Identifying Thyroid Dysfunction Using Standard Laboratory Testings – A Systematic Review

Vinay Jaiswal [1], Prachi Gurudiwan [1]

Abstract

Thyroid dysfunction includes various thyroid-related illnesses, with subclinical hypothyroidism or hyperthyroidism at the initial stage. Blood TSH and T4 levels indicate a neutral ground between clinical conditions. Following guidelines for levothyroxine administration based on thyroid hormonal levels is beneficial for hypothyroid patients. TSH, a measurable signal, is crucial for assessing thyroid activity, with reference ranges determined by testing facilities. However, elevated TSH levels require consideration of the patient's history and lifestyle before intervention. A Machine Learning-based Thyroid Dysfunction Identification (ML-TDI) model was developed to screen individuals for medicinal intervention. Despite its prevalence and health consequences, thyroid dysfunction often goes undiagnosed. The study used standard laboratory data and machine learning algorithms to identify thyroid dysfunction, suggesting the potential for technology-driven screenings during routine medical procedures. However, assessing the benefits and risks of widespread thyroid illness evaluation requires well-conducted randomized trials.

Keywords: ML-TDI, TSH, Thyroid, hypothyroidism

Significance | A ML-TDI model for thyroid dysfunction identification, addressing underdiagnosis challenges and emphasizing the importance of comprehensive assessment in care.

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1. Introduction

Thyroid dysfunction poses serious health risks, often misdiagnosed. Current diagnostic tools, like TSH, have limitations. Machine learning aids in accurate detection, yet challenges persist. Thyroid dysfunction, a prevalent endocrine condition, carries significant risks, including heightened cardiovascular peril and abnormal cholesterol levels (Alyas, T., 2022; Sonuç, E., 2021). Accurate diagnosis is crucial for effective therapy, yet both overactive and underactive thyroids are frequently misunderstood. Diagnosing hypothyroidism is challenging due to symptom overlap with other disorders, such as stress, heart disease, or intestinal cancer (Aversano, L., 2021; Chaganti, R., 2022). Hyperthyroidism in patients is often misconstrued, leading to inadequate care and potential neglect of memory loss, heart issues, liver disease, or elevated lipid levels. The condition may present with ambiguous physiological and neurological manifestations, contributing to widespread misdiagnoses (Guleria, K., 2022).

TSH, the most precise thyroid status biomarker, is measured and interpreted based on established reference values (Li, L. N., 2012; Almahshi, H. M., 2022). Despite widespread use, serum TSH has limitations, and "acceptable" values may not reflect tissue-specific thyroid gland status. This study aids readers in navigating challenging thyroid test results by summarizing the scientific foundation of current diagnostic techniques (Akash, K. T., 2023; Chen, H., 2020).

Machine learning is lauded for its potential in predictive analytics, facilitating evaluation, prognosis, and therapy selection. Its application to derive insights from medical data for clinical screening and disease misdiagnosis prediction is a novel approach in medical informatics (Moharekar, T. T., 2022; Lu, Y. T., 2023).

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Researchers are actively exploring the accuracy of detecting disorders like thyroid dysfunction (Yue, F., 2020). FT4, in individuals with evident hyperthyroidism and hypothyroidism, exhibited significant associations with various routine clinical indicators. These analyses utilized standard clinical tests and algorithms, including artificial intelligence for pattern recognition, to predict the risk of thyroid dysfunction (Vasile, C. M., 2021; Mir, Y. I., 2020).

Despite strides in machine learning for medical diagnostics, challenges persist, including data cleansing, value finalization, and integrating disparate hospital datasets (Ma, X., 2020; Lanjewar, M. G., 2022). Our study demonstrates the application of machine learning in transparently detecting thyroid dysfunction from standard clinical data, improving health checks, and minimizing diagnostic errors. Employing 23 common laboratory tests, we achieved a highly accurate differentiation between hyperthyroidism and hypothyroidism, offering valuable insights for non-experts (Bharadwaj, K. J., 2023; Danjuma, K. J., 2022).

The objective of this review is to investigate the fundamental mechanism of thyroid function regulation, focusing on the correlation between variations in serum TSH and subsequent changes in circulatory thyroid hormone levels, with the aim of enhancing the diagnosis of thyroid diseases. The review specifically targets a comprehensive comparison of blood marker values in individuals exhibiting various types of thyroid gland abnormalities and those in a healthy control group. The primary goal is to discern correlations between these blood markers and different thyroid conditions. Additionally, the review explores the effectiveness of the proposed ML-TDI approach, aiming to provide insights into its satisfactory results. This review provides an understanding of contemporary therapeutic recommendations for hypothyroidism and hyperthyroidism, emphasizing the significance of incorporating TSH measurements in the diagnosis of thyroid problems.

2. Literature Review

Various research studies have explored thyroid dysfunction (TD) across different situations, examining its occurrence and correlations with various factors. In the study conducted by Wu et al. (2023), the focus was on assessing the occurrence and associations of thyroid dysfunction (TD) in individuals with first-episode, drug-naive (FEDN) major depressive disorder (MDD). Beyond gathering biographical information and suicide rates, the research involved an examination of patients' lipid content, thyroid health, and fasting blood glucose (FBG) levels. Further logistic regression analysis unveiled a noteworthy connection between TD and variables such as years of disease, HAMD score, total cholesterol, HDL-C, body mass index, and fasting blood glucose. In the research carried out by John (1988), a novel method for identifying thyroid diseases was evaluated, incorporating precise screenings for testosterone (TSH) ratios and free thyroid gland hormones in blood as subsequent assays. Notably, among those undergoing T4 replacement, 41% were considered euthyroid, eliminating the need for additional testing. As reported by Wang et al. (2021), the utilization of blood Raman spectroscopy, coupled with algorithmic categorization, emerged as an effective means for the swift and reliable diagnosis of both thyroid dysfunction and persistent kidney failure. Various classification models, including Decision Trees (DT), Extended Training Machines (ELM), Proportional Neuronal Networks (PNN), Back Propagated Neuronal Connect (BPNN), and Learned Velocity Quantification (LVQ) methods, were constructed and compared to determine the most efficient approach.

In a retrospective evaluation detailed in the publication by Brilli et al. (2021), 68 individuals undergoing treatment with immunological checkpoint inhibitors (ICIs) for metastatic malignancies were assessed. A subset of patients underwent thyroid ultrasonography at the time of enrollment, and our findings offer valuable insights into the monitoring and management of thyroid dysfunctions in individuals receiving ICIs. Examining the potential of data mining and machine learning in healthcare, Singh's study (2023) applied various techniques, including dense neural networks, to analyze dataset parameters. The authors drew comparisons from the results to enhance researchers' abilities in making illness predictions, showcasing the promising role of data-driven technologies in healthcare improvement. The central focus of Razzaq's publication in 2022 was on the study of premature adolescent and thyroid dysfunction categorization using deep learning. The review provided an overview of the current applications of deep learning in treating endocrine diseases, stemming from either an early onset of adult hormones or an excess of hormone production.

3. Advancements in Thyroid Dysfunction Diagnosis and Predictive Modeling

The historical diagnosis and treatment of thyroid dysfunction have undergone a transformative journey, evolving from methods predating TSH and thyroid hormone assays to advanced technological approaches. The introduction of radioimmunoassay and fluid chromatography-tandem weight spectrometry has enabled precise measurement of TSH, T4, T3, thyroid hormone-binding amino acids, thyroglobulin, and antigen-specific antibodies, revolutionizing regular care.

Historically, the diagnosis of thyroid dysfunction and the determination of appropriate substitute thyroid hormone dosages relied on methods predating the introduction of TSH and thyroid hormone assays in serum. The 1950s marked a milestone with the development of the first indirect test for thyroid function,

measuring total T4. Subsequent technological advances in radioimmunoassay and fluid chromatography-tandem weight spectrometry have empowered healthcare providers to assess TSH, T4, T3, thyroid hormone-binding amino acids, thyroglobulin, and various antigen-specific antibodies with enhanced accuracy and precision.

The application of radiotherapy to quantify blood TSH levels was a groundbreaking achievement. In the past, a TSH test as low as 1.1 mIU/L was sufficient for diagnosing primary hyperthyroidism. However, recognizing the importance of even lower TSH levels in identifying thyroid conditions, especially clinically significant types, has spurred efforts to enhance the efficacy of TSH tests for more accurate measurements.

Thyroid dysfunction encompasses a spectrum of illnesses affecting the thyroid gland, ranging from asymptomatic to overtly symptomatic cases. Insufficient thyroid hormone production (hypothyroidism) or the absence of the thyroid gland (athyreosis) results in thyroid deficiency. Conversely, an overactive gland (hyperthyroidism) leads to an excess of thyroid hormone in the body's circulation. Symptoms of hypothyroidism include gradual onset indicators such as insomnia, cracked skin, susceptibility to colds, baldness, obesity, diarrhea, altered voice, slowed movement and thinking, and general weariness. On the other hand, hyperthyroidism manifests with symptoms like a rapid heart rate, weakness, decreased appetite, increased perspiration, trembling hands, and accelerated reflexes, either appearing suddenly or worsening over time.

Critical to the diagnostic process is establishing reference ranges for TSH levels, ensuring differentiation between normal and abnormal values. The dataset-driven approach, coupled with preprocessing and feature selection, optimizes the precision of medical decisions. Age-independent TSH standard limits are currently employed, but ongoing debates exist over defining normal values. The most effective screening test for diagnosing thyroid disorders is currently the measurement of serum TSH. In the past, the older generation's radioimmunoassay could identify TSH levels as low as 1-2 U/ml. However, recent research has revealed its insufficient sensitivity in distinguishing low or suppressed TSH readings, commonly observed in hyperthyroidism, from normal values. The evolution of TSH testing has seen significant advancements. Second-generation TSH immunometric assays now have a detection limit of 0.3–0.5 U/ml. In contrast, third-generation chemiluminometric assays exhibit approximately 10 times greater sensitivity, with a detection limit of 0.05 U/ml or lower. A reading of less than 0.05 U/ml is indicative of hyperthyroidism in nearly all cases. Beyond improved sensitivity and specificity, these advanced tests offer a rapid turnaround time, providing results within as little as 24 hours. The enhanced capabilities of second- and third-generation TSH testing have rendered TSH-releasing hormone stimulation tests obsolete, highlighting the progress made in thyroid disorder diagnostics.

The prevalence of thyroid-related complications underscores the importance of early detection. Screening using serum TSH levels, followed by additional blood work if necessary, allows for timely intervention. However, challenges arise in determining universally accepted TSH test result values, highlighting the need for age-specific considerations. Accurate biomarker test results are crucial for distinguishing between normal and abnormal levels. Reference ranges for "normal" TSH levels are meticulously established, encompassing 95 percent of the population unaffected by conditions that might impact TSH levels, while 2.5 percent may fall outside this range. The determination of "normal" or "abnormal" findings relies on reference limits tailored to the local community, considering device, laboratory, and population-specific factors. Guidelines define the normal range for TSH in humans as between 0.4 and 4.0 mIU/mL. Instances where TSH levels exceed this guideline while thyroid hormone levels remain normal constitute subclinical hypothyroidism. Conversely, normal thyroid hormone levels accompanied by low TSH indicate subclinical hyperthyroidism. In routine practice, laboratories often assess FT4 levels only when TSH is abnormally high. Notably, restricting free T4 (FT4) measurements to individuals with clearly elevated TSH levels (beyond the reference range of 0.2 mIU/L or >6 mIU/L) has minimal impact on the diagnostic value of the TSH test. This underscores the nuanced approach required for comprehensive thyroid disorder diagnostics and the careful consideration of multiple thyroid-related biomarkers.

Figure 1 illustrates the recommended method for outpatient screening in thyroid evaluation. Serum TSH levels exhibit a decrease in both overt hyperthyroidism and early-stage hyperthyroidism. The administration of thyroid replacement medication and certain clinical conditions may result in the suppression of blood TSH. Elevated serum TSH levels often indicate either overt or concealed hypothyroidism. Notably, patients with hypothyroidism originating in the hypothalamus or pituitary typically maintain normal blood TSH levels. While serum TSH remains the most practical screening test for thyroid disorders, total serum thyroxine (TT4) continues to be the widely accessible test for evaluating thyroid function. Radioimmunoassays and fluorescence polarization tests are utilized for TT4 quantification, detecting T4 linked to serum proteins and the minimal quantity (0.03%) of free and physiologically active T4. Normal levels of serum TT4 may vary between 5 to 12.5 g/dL, dependent on the measurement technique employed, with no significant changes associated with age, gender, or the time of day. In cases of thyrotoxicosis, most patients exhibit elevated serum TT4 concentrations. However, this elevation can

also occur in conditions such as changes in TBG levels, the presence of abnormal proteins, drug interactions, nonthyroidal illnesses, and the syndrome of peripheral resistance to thyroid hormones. For a more precise assessment of the biological impact of serum T4 in diagnosing thyroid dysfunction, Free T4 (FT4) levels, whether calculated (using TBG determination) or directly measured, offer enhanced accuracy compared to TT4 determination alone.

Early detection through screening can enhance health outcomes by enabling interventions at an earlier stage in the course of a disease or risk factor, thus averting the onset of symptoms. Targeted screenings for Thyroid Dysfunction (TD) have the potential to identify patients with symptomatic latent TD or overt TD who may otherwise go unnoticed or untreated. As a primary step in diagnosing and ruling out TD, serum TSH levels are typically measured during screenings. If TSH levels are elevated, further blood work, including an assessment of the free T4 and free T3 ratio, may be ordered by the doctor. Debates exist regarding the definition of normal values for TSH test results, with age not currently factored into determining standard TSH limits. The consequences of screening, including potential incorrect diagnoses and excessive therapy, can have unfavorable effects on health and contribute to increased medical care costs. The "labeling effect" underscores that a patient's Quality of Life (QoL) may be negatively influenced by the psychological repercussions of a medical diagnosis. To explore the impact on health-related quality of life, questionnaires were administered in two investigations: one involving participants with abnormal TSH readings and another focusing on women with subclinical thyroid illness. Both studies indicated that abnormalities in TSH and thyroid hormone levels were not correlated with poor health-related quality of life, suggesting that the labeling effect might be responsible for the observed outcomes.

Uncorrected hypothyroidism may lead to an increased prevalence of various health issues, including heart problems, high cholesterol levels, mental retardation, neurological disorders, psychiatric indications, and fertility problems in non-pregnant individuals. Similarly, untreated hyperthyroidism has been associated with elevated risks of cardiac complications, such as ventricular fibrillation, cardiomyopathy, and heart attacks, along with systemic and neuropsychological symptoms, decreased bone mineral density, and fractures. Certain demographic factors contribute to a higher risk of developing Thyroid Dysfunction (TD). Women, individuals over the age of 60, those with a personal or family history of thyroid illness, and recently pregnant women are at an elevated risk. Additional risk factors include other autoimmune illnesses, goiter, past hyperthyroidism, and individuals who have undergone surgery or radiation treatment on the thyroid gland or head and neck region. Several variables affect Thyroid-Stimulating Hormone (TSH) levels, impacting the diagnosis of hypothyroidism. TSH threshold levels play a crucial role, as even a slight increase can lead to a lifetime medical disorder classification. Demographic, screening, and disease-related factors should be considered when diagnosing hypothyroidism, and the influence of multiple drugs and supplements on thyroid function testing must be addressed. For instance, the medication Metformin, commonly used for type 2 diabetes, may lower TSH levels without affecting Free T4 (FT4) in individuals with hypothyroidism or harmless thyroid nodules. The impact of treating subclinical hyperthyroidism on lipid levels remains inconsistent, with some studies suggesting possible benefits but others showing variable and ambiguous outcomes for clinical use. The relationship between therapy-related interim results and reliable indicators of cardiovascular morbidity or death is unclear, and no studies have directly examined the impact of treating subclinical thyroid dysfunction on ultimate health outcomes such as cardiac death or morbidity.

Several drugs and substances, including alemtuzumab, proton pumps, antiepileptics, steroids, rexinoids, dopamine analogs, hormone analogs, interferon-α, and tyrosine kinase inhibitors, have the potential to alter Thyroid-Stimulating Hormone (TSH) levels. Additionally, dietary factors such as bromide doses can enhance TSH activity, while local iodide consumption may impact TSH reference ranges. Dietary components like soya and medications containing magnesium or iron may impede synthroid absorption, resulting in elevated TSH levels. Before initiating therapy, it is crucial to conduct a comprehensive clinical history and examination of the patient to determine the cause and severity of Thyroid Dysfunction (TD). The treatment for hypothyroidism typically involves thyroid hormone replacement, specifically L-thyroxine therapy. However, excessive use of L-thyroxine can lead to hyperthyroidism and its associated side effects, including agitation, palpitations, atrial fibrillation, heart failure, exacerbation of angina pectoris, weight loss, and decreased bone mineral density, increasing the risk of fractures. In cases of overt hypothyroidism or subclinical hypothyroidism with TSH values exceeding 10.0 mIU/L, treatment is often warranted. Potential treatments for hyperthyroidism include anti-thyroid medications like methimazole and propylthiouracil, iodine radiation therapy, and thyroid transplantation. It is important to note that anti-thyroid medications may be associated with side effects such as itching, anemia, arthritis, sickness, stomach discomfort, lethargy, pale or dark-colored feces, diarrhea, fever, and sore throat.

The augmentation process, as depicted in Figure 3, integrates machine learning techniques for efficient analysis. Dimensionality reduction, feature selection, and predictive modeling contribute to precise data extraction, aiming to improve medical decisions. The

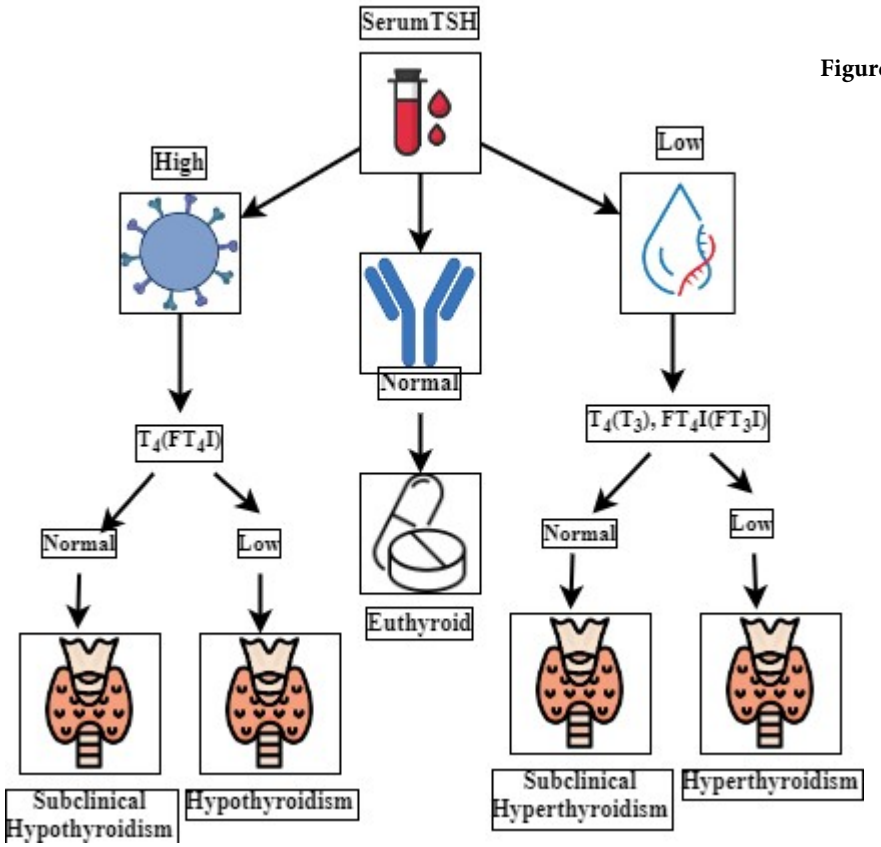

Figure 1. Screening of Thyroid dysfunction

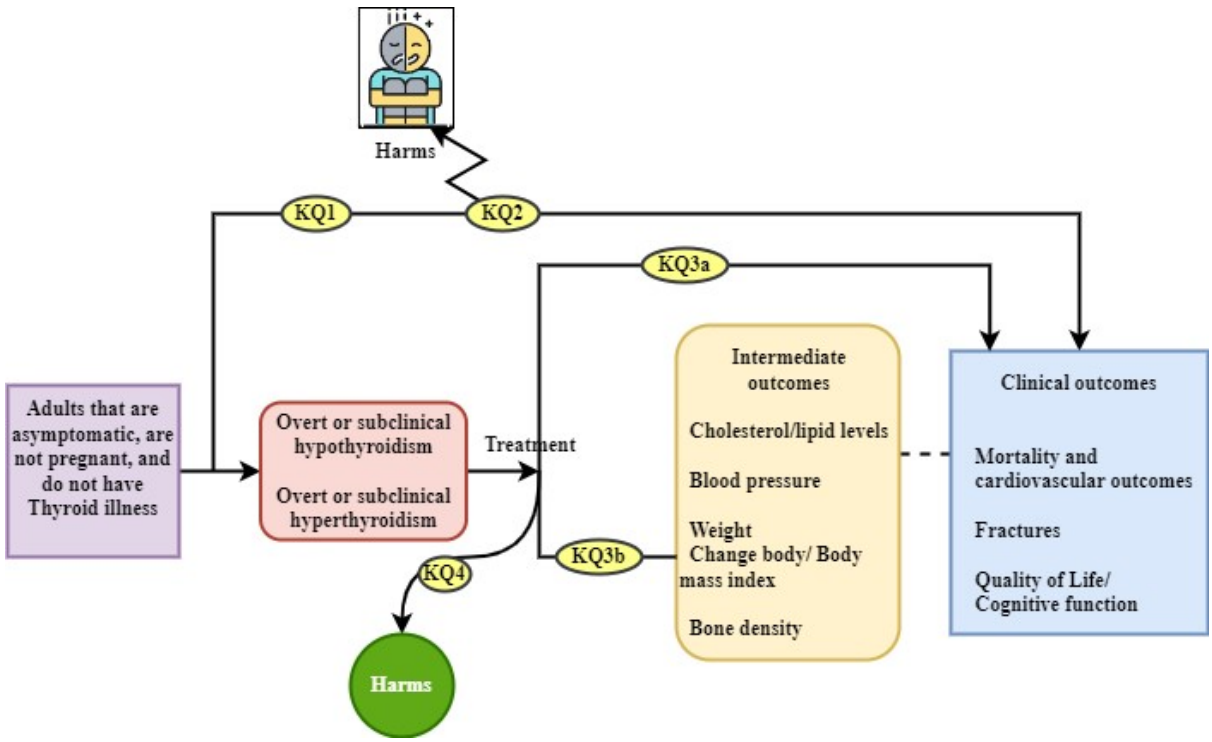

Figure 2. Potential Harms of Regular Screening

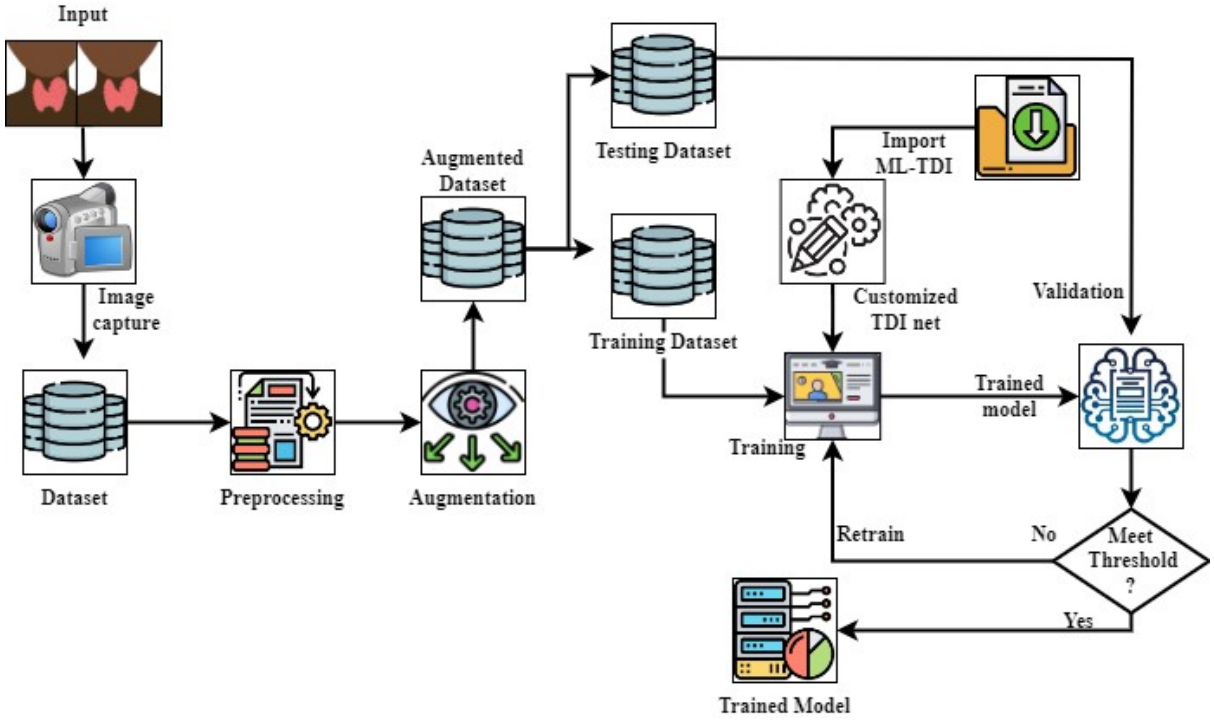

Figure 3. Machine Learning-based TD Identification

research emphasizes the importance of addressing gaps in data collection and considers various demographic and disease-related variables in the analysis. The proposed framework begins with a dataset as its foundation, which is then directed to the preprocessing section. Picture normalization occurs in this preprocessing stage, where photos undergo preprocessing before the augmentation procedure commences. In the augmentation setup, the dataset is divided into a training set and a test set. Figure 3 outlines the steps involved in importing the ML-TDI after the augmentation process, conducting a comparison with the modified ML-TDI, and subsequently saving the results as a trained model. During the initial processing phases, a thorough check for any missing data is performed. When a missing value is identified, it is substituted with the median as part of the data correction process.

Enhancing future medical decisions hinges on extracting accurate data for medical purposes. A crucial step in this process involves dimensionality reduction through feature selection in the dataset. This method effectively eliminates redundant or duplicate data, resulting in more precise and reliable outcomes. In the context of classification issues, feature selection identifies the most crucial characteristics for categorization. Addressing gaps in data collection, often arising from repeated extractions, is paramount. Key demographics encompass information about the individual's age, gender, medications, condition, and hormone levels (TSH, T3, and TT4), forming the foundation for classification. Within this framework, two distinct groups, denoted as Classes 0 and 1, represent negative and positive outcomes, respectively. Normal thyroid levels in a patient suggest the absence of thyroid illness.

As thyroid dysfunction carries significant health implications, the study explores the impact of screening on health outcomes, addressing potential risks such as overdiagnosis and unnecessary therapy. The labeling effect, where a medical diagnosis negatively affects a patient's quality of life, is considered, emphasizing the importance of thoughtful screening strategies. The research underscores the dynamic landscape of thyroid dysfunction diagnosis, leveraging advanced technologies and predictive modeling for improved accuracy and early intervention. The integration of machine learning in the diagnostic process holds promise for more precise and personalized healthcare decisions.

4. Conclusion

In conclusion, this review highlights the complexities in diagnosing thyroid dysfunction and the limitations of relying solely on TSH test results. We have discussed about the machine-learning screening tool, which can reduce incorrect diagnoses and provide quick and accurate diagnostic assistance in clinical settings. There are many potential benefits for widespread use, but further validation through clinical studies is essential before integrating this approach into routine medical practice. Thyroid dysfunction is often characterized biologically, leading to ongoing debates on diagnostic thresholds and contributing to potential overdiagnosis. The gold standard biomarker for diagnosing thyroid dysfunction is Thyroid-Stimulating Hormone (TSH), despite various challenges and confounding factors. To address the issue of incorrect diagnoses, this review discussed how a machine-learning approach can be useful as a screening tool for distinguishing hyperthyroidism and hypothyroidism using medical records and standard laboratory test data. The algorithm or preditive model might have high accuracy in differentiation, providing a potential solution for those without expertise in thyroid diseases.

Author Contributions

V. J. and P.G. conceptualized on thyroid disease, wrote and reviewed on diagnosis and models.

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Competing financial interests

The authors have no conflict of interest.

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