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THE ROLE OF ARTIFICIAL INTELLIGENCE APPROACHES IN THE DIAGNOSIS OF CELIAC DISEASE FROM DUODENAL BIOPSY IMAGES: A SYSTEMATIC REVIEW OF THE LITERATURE

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ABSTRACT

Background: Celiac disease (CD) is a common autoimmune condition with complex diagnostic pathways. Diagnostic accuracy is critical in ensuring timely treatment and preventing long-term complications. In the past few years, there has been a surge in research exploring the application of artificial intelligence (AI) and machine learning (ML) in the diagnosis of CD. This systematic review aimed to collate and assess recent studies investigating the role of AI and ML in CD diagnosis. **Methods:** A comprehensive literature search was conducted in PubMed, Scopus, Web of Science, and Google Scholar using relevant keywords and MeSH terms. Original research studies published in the last twenty years were included if they focused on AI/ML application in CD diagnosis and provided sufficient data for analysis. The selection, data extraction, and synthesis were conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. **Findings:** Nine studies were selected for review, which demonstrated promising results in the application of AI/ML for CD diagnosis. A variety of models and techniques, including Support Vector Machine (SVM), T-cell receptor sequencing, Steerable Pyramid Transform (SPT), and convolutional neural networks (CNNs), demonstrated high accuracies in distinguishing CD from non-CD cases. The review also highlighted the potential role of AI/ML in clinical decision support systems. **Conclusion:** This systematic review highlights the significant potential of AI/ML in enhancing the diagnostic process of CD. As AI/ML technologies continue to evolve, their integration into routine clinical practice could revolutionize CD management. Nevertheless, continual research and appraisal are essential in navigating the evolving landscape of these technologies and harnessing their full potential for patient benefit.

KEYWORDS: Celiac Disease, Artificial Intelligence, Machine Learning, Diagnosis, Systematic Review.

Glossary of Terms for The Layman

1. **Artificial Intelligence (AI)**: A branch of computer science dealing with the simulation of intelligent behavior in computers, enabling them to perform tasks that would typically require human intelligence. Examples include image and speech recognition, learning, and problem-solving.

2. **Machine Learning (ML)**: A subset of AI, where computers are programmed to learn and improve from experience. It involves creating mathematical algorithms that allow computers to learn from (and make predictions or decisions based on) data.
3. **Support Vector Machine (SVM)**: A type of machine learning algorithm used in classification and regression analysis. It is particularly useful in cases where the data has many attributes or features.
4. **T-cell Receptor Sequencing**: This is a technique used to determine the sequence of the T-cell receptor (a molecule found on the surface of T cells, a type of white blood cell). Variations in this sequence can indicate different disease states.
5. **Steerable Pyramid Transform (SPT)**: A multi-scale image representation method used in image processing that allows one to perform localized operations on images.
6. **Convolutional Neural Networks (CNNs)**: A deep learning algorithm that is particularly effective for processing grid-like data, such as an image. CNNs are structured to recognize spatial hierarchies in an image, making them a popular choice for image recognition tasks.
7. **Clinical Decision Support System (CD-CDSS)**: A health information technology system designed to provide physicians and other health professionals with clinical decision support, that is, assistance with clinical decision-making tasks.
8. **Non-Celiac Duodenitis (NCD)**: A condition characterized by inflammation of the duodenum (the first part of the small intestine), but not caused by celiac disease.
9. **Villous Atrophy**: A condition where the microscopic finger-like projections (villi) that line the small intestine are damaged or destroyed. It is a hallmark of celiac disease.
10. **Histopathological Diagnosis**: The diagnosis of diseases based on the microscopic examination of tissue samples.
11. **Enteropathies**: Diseases of the intestine.
12. **High-Resolution Biopsy Images**: Images of tissue samples that have a high level of detail, allowing for more accurate analysis and diagnosis.
13. **Ensemble in ML**: An ensemble method in machine learning uses multiple learning algorithms to obtain better predictive performance than could be obtained from any of the constituent learning algorithms alone.

INTRODUCTION

Celiac disease (CD) is a chronic autoimmune disorder triggered by the ingestion of gluten in genetically predisposed individuals. The global prevalence of CD is about 1% and, in the United States, it affects about one in 133 people.[1] CD primarily affects the small intestine and can lead to various clinical manifestations, ranging from typical gastrointestinal symptoms such as diarrhea, abdominal pain, and weight loss, to atypical symptoms such as iron-deficiency anemia, osteoporosis, and neurological disorders.[2]

Diagnosis of CD has traditionally relied on the combination of clinical symptoms, serology, and histology, with the latter often regarded as the gold standard.[3] Histological examination of duodenal biopsy specimens demonstrating villous atrophy and intraepithelial lymphocytosis is considered diagnostic for CD.[4] However, due to the patchy nature of the disease, the histological changes may sometimes be missed, leading to underdiagnosis.[5] Additionally, other conditions, such as tropical sprue, Crohn's disease, and immune deficiencies, may mimic CD histologically, causing diagnostic confusion.[6] Moreover, interpretation of histopathological slides requires a high level of expertise and can be time-consuming.[7]

In recent years, advancements in artificial intelligence (AI) and machine learning (ML) have revolutionized many fields, including medicine and healthcare. In particular, deep learning, a subset of ML, has shown great promise in image recognition tasks.[8] Given the visual nature of histopathology, there is growing interest in applying AI/ML technologies to assist pathologists in diagnosing various diseases, including CD. Several studies have demonstrated the potential of AI/ML in CD diagnosis using histopathological images, achieving high accuracy rates.[9–11].

This review aims to systematically analyze the recent literature on the application of AI/ML in the diagnosis of CD. The objectives are to assess the types of AI/ML technologies used, the datasets employed, the measures used to evaluate their performance, and their key findings. This will not only provide an overview of the current state of AI/ML applications in CD diagnosis but also highlight gaps in the research that could guide future studies in this area.

METHODS

The methodology for this systematic review was developed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The review aimed to provide a comprehensive examination of recent literature to assess the latest advancements in AI and Machine Learning (ML) applications for diagnosing Celiac Disease (CD).

Search Strategy

A systematic literature search was conducted focusing on the research published within the last twenty years. This temporal limit ensured the incorporation of the most recent and thus, most relevant studies. The search was carried out on four databases, namely PubMed, Scopus, Web of Science, and Google Scholar, for relevant studies. Keywords and MeSH terms such as 'Artificial Intelligence', 'Machine Learning', 'Celiac Disease', 'Diagnosis', and their combinations were used for the search. No restrictions were imposed based on language

or geographical location, and only peer-reviewed articles were considered for inclusion.

Study Selection

The articles retrieved from the initial search were independently screened by two reviewers based on their titles and abstracts for relevance. Any discrepancies between the reviewers were resolved through discussion or consultation with a third reviewer if needed. The full texts of the shortlisted articles were obtained for further in-depth scrutiny. Studies were included if they met the following criteria: original research studies published within the last twenty years, studies focusing on AI and ML approaches in diagnosing CD, and studies that provided sufficient data for extraction and analysis.

Data Extraction and Synthesis

Data from the included studies were systematically extracted by the research team. The data extracted encompassed the following details: author names, year of publication, study design, AI/ML approach used, the dataset used or population studied, outcome measures, and key findings. The extracted data were then synthesized and analyzed qualitatively. The key findings were consolidated and summarized, and the results were categorized based on the study design, AI/ML approach, and the dataset used. This provided an overview of the current state of AI and ML applications in CD diagnosis. The synthesis also highlighted the potential impact of these studies on the field of CD diagnosis and identified gaps in the existing research for future exploration.

RESULTS

Of the 614 studies identified from the database search, 57 duplicates were removed. Therefore, a total of 557 studies were screened for titles and abstracts. Of these, only 42 studies were reviewed using full-texts, after which 9 studies were included in this systematic review (**Figure 1**). The characteristics of the included studies are listed in **Table 1**.

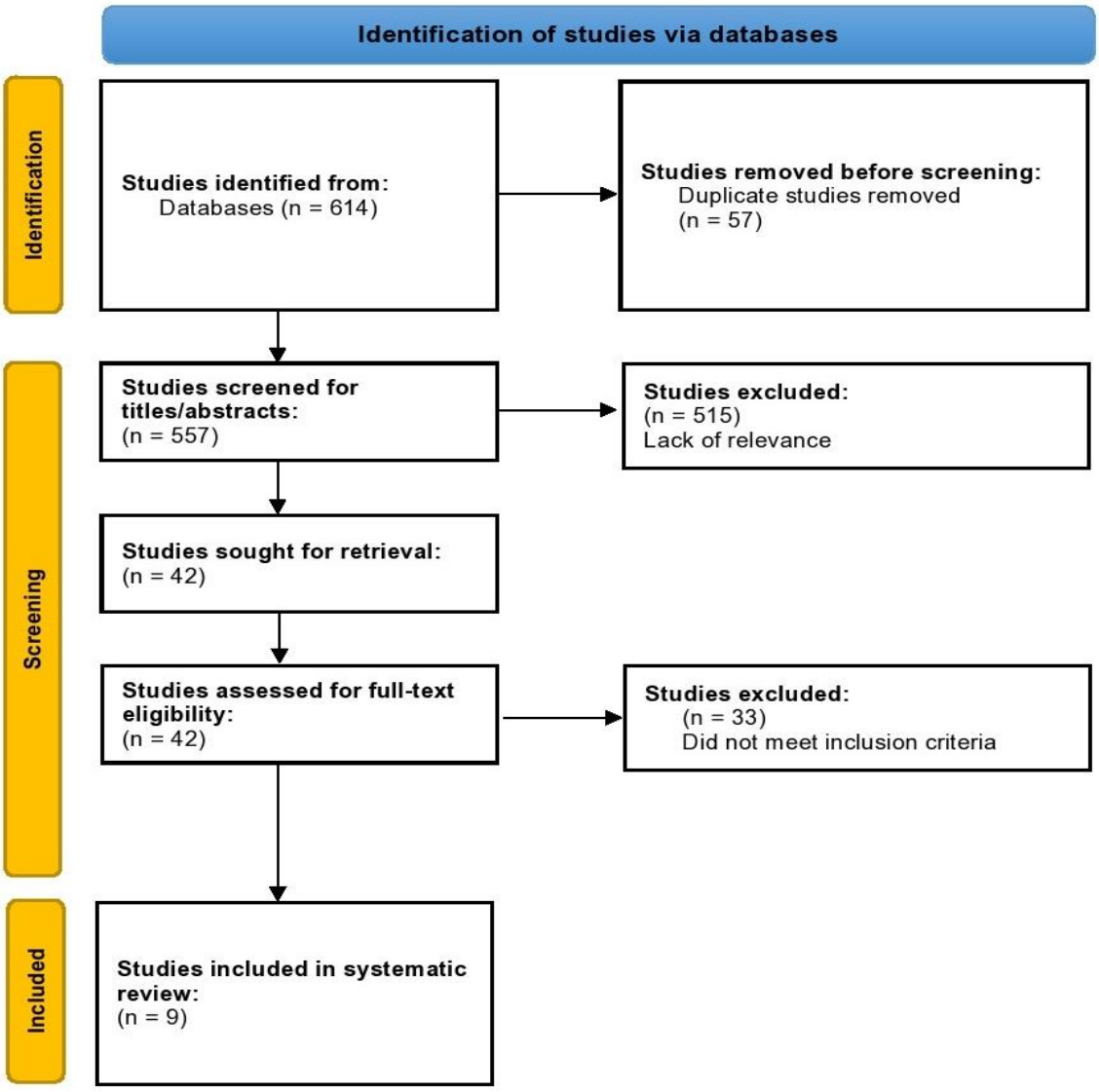

Figure 1: PRISMA flowchart depicting the study selection process.

Table 1. Characteristics of the Included Studies (N=9).

Author, Year	Title	Study Design	Intervention (AI/ML Approach)	Dataset Used/Population	Outcome Measures	Key Findings
Faust, 2023 (12)	Automated analysis of small intestinal lamina propria to distinguish normal, Celiac Disease, and Non-Celiac Duodenitis biopsy images	Comparative study of AI models	Support Vector Machine (SVM)	High magnification biopsy images of duodenal LP from different clinical stages of CD, NCD, and normal controls	Accuracy of AI model in distinguishing normal, CD, and NCD	SVM achieved 98.53% accuracy in distinguishing normal controls from CD patients and 98.55% in distinguishing normal controls from NCD
Foers, 2021 (13)	Classification of intestinal T-cell receptor repertoires using machine learning methods can identify patients with coeliac disease regardless of dietary gluten status	Comparative study of T-cell receptor sequencing and histopathological diagnosis	Machine learning-based analysis of the TCR repertoire	Duodenal biopsies from CeD (n = 44) and non-CeD (n = 32) patients	Accuracy of TCR sequencing in diagnosing CeD	100% accuracy with TRD repertoire, 94.4% accuracy with TRG repertoire. Particularly useful for diagnosing patients unable to tolerate dietary gluten or with equivocal biopsy features
Koh, 2021 (14)	Automated interpretation of biopsy images for the detection of celiac disease using a machine learning approach	Development and testing of an AI-based diagnostic tool	Steerable Pyramid Transform (SPT) with six classifiers	H&E stained and RGB biopsy images	Accuracy of AI tool in classifying villous atrophy	88.89% accuracy for two-class classification of H&E stained biopsy images, 82.92% for RGB images, and 72% for multi-class biopsy images
Syed, 2021 (15)	Artificial Intelligence-based Analytics for Diagnosis of Small Bowel Enteropathies and Black Box Feature Detection	Development and testing of an AI-based diagnostic platform	Deep learning convolutional neural networks (CNNs) including one with multizoom architecture	High-resolution biopsy images from 150 children	Accuracy of AI in classifying small bowel enteropathies	ResNet50 and shallow CNN demonstrated 98% and 96% case-detection accuracy, respectively, increasing to 98.3% with an ensemble
Pastore, 2019 (16)	Physician Review of a Celiac Disease Risk Estimation and Decision-Making Expert System	Development and validation of a clinical decision support system	Exsys Corvid for expert analysis (CD-CDSS)	Evaluation by 13 experts in the field of celiac disease	Agreement of experts on the utility and accuracy of CD-CDSS	100% agreement among experts that CD-CDSS is medically accurate and capable of guiding health care professionals through the diagnostic process
Sali, 2019 (17)	CeliacNet: Celiac Disease Severity Diagnosis on Duodenal Histopathological Images Using Deep Residual Networks	Diagnostic model development	Deep residual networks	120 whole slide images from 15 CD patients	AUC	Model achieved an AUC greater than 0.96 in all classes for CD severity classification using histological images
Syed, 2019 (18)	Assessment of Machine Learning Detection of Environmental Enteropathy and Celiac Disease in Children	Prospective diagnostic study	Convolutional Neural Network (CNN)	Duodenal biopsy slides from 102 children at three hospitals	Classification accuracy, incorrect classification rate	The model demonstrated 93.4% case-detection accuracy with a false-negative rate of 2.4%. Most incorrect classifications were between patients with CD and healthy patients

Wei, 2019 (19)	Automated Detection of Celiac Disease on Duodenal Biopsy Slides: A Deep Learning Approach	Diagnostic model development	Residual convolutional neural network	Independent set of 212 duodenal biopsy images	Accuracy, area under the receiver operating characteristic curve	Model identified CD, normal tissue, and nonspecific duodenitis with accuracies of 95.3%, 91.0%, and 89.2%, respectively. AUC was >0.95 for all classes
Lahner, 2005 (20)	Possible contribution of artificial neural networks and linear discriminant analysis in recognition of patients with suspected atrophic body gastritis	Diagnostic model development	Artificial Neural Networks (ANNs) and Linear Discriminant Analysis (LDA)	Data from 350 consecutive outpatients (263 with ABG, 87 controls)	Accuracy	Overall accuracies of ANNs and LDA for predicting patients with ABG were as high as 98.8% and 96.8%, respectively, depending on the variables included in the model

Abbreviations: AI: Artificial Intelligence; SVM: Support Vector Machine; LP: Lamina Propria; CD: Celiac Disease; NCD: Non-Celiac Duodenitis; TCR: T-cell Receptor; CeD: Coeliac Disease; TRD: T-cell Receptor; Delta (a type of T-cell receptor); TRG: T-cell Receptor Gamma (a type of T-cell receptor); SPT: Steerable Pyramid Transform; H&E: Hematoxylin and Eosin (a type of stain used in histology); RGB: Red, Green, Blue (a color model used in imaging); CNN: Convolutional Neural Networks; CD-CDSS: Celiac Disease Clinical Decision Support System; AUC: Area Under the Curve; ANNs: Artificial Neural Networks; LDA: Linear Discriminant Analysis; ABG: Atrophic Body Gastritis.

Faust and colleagues (2023) conducted an automated analysis of small intestinal lamina propria to distinguish between normal, Celiac Disease (CD), and Non-Celiac Duodenitis (NCD) biopsy images.[12] They used a Support Vector Machine (SVM) and achieved impressive accuracies of 98.53% and 98.55% for distinguishing normal controls from CD patients and normal controls from NCD, respectively.

Foers et al. (2021) carried out a study on the classification of intestinal T-cell receptor repertoires using machine learning methods to identify patients with celiac disease (CeD) regardless of dietary gluten status.[13] They found that T-cell receptor (TCR) sequencing yielded an accuracy of 100% with TRD repertoire and 94.4% with TRG repertoire. This approach was particularly useful for diagnosing patients unable to tolerate dietary gluten or with equivocal biopsy features.

In their study, Koh and colleagues (2021) used a machine learning approach to interpret biopsy images for detecting CD.[14] They employed the Steerable Pyramid Transform (SPT) with six classifiers and achieved an accuracy of 88.89% for two-class classification of H&E-stained biopsy images, 82.92% for RGB images, and 72% for multi-class biopsy images.

Syed et al. (2021) developed an AI-based diagnostic platform using deep learning convolutional neural networks (CNNs), including one with multizoom architecture, to diagnose small bowel enteropathies.[15] Their approach achieved 98% and 96% case-detection accuracies using ResNet50 and shallow CNN, respectively. These accuracies were further improved to 98.3% with an ensemble.

Pastore and colleagues (2019) developed and validated a clinical decision support system (CD-CDSS) for celiac disease (CD) risk estimation and decision-making.[16] The system was evaluated by 13 experts in the field of CD, all of whom agreed that the CD-CDSS was medically accurate and capable of guiding health care professionals through the diagnostic process.

Sali and colleagues (2019) utilized a deep residual network model to diagnose CD severity, leveraging a histological scoring system named the modified Marsh score.[17] The model achieved impressive results, with an Area Under the Curve (AUC) exceeding 0.96 for all classes. These results indicate a significant potential of the proposed model for CD severity classification.

In an attempt to differentiate between environmental enteropathy (EE) and CD in children, Syed et al. (2019) employed a Convolutional Neural Network (CNN) on duodenal biopsy images.[18] Despite the histopathological similarities between EE and CD, the model attained an overall 93.4% case-detection accuracy. However, the model most frequently misclassified between patients with CD and healthy patients, indicating a need for model refinement.

Wei et al. (2019) developed a model for detecting CD on duodenal biopsy images using a residual convolutional neural network.[19] The model exhibited high performance, identifying CD, normal tissue, and nonspecific duodenitis with accuracies of 95.3%, 91.0%, and 89.2%, respectively. The study concludes that their automated biopsy analysis system could support

pathologists in improving the accuracy and efficiency of CD diagnosis.

Lahner and colleagues (2005) investigated the use of both Artificial Neural Networks (ANNs) and Linear Discriminant Analysis (LDA) in identifying patients with Atrophic Body Gastritis (ABG).[20] The study achieved high overall accuracies, up to 98.8% and 96.8% for ANNs and LDA, respectively, in predicting ABG. The study suggests the potential of advanced statistical methods in improving biopsy sampling and disease diagnosis.

DISCUSSION

This systematic review followed the PRISMA guidelines and has meticulously examined the role of artificial intelligence (AI) and machine learning (ML) in the diagnosis of celiac disease (CD). The analysis of the studies included in this review suggests a promising role of AI and ML in the field of gastroenterology, particularly in the diagnosis of CD.

AI and ML methods, specifically deep learning techniques, have shown a remarkable capacity to classify and interpret high-resolution biopsy images. For example, Faust's study in 2023 revealed a high accuracy rate of 98.53% using Support Vector Machine (SVM) to distinguish between CD, non-CD duodenitis, and normal control groups.[12] Similarly, a 2021 study by Syed demonstrated that ResNet50 and shallow CNN, both deep learning convolutional neural networks, achieved a case-detection accuracy of 98% and 96% respectively.[15] These findings highlight the potential of AI/ML technologies in supporting histopathological diagnosis, thereby increasing the likelihood of accurate CD detection.

The application of ML goes beyond image analysis, as seen in the study by Foers.[13] The team used ML techniques to classify intestinal T-cell receptor repertoires, achieving 100% diagnostic accuracy with TRD repertoires. This finding indicates that ML technologies can provide valuable insights not only from images but also from complex immunological data. Importantly, this approach could be beneficial in situations where dietary gluten restriction or equivocal biopsy features complicate diagnosis.

However, the utilization of AI/ML in CD diagnosis is not without its challenges. One notable issue pertains to the 'black box' nature of many AI/ML algorithms, which can be challenging to interpret and understand. This issue was addressed by Syed's study that used 'black box' feature detection, increasing transparency and interpretability of the model.[15]

Another challenge relates to the quality and diversity of data used for training AI/ML models. All models are reliant on the datasets they are trained on, and these datasets must be representative of the broader population for the model to generalize effectively. If data are skewed towards certain demographics or clinical characteristics, the model's performance might suffer when applied to different populations.

Moreover, while the accuracy rates reported by studies such as Faust (2023) and Syed (2021) are impressive, it is essential to note that these accuracies were achieved in a controlled research environment. When implementing these AI/ML models in a real-world clinical setting, several factors could potentially reduce their performance. Factors such as image quality, variability in biopsy procedures, and interpretation of results across different clinical contexts could impact the model's ability to accurately diagnose CD.

The development of a clinical decision support system (CD-CDSS), as outlined by Pastore.[16], is a vital example of the practical implementation of AI/ML technologies in clinical practice. The CD-CDSS can augment healthcare professionals' decision-making processes, ensuring accurate and timely diagnosis of CD. It does so by integrating a broad range of relevant clinical information and synthesizing it into actionable insights, facilitating a more holistic understanding of the patient's condition.

Existing literature emphasizes the importance of such decision-making tools. Studies show that clinical decision support systems have improved patient outcomes and increased adherence to guidelines in other areas of medicine.[21,22] Furthermore, the adoption of AI/ML in decision-making processes has also shown promise in tackling challenges such as overdiagnosis and underdiagnosis, thereby enhancing overall healthcare quality.[23] The implementation of such tools in the diagnosis of CD could have similar benefits, aiding in the precision and efficiency of diagnoses and leading to personalized patient care.

However, it is also important to consider potential limitations and obstacles to the use of AI/ML in clinical practice. Notably, the data protection and patient privacy concerns arising from the use of AI/ML technologies are an area of ongoing debate. In addition, healthcare professionals might be apprehensive about relying on AI/ML tools due to their 'black box' nature. These challenges emphasize the need for transparent and interpretable AI/ML models, alongside robust ethical guidelines and education efforts to ensure responsible and effective use of these technologies.

The alignment of findings from our review with current literature emphasizes the growing recognition of AI/ML's potential in improving CD diagnosis and management. It also underlines the importance of continuous research and development to address the challenges associated with the adoption of these technologies in healthcare. As our understanding of these technologies evolves, so too does the potential to refine

their application, maximizing their benefits in the diagnosis and management of CD and other medical conditions.

Limitations and Strengths

The key limitations of this review largely pertain to the inherent constraints of the studies examined. Several of the studies utilized relatively small sample sizes, potentially limiting the generalizability of the results. Further, the specificity of diagnostic tools tested for celiac disease may vary when applied to diverse patient cohorts with differing genetic backgrounds and comorbidities. Moreover, the studies evaluated adopted different machine learning models and varied imaging techniques, complicating direct comparisons. Finally, while all the studies were recent, their rapid pace of evolution in AI technology means that even recent research may not reflect the most current AI capabilities.

Conversely, there are notable strengths of our study. By focusing on all key literature published in the past twenty years, we have provided a timely and relevant snapshot of the latest developments in AI/ML for diagnosing celiac disease. The studies included spanned diverse geographic regions, broadening the relevance of the findings. Additionally, the systematic, PRISMA-guided approach made our methodology rigorous, ensuring an exhaustive and objective analysis of the literature. Most importantly, the high degree of accuracy demonstrated across the AI/ML models strengthens the case for their use in clinical practice.

Implications

The implications of our review are manifold and far-reaching. By spotlighting the emerging role of AI/ML in celiac disease diagnosis, we provide healthcare practitioners, researchers, and policymakers with valuable insights to inform future practice and research. As these technologies become increasingly sophisticated, this study brings to light the urgent need for guidelines to regulate their use, to address ethical considerations, and to facilitate their integration into routine clinical practice.

CONCLUSION

In conclusion, this review has illuminated the emerging role and remarkable potential of AI/ML in the diagnosis of celiac disease. It is evident that these innovative technologies are evolving from auxiliary tools to potentially indispensable elements in the diagnostic process. Despite the challenges and considerations their implementation may pose, their benefits, most notably the enhanced diagnostic accuracy and efficiency, could revolutionize the management of celiac disease. Ultimately, as the landscape of AI/ML technologies rapidly evolves, ongoing research and vigilant appraisal are paramount in harnessing their full potential for patient benefit, thereby shaping a new frontier in medical diagnostics.

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