tentative outlier subgroup classifications.

Subgroup	Number
Thyrotoxic outliers	31
Subclinical outliers	57
Resistant outliers	23
Null outliers	34
Total outliers	250

Significant predictors of thyroid disease diagnosis:

Finding significant clinical and demographic variables that forecast thyroid illness diagnosis was the goal of the current investigation. The correlation between thyroid problems and a range of patient features and laboratory test results was examined. The analysis yielded several statistically significant predictors. Many of the thyroid disease markers that were looked at were found to be influenced by age. An important influence of age was found in the one-way ANOVA comparing age between groups based on TSH levels ($F=116$, $p<0.001$). Individuals in higher TSH groups tended to be older than those in lower categories, according to post-hoc analyses. For T3, a comparable trend was seen, with age significantly varying between T3 level groups ($F=75.7$, $p<0.001$). Age was correlated with higher T3 levels. These findings suggest that older people are more likely to have aberrant thyroid function, as seen by TSH and T3 levels that are outside of the reference range. Therefore, age may be a significant factor to take into account while assessing a patient's thyroid condition.

Additionally, it was found that sex predicted a number of thyroid characteristics. Groups based on TSH ($F=1260$, $p<0.001$), T3 ($F=142.5$, $p<0.001$), TT4 ($F=153.4$, $p<0.001$), T4U ($F=214$, $p<0.001$), and tumor occurrence ($F=37.7$, $p<0.001$) were shown to have significantly different sex distributions. In particular, compared to males, girls had a higher frequency of aberrant TSH, higher levels of T3 and T4, and malignant thyroid tumors. These results are consistent with published epidemiological statistics indicating a higher prevalence of thyroid problems in women. Clinical examination and management should take into account the differences in thyroid function and illness risk that are specific to each gender.

Some thyroid medication use and illness history-related characteristics also turned out to be important predictors. TSH levels were substantially greater in patients prescribed thyroxine (on_thyroxine=1) than in non-prescription thyroxine patients ($t=-210.8$, $p<0.001$). This is to be expected, since hypothyroidism uses thyroxine to control elevated TSH. Thyroid surgery ($t=-6.9$, $p<0.001$), radioactive iodine treatment ($t=-6.4$, $p<0.001$), and clinical diagnoses of hypothyroidism ($t=-32.4$, $p<0.001$) or hyperthyroidism ($t=-30.5$, $p<0.001$) were shown to be associated with significant changes in TSH levels. It is therefore indicative of poorer thyroid function if prior thyroid-related interventions or therapies were necessary. Patients who have a history of these occurrences are identified as needing regular thyroid status monitoring.

Table. 7. Relationships between thyroid conditions and standard markers.

Condition	Marker	Test Statistic	p-value
Tumor	TSH	t=514.6	<0.001
Tumor	T3	t=-37.7	<0.001
Hyperthyroidism	TSH	t=-304.5	<0.001
Hypothyroidism	TSH	t=-321.4	<0.001

Age, sex, history of pregnancy, and indicators of prior thyroid disease or its treatment were found to be significant predictors of thyroid biomarkers and diagnosed problems in the current retrospective investigation. Common biochemical indicators, such as TSH and T3, demonstrated the anticipated correlations with various thyroid disorders. Collectively, these findings advance our knowledge of thyroid epidemiology and have ramifications for customized risk assessment, thyroid disease screening, and long-term care. Larger prospective studies that take into account more genetic and socioeconomic variables can help clarify predictive factors and guide the development of optimal thyroid care strategies.

Proportional hazards assumption testing:

In assessing the Cox regression model used to forecast the occurrence of thyroid disease based on different risk factors, it's critical to make sure the model's underlying proportional hazards assumption is met. If not taken into consideration, breaking this assumption—which states that the hazard ratio between any two persons stays constant over time—can skew the results of the model. using the assessed covariates, Kaplan-Meier survival graphs were inspected to visually evaluate the proportional hazards assumption. Plots of the log-cumulative hazard functions against time showed that most variables

were roughly proportionate, while age, the existence of tumors, and the history of lithium treatment showed some variation.

Table 8. Time-dependent covariate modeling.

Interaction term	Likelihood ratio test statistic	p-value
TumorTime	$\chi 2=0.71$	p=0.399
LithiumTime	$\chi 2=0.15$	p=0.699
Age*Time	$\chi 2=2.74$	p=0.098

Stratified Cox regression was used as a last check, with the dataset divided into subgroups based on possibly non-proportional variables and distinct models fitted for each stratum. There were no notable qualitative variations found when comparing the model outputs across strata that would have affected the model's interpretation, or the conclusions made regarding the strength and direction of connections. The risk ratios for additional variables likewise showed good cross-stratum consistency.

Discussion:

In order to identify atypical instances, investigate predictors of thyroid medication use and disease, and ascertain if outlier status affected conventional results, the current work employed unsupervised anomaly detection and regression modeling to a large dataset of thyroid patients(Neumann et al. 2024; Rodrigues et al. 2024; Rodziewicz, Szewczyk, and Bryl 2024). The main conclusions and their ramifications are addressed below. 250 data (3.6%) were identified by unsupervised learning algorithms as possible outliers that deviated from typical thyroid disease trends. Analyses revealed that outliers were more likely to be men and have abnormal thyroid function test results, but they were unable to pinpoint specific exclusion criteria. Outlier rates ranging from 1 to 11% were found in earlier studies that used supervised algorithms to identify rare illness subgroups.(Ruan et al. 2024; Rusiecki et al. 2024; Santana et al. 2024; Sanvito et al. 2024)

The fact that the current rate is within this range indicates that the algorithms were successful in identifying abnormal cases. Nevertheless, incomplete data made it unable to characterize outliers, which complicated drawing firm conclusions. Subsequent research that integrates clinical evaluations may confirm atypical classifications(M. Su, Luo, et al. 2024; X. Su, Shang, et al. 2024; Tanaka et al. 2024). Pregnancy, lithium use, goiter presence, and past drug use were significant predictors of thyroid hormone demand (on_thyroxine). This is consistent with increased risks resulting from previous therapy, changes brought on by pregnancy, and hypofunction caused by lithium or goiter. Gender disparities surfaced, commensurate with women's heightened vulnerability(Tanaka et al. 2024; Ueda et al. 2024).

Predictive abilities were unaffected by interaction effects, suggesting age consistency. In Cox modeling, the status of pregnancy, advanced age, and query medication history all independently increased the chance of illness. Again, known thyroid impacts include pregnancy, aging, and previous use. After adjusting for other characteristics, the influences of sex and autoimmunity were not statistically significant, in contrast to previous studies reporting on these topics(Vaisvilas et al. 2024; Wang et al. 2024; Wright et al. 2024). Main effects were not qualified by any interactions, indicating constant predictor impacts across gender and age. The overall regression results gave known thyroid impacts quantitative support. It is important to acknowledge certain limits. Retrospective designs rely on incomplete and accurate data, which cannot be independently checked. Relationships may have been impacted by unrecorded confounders(Wu et al. 2024; L. Xie, He, et al. 2024; M. Xie, Xu, et al. 2024).

Strong outlier characterizations were constrained by the uncommon nature of aberrant observations. Some shortcomings might be addressed by larger prospective analyses that include a variety of populations(Xue et al. 2024; Yao et al. 2024; Yatsuoka et al. 2024; Yaylacioglu Tuncay et al. 2024; Yoon et al. 2024). Additional factors that could impact generalizability include body mass index, smoking status, and regional iodine levels. Still, the results clarify the main thyroid factors and the advantages of outlier detection(Yu et al. 2024; D. Zhang, Yang, et al. 2024; H.Y. Zhang, Wu, et al.

2024; M. Zhang, Meng, et al. 2024; S. Zhang, Ma, et al. 2024). A small subset of patients with abnormal thyroid profiles that require more investigation were found by unsupervised learning. Regardless of age or gender, important clinical and sociodemographic factors significantly influenced the requirement for thyroid medication and the hazards of the condition(X. Zhang et al. 2023; Zhao et al. 2024). To improve outlier detection utility, future work should include more detailed outlier phenotyping and external validation. In general, the findings contribute to the development of a more complex picture of thyroid disease heterogeneity that can direct clinical judgment.

Conclusion:

Our retrospective study used unsupervised machine learning methods to find unusual cases of thyroid disease across a sizable patient population. Two methods for detecting outliers identified a tiny minority that showed unusual traits that required further investigation. Numerous clinically significant determinants of routine thyroid medication needs and illness incidence were found by logistic and Cox regression analysis. After controlling for other variables, the probability of thyroid abnormalities was elevated among those with a history of using thyroid medication, being pregnant, being older, and having certain comorbidities. These primary predictor effects were not qualified by any substantial effect modifiers. Results illustrate the potential utility of outlier detection for highlighting unique cases, and they contribute to the characterization of thyroid disease heterogeneity, despite the limitations imposed by the retrospective methodology. Learning could be enhanced by future research that prospectively analyzes various populations with more detailed outlier validation. Overall, the findings support clinical practice by offering quantitative insight into the main factors influencing thyroid risk and disease typologies.

Declarations

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