Machine Learning and Artificial Intelligence in Thyroid Cancer Screening and Diagnosis: A Comprehensive Systematic Review

Abstract

This systematic review explores the role of artificial intelligence (AI) and machine learning (ML) technologies in the diagnosis and treatment of thyroid cancers (TC), focusing on enhancing precision, risk assessment, and tailored care. By analyzing ten studies, the review highlights how AI and ML technologies, such as deep learning (DL) and computer-aided diagnostics (CAD), improve the accuracy of ultrasound imaging, risk stratification, and the detection of high-risk nodules. Despite advancements, challenges persist in transitioning to personalized care, including uneven prognostication and diagnostic uncertainty. The review evaluates the effectiveness of AI and ML compared to conventional methods, their ability to address diverse tumor characteristics, and their strengths and limitations in prognosis prediction. Findings suggest AI's potential in improving precision and risk assessment, but limitations such as inconsistent approaches and biases highlight the need for larger datasets and standardized procedures. Moreover, the review underscores the importance of interpretability and transparency in AI models and calls for further research to validate findings in clinical settings. Despite limitations and challenges, AI's transformative potential in TC management is evident, underscoring the need for ongoing investigation and integration into clinical practice.

Introduction

Over the past two decades, there has been a notable increase in the incidence of thyroid cancers (TC); the majority of TC cases are indolent [1][2]. Addressing these trends is crucial, given the continuous rise in incidence and death rates for aggressive papillary thyroid carcinomas (PTC) and advanced thyroid malignancies [1,3,4]. Accurate and efficient risk assessment is essential in the era of customized healthcare to tailor therapy effectively. Understanding TC's biological function, characterized by diverse morphological traits and molecular elements, is the initial step[40-43]. While image analysis remains the primary diagnostic method for TC, its limitations in providing a thorough evaluation are evident [5]. Primary human cell cultures from surgical biopsies and fine-needle aspiration (FNA) samples offer opportunities for customized treatments, though challenges persist in transitioning to personalized care [6], such as uneven prognostication and uncertainty surrounding cytopathological diagnosis.

Radiologists have identified computer-aided diagnostics (CAD) as valuable for identifying cancers beyond breast cancer [11]. Assessing disease phases aids in determining the extent of thyroid cancer progression. Deep learning (DL) enhances ultrasound (US) accuracy by extracting nonlinear features [12]. Artificial intelligence (AI) facilitates improved operational performance and swift access to critical information for physicians. CAD and AI simplify risk-stratification systems, enhancing thyroid nodule detection and evaluation [13]. Molecular testing combined with machine learning (ML) techniques helps forecast and detect high-risk nodules [14]. ML's intrinsic power in drawing conclusions beyond traditional statistical approaches is evident [15]. Classification models developed using ML methods show promise in improving thyroid imaging assessment CAD systems [16].

Machine learning (ML) enables completion of complex tasks, such as photo interpretation [18]. DL aids in lung cancer detection on CT images. ML applications are growing, offering a comprehensive approach to cancer diagnosis and prevention [25]. Clinical parameters influence disease prognosis, with ML generating predictions to assist in patient disease management [22,23]. Protein markers and microarray data are increasingly relied upon in cancer diagnosis [24]. ML techniques, including supervised and unsupervised methods, are expanding in healthcare domains [26]. Metabolomics technology sheds light on lung cancer characteristics [25]. ML aids in diagnosing cancer types, predicting susceptibility, and screening individuals [27]. ML models improve tumor diagnostic accuracy and optimize therapeutic approaches [27].

The most frequently used neural networks in oncology are the convolution neural network (CNN), recurrent neural network (RNN), and multilayer perceptron (MLP). Cytopathology and histology are common methods for cancer diagnosis [28]. Histology-based CNNs classify prostate, breast, and colon cancers successfully [29]. DL effectively distinguishes between benign and malignant tissues in lung cancer using whole-slide imaging. ML aids in forecasting tumor origins, even when unknown causes contribute to cancer cases [30].

Objective

The systematic review aimed to carefully assess and gather data on how machine learning (ML) and artificial intelligence (AI) are used in thyroid tumors (TC). The main goal was to see how AI and ML can improve diagnosing, predicting outcomes, and treating thyroid cancer. The study looked at both the good and bad sides of using AI and ML to process diagnostic images. It focused on answering these questions:

1. How well do AI and ML technologies find thyroid cancers compared to traditional image analysis methods?
2. Can AI and ML deal with the different biological and physical aspects of thyroid tumors to give better risk assessments and personalized treatment?
3. What are the strengths and weaknesses of current AI and ML models in telling if a thyroid nodule is harmless or cancerous?
4. How much can AI and ML help in predicting the outcome and spotting thyroid cancer early, especially before symptoms appear?

Methodology

Search Strategy

We extensively searched through various databases like Embase, Web of Science, PubMed, and Scopus to find studies about how artificial intelligence (AI) and machine learning (ML) are used in dealing with thyroid cancer. To make sure we found everything relevant, we used different combinations of keywords related to AI, ML, thyroid cancers, and related topics. Our search method was carefully designed with boolean operators to match the syntax of each database.

Eligibility Criteria

Inclusion Criteria

We extensively searched through various databases like Embase, Web of Science, PubMed, and Scopus to find studies about how artificial intelligence (AI) and machine learning (ML) are used in dealing with thyroid cancer. To make sure we found everything relevant, we used different combinations of keywords related to AI, ML, thyroid cancers, and related topics. Our search method was carefully designed with boolean operators to match the syntax of each database.

Exclusion Criteria

To maintain the focus and quality of our review, we excluded studies that didn't meet certain criteria. Publications not in English were excluded for clarity. We also left out conference abstracts, letters, editorials, and case reports because they lack the depth needed for a systematic review. Materials that didn't specifically talk about using AI or ML for thyroid tumors were also excluded to stay on topic. We avoided duplicating data by excluding duplicate articles. Table 1 shows the PICOS framework and our criteria for this review.

Table 1: PICOS framework and eligibility criteria

Criteria	**Description**
Population	Human subjects diagnosed with thyroid cancers.
Intervention	Original research articles or reviews focusing on the application of AI and ML in the context of thyroid cancers.

Comparison	Not applicable (as this is not a comparative study).
Outcomes	Studies reporting outcomes related to the diagnosis, prognosis, or management of thyroid cancers using AI or ML techniques.
Study Design	Various study designs, including observational studies, clinical trials, and reviews.

Data Extraction

We carefully gathered all relevant information from each included study to synthesize our findings. This included details like authors, publication year, research design, and participant demographics. We explained the AI and ML techniques used in each study to help readers understand the methods. We also extracted data about how AI or ML methods were used for diagnosing, predicting outcomes, and treating thyroid cancers. Key results and conclusions from each study were noted to give a comprehensive overview.

Quality Assessment

We used established tools to assess the quality of the included studies based on their research designs. For clinical trials, we used the Cochrane Risk of Bias tool, and for observational research, we used the Newcastle-Ottawa Scale. Two reviewers independently evaluated each study, resolving any discrepancies through discussion or consultation with a third reviewer if needed.

Results

Study Selection

A systematic search across PubMed, Cochrane Library, and Google Scholar databases yielded a total of 218 records. After removal of duplicates, 121 records remained. Screening of titles and abstracts narrowed down the selection to 74 potentially relevant records. Following full-text screening, 10 studies met the inclusion criteria for the systematic review. Figure 1 illustrates the comprehensive flow diagram depicting the search and selection process.

Figure 1; PRISMA Flow Chart

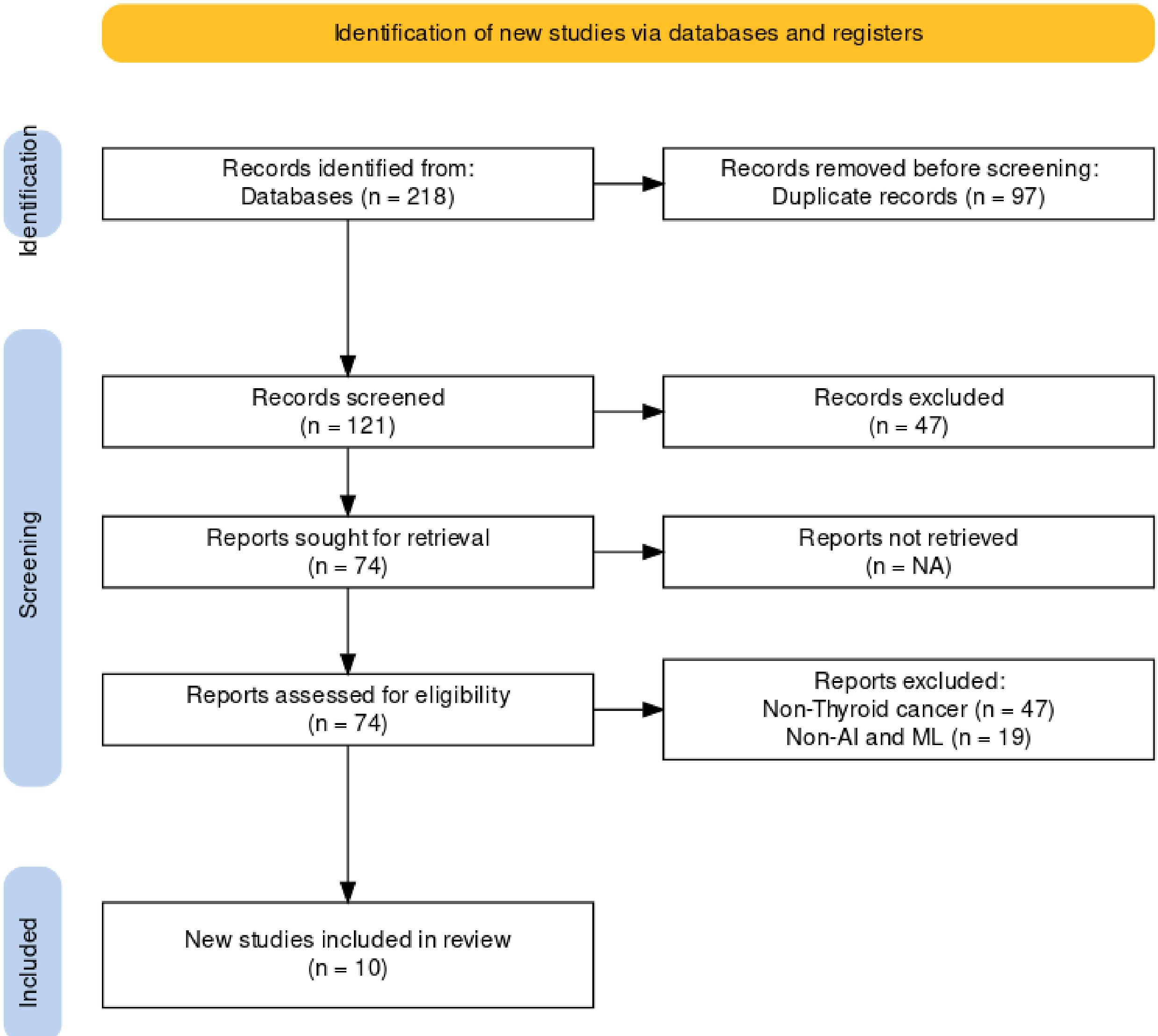
Identification of new studies via databases and registers
Identification
Records identified from:
Databases (n = 218)
Records removed before screening:
Duplicate records (n = 97)
Screening
Records screened
(n = 121)
Records excluded
(n = 47)
Reports sought for retrieval
(n = 74)
Reports not retrieved
(n = NA)
Reports assessed for eligibility
(n = 74)
Reports excluded:
Non-Thyroid cancer (n = 47)
Non-AI and ML (n = 19)
Included
New studies included in review
(n = 10)

Table 2 outlines the studies incorporated in this article.

Table 2: Characteristics of included studies

Author & Year	**Study Design**	**Interventions**	**Population**	**Outcome Measures**	**Findings**

Yoon et al. (2020)	Retrospective Observational Study	Computer-aided diagnosis (CAD) program using deep learning Convolutional Neural Network (CNN)	469 patients with thyroid cancer (380 positive, 89 negative for BRAFV600E mutation)	Association of CAD value with BRAFV600E mutation, Area Under the Receiver Operating Characteristic (AUC) of Receiver Operating Characteristic (ROC) curves for CAD value and multivariable model	Older age, smaller size, and higher CAD value significantly associated with BRAFV600E mutation. CAD value yielded an AUC of 0.646 for predicting BRAFV600E mutation. Multivariable model (age, size, and CAD value) had an AUC of 0.706, significantly better than CAD value alone. Deep learning-based CAD program shows promise in predicting BRAFV600E mutation in thyroid cancer. Multicenter studies with larger sample sizes are recommended for further validation.

Bellantuono et al. (2023)	eXplainable Artificial Intelligence analysis	Machine Learning procedure for discrimination of healthy/benign vs. malignant nodules using Raman spectra, Boruta feature selection, Synthetic Minority Over-sampling Technique (SMOTE) algorithm for imbalanced dataset, Random Forest, eXtreme Gradient Boosting (XGBoost), Support Vector Machine (SVM), and Gaussian Naïve Bayes classifiers	Patients with thyroid nodular pathology, 54 subjects (34 females, 20 males), aged 46.3 years on average, who underwent surgery (total thyroidectomy) after a cytological diagnosis of indeterminate, suspicious, or malignant nodules	Classification performance of Machine Learning algorithms (Random Forest, XGBoost, SVM, Gaussian Naïve Bayes) quantified by AUC, feature importance using Boruta, and synthetic data generation using SMOTE	Random Forest is identified as the best classifier (median AUC 0.9441, interquartile range 0.0049) for healthy/benign vs. cancer tissue classification. XGBoost, SVM, and Gaussian Naïve Bayes also explored. eXplainable Artificial Intelligence (XAI) analysis (SHapley Additive exPlanations - SHAP values) for interpretability. Performance evaluated on 72 samples (59 unambiguous and 13 ambiguous). Identified limitations in classifying ambiguous spectra with reduced AUC (median 0.7949, IQR 0.0135). Impactful features include carotenoid and oxidized cytochrome bands.

Ha, E. J., & Baek, J. H. (2021)	Review and developmental overview of AI-based CAD systems	Application of CAD systems by loading ultrasound images from Picture Archiving and Communication System (PACS). Real-time application during Ultrasound (US) examinations	Patients with thyroid nodules undergoing ultrasound imaging	Analysis of sonographic characteristics (echogenic foci, echogenicity, texture, margin, anechoic areas, height/width ratio, nodule shape, and size) and risk of malignancy based on Thyroid Imaging Reporting and Data System (TI-RADS) classifications	AmCAD-UT: Similar sensitivity (87.0%) but lower specificity (68.8%) compared to clinical experts using TI-RADS. Food and Drug Administration (FDA) 510(k) cleared. S-Detect 1: Comparable sensitivities (80.0%-92.0%) but lower specificity (74.6%-88.1%) compared to experienced radiologists. FDA approval in progress. S-Detect 2: Comparable sensitivities (81.4%) but lower specificity (68.2%-81.9%) compared to experienced radiologists.

Agarwal et al. (2021)	Evaluation and comparison of AI algorithms	Implementation of AI algorithms and machine learning models to analyze diagnostic imaging data	Individuals undergoing diagnostic tests for cancer, including imaging tests, endoscopic procedures, biopsy, and cytology	Assessment of the diagnostic accuracy of AI algorithms and machine learning models in differentiating benign and malignant tumors	AI improves diagnostic accuracy by analyzing large imaging datasets, leveraging technical advances and hardware enhancements for neural network training. It excels in early diagnosis, particularly in breast and lung cancer, surpassing human specialists in breast cancer prognosis and providing early lung cancer predictions. In gastric cancer, Convolutional Neural Networks aid in invasion depth diagnosis through gastric endoscopy. AI techniques, coupled with imagery, enable early identification of oral cancer. Overall, AI significantly enhances cancer diagnosis precision and extends forecasting capabilities.

Xi et al. (2022)	Prospective study using machine learning	Six machine learning models trained on a clinical dataset from 724 patients undergoing thyroidectomy. Models included Gradient Boosting, Logistic Regression, Linear Discriminant Analysis, SVM, and Random Forest	724 patients at Shengjing Hospital, China, with demographic info, ultrasound features, and blood test results	Models demonstrated superior accuracy, with Random Forest leading. Gradient Boosting excelled in sensitivity, Logistic Regression in specificity. Variable importance analysis highlighted key predictors. Models outperformed expert assessment in accuracy and F1 score	Machine learning, especially Random Forest and Gradient Boosting, improved thyroid nodule malignancy prediction compared to expert assessment. Models offered valuable insights into nodule characteristics, enhancing preoperative thyroid cancer diagnosis.

Peng et al. (2021)	Multicentre Diagnostic Study	Development and application of the deep-learning AI model (ThyNet) for differentiating thyroid nodules	Patients aged 18 or older with thyroid nodules at least 3 mm in diameter identified via ultrasound	Primary Endpoint: Area Under the Receiver Operating Characteristic Curve (AUROC) for thyroid nodule diagnosis. Secondary Endpoints: Accuracy, Sensitivity, Specificity, Positive Predictive Value (PPV), Negative Predictive Value (NPV)	ThyNet AUROC: 0.922 (95% CI 0.910–0.934) was significantly higher than radiologists ($p < 0.0001$). ThyNet-assisted strategy improved radiologists' AUROC from 0.837 to 0.875 ($p < 0.0001$). In a simulated scenario, ThyNet-assisted strategy reduced unnecessary fine needle aspirations by 26.7%. Missed malignancy decreased from 18.9% to 17.0% with ThyNet-assisted strategy.

Olatunji et al. (2021)	Retrospective Case Study	Machine learning-based tools development for early detection of thyroid cancer (TC)	Techniques used: Random Forest (RF), Artificial Neural Network (ANN), Support Vector Machine (SVM), Naïve Bayes (NB)	Patients from the Kingdom of Saudi Arabia	RF technique demonstrated the highest accuracy at 90.91%. SVM, ANN, and NB achieved accuracy rates of 84.09%, 88.64%, and 81.82%, respectively. Emphasis on early detection at pre-symptomatic stages. RF recommended as the preferred technique for this specific problem.

Zhou et al. (2022)	Experimental Study (Comparison of new ultrasound technologies)	Ultrasonic intelligent diagnosis of papillary thyroid cancer based on machine learning, involving Contrast-Enhanced Ultrasound (CEUS) and Ultrasound Elastography (UE) technologies	Patients with papillary thyroid carcinoma (PTC), 70 cases (10 male, 60 female), tumor diameter ≤10 mm, 107 lymph nodes	Characteristics of ultrasound images (CEUS and UE). Diagnostic effectiveness of new ultrasound technologies (CEUS and UE) in distinguishing between benign and malignant nodules	CEUS and UE showed significant differences in enhancement mode, intensity, early regression, and edge enhancement between micro benign and malignant tumors. UE demonstrated higher sensitivity and diagnostic efficiency compared to CEUS in the differential diagnosis of thyroid micro benign and malignant nodules. Combined use of CEUS and UE resulted in 78.43% sensitivity and 78.67% specificity for diagnosing thyroid micro benign and malignant nodules.

Zhao et al. (2019)	Meta-analysis	Evaluation of computer-aided diagnosis system (CAD) for thyroid nodules on ultrasound	536 patients with 723 thyroid nodules	Sensitivity, Specificity, Positive Likelihood Ratio (LR), Negative LR, Diagnostic Odds Ratio (DOR)	Findings (CAD System): Sensitivity: 0.87 (95% CI, 0.73–0.94), Specificity: 0.79 (95% CI, 0.63–0.89), Positive LR: 4.1 (95% CI, 2.5–6.9), Negative LR: 0.17 (95% CI, 0.09–0.32), DOR: 25 (95% CI, 15–42), Summary Receiver Operating Characteristic (SROC) AUC: 0.90 (95% CI, 0.87–0.92). Findings (Experienced Radiologists): Sensitivity: 0.82 (95% CI, 0.69–0.91), Specificity: 0.83 (95% CI, 0.76–0.89), Positive LR: 4.9 (95% CI, 3.4–7.0), Negative LR: 0.22 (95% CI, 0.12–0.38), DOR: 23 (95% CI, 11–46), SROC AUC: 0.96 (95% CI, 0.94–0.97).

Kuang et al. (2022)	Metabolomic analysis, machine-learning model development	Analysis of existing data of thyroid cancer (TC) metabolites, development of a machine-learning model using metabolite biomarkers	The study involved datasets related to papillary thyroid cancer (PTC) patients	Classification accuracy of machine-learning models (LogitBoost, AdaBoostM1, RandomForest, etc.) through 10-fold cross-validation. Identification of metabolic pathways related to TC	Highest classification accuracy: LogitBoost - 87.30%, Various classifiers achieved accuracies above 80%. Independent testing showed 100% accuracy in identifying TC-related metabolites .

Discussion

A deep learning convolutional neural network (CNN)-based computer-aided diagnostic (CAD) tool was developed for diagnosing thyroid cancer in a retrospective observational study conducted by Yoon et al. in 2020 [30]. Out of the 469 patients with thyroid cancer included in the study, 380 tested positive for the BRAFV600E mutation, while 89 did not. The association between the CAD value and the BRAFV600E mutation was assessed by calculating the area under the receiver operating characteristic (ROC) curve (AUC) for the CAD value and a multivariable model. It was found that the BRAFV600E mutation was significantly correlated with higher CAD values, smaller sizes, and older ages. The CAD value yielded an AUC of 0.646 for predicting the BRAFV600E mutation. When age, size, and CAD value were combined in the multivariable model, the AUC increased to 0.706, which was significantly higher than using the CAD value alone. Based on these results, the deep learning-based CAD program may have the ability to predict the BRAFV600E mutation in thyroid cancer. However, the authors suggest further validation through multicenter research with larger sample sizes.

Thyroid cancer detection was explored by Bellantuono et al. in a paper published in 2023 using eXplainable Artificial Intelligence (XAI) analysis of Raman spectra [31]. Various classifiers such as Random Forest, XGBoost, Support Vector Machine, and Gaussian Naïve Bayes were employed, along with Boruta feature selection, the synthetic minority oversampling technique (SMOTE) algorithm for imbalanced datasets, and Raman spectra, to differentiate between benign and malignant nodules. The study included 54 patients with thyroid nodular pathology (mean age 46.3 years) who underwent total thyroidectomy following a cytological diagnosis of ambiguous, suspicious, or malignant nodules. The Random Forest classifier performed the best, achieving a median AUC of 0.9441 for classifying tissue as either cancerous or healthy. Important features like oxidized and carotenoid cytochrome bands were identified using XAI analysis and SHAP values for interpretability. The study highlighted the challenges of identifying ambiguous spectra while showcasing the potential of machine learning in diagnosing thyroid cancer with the assistance of XAI.

Ha and Baek provided a comprehensive analysis and overview of AI-based computer-aided diagnostic (CAD) techniques for thyroid nodules in 2021 [32]. CAD systems were used in real time during ultrasonography tests by importing ultrasound images from Picture Archiving and Communication Systems (PACS). The study focused on sonographic features, using the Thyroid Imaging Reporting and Data System (TI-RADS) categories to determine malignancy risk. Various CAD systems like AmCAD-UT, S-Detect 1, and S-Detect 2 were evaluated against radiologists and clinical specialists. Although the sensitivity of CAD systems was similar to or slightly lower than that of clinical specialists, the results showed that CAD systems can be used in real-time ultrasound exams.

Agarwal et al. compared machine learning models and AI algorithms for cancer diagnosis in 2021 [33]. Using AI algorithms and machine learning models, the study analyzed diagnostic imaging data from patients undergoing various cancer diagnostic procedures, focusing on differentiating between benign and malignant cancers. The findings demonstrated how AI techniques can improve the precision of cancer diagnosis by leveraging hardware updates and technology breakthroughs to train neural networks. It was shown that AI algorithms can be used for early detection, prognostication, and enhanced accuracy in various cancer types, including stomach, oral, lung, and breast cancer. The study emphasized how AI-generated predictions, which are more detailed and accurate, can enhance overall cancer detection.

Xi et al. used ten-fold cross-validation and machine learning with bootstrap analysis in a prospective study to predict thyroid nodule malignancy [34]. Using a clinical dataset of 724 patients undergoing thyroidectomy, six machine learning models were developed, with Random Forest performing the best overall. Logistic Regression showed excellent specificity, while Gradient Boosting had better sensitivity. The models were better in terms of accuracy and F1 score than expert judgment, demonstrating the potential of machine learning, especially Random Forest and Gradient Boosting, in preoperative thyroid cancer diagnosis.

Peng et al. created and utilized the ThyNet deep-learning AI model to differentiate thyroid nodules in a multicenter diagnostic investigation [35]. ThyNet outperformed radiologists in identifying thyroid nodules, improving accuracy and reducing unnecessary procedures. Olatunji et al. conducted a retrospective case study in 2021, demonstrating high accuracy rates for early thyroid cancer identification using machine learning techniques [36]. Zhou et al. evaluated machine learning for thyroid nodule identification, highlighting the potential of combining ultrasound elastography (UE) and contrast-enhanced ultrasound (CEUS) for improved accuracy [37]. Lastly, Zhao et al. compared a computer-aided diagnostic system (CAD) with skilled radiologists, showing that the CAD system outperformed radiologists in identifying thyroid nodules [38]. Kuang et al. used metabolomic analysis and machine learning to classify metabolite biomarkers associated with thyroid cancer, showing promising results in efficiently identifying thyroid cancer [39].

Limitations

The reviewed literature, despite its promising implications, exhibits significant limitations. The wide variations in research methodologies, patient cohorts, and AI models make it challenging to draw definitive conclusions applicable across different contexts. Given that many studies rely on observational or retrospective designs, larger-scale randomized controlled trials may be essential to ascertain the therapeutic effectiveness of AI and ML in diagnosing and treating thyroid cancer. Moreover, the diversity of data sources, imaging techniques, and diagnostic criteria among studies introduces potential biases and hampers the generalizability of findings. For instance, Bellantuono et al.'s study illustrates the challenges in distinguishing ambiguous spectra, underscoring practical limitations.

Yoon et al.'s suggestion for larger, multicenter investigations underscores the need for more comprehensive validation and highlights the constraints imposed by current sample sizes. Addressing issues related to interpretability and transparency of AI models, as demonstrated by Bellantuono et al.'s XAI project, is imperative before widespread adoption of AI technology in healthcare settings. Furthermore, the focus on specific AI applications and exclusion of non-English research may introduce publication bias and limit our understanding of the field.

Conclusion

In conclusion, while significant advancements have been made in AI and ML for diagnosing and prognosticating thyroid cancer, caution is warranted due to discrepancies and shortcomings noted in various studies. Future research in this area should prioritize standardized methodologies, larger and more diverse sample sizes, and inclusion of various patient demographics to enhance therapeutic utility and generalizability. Additionally, considerations of interpretability, transparency, and ethical implications will be pivotal in the seamless integration of AI and ML into routine clinical practice. Overall, this systematic review underscores the need for further investigation and validation in real-world clinical settings and emphasizes the transformative potential of AI in the management of thyroid cancer.

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