Radiology Science

Review

The role of artificial intelligence in the differential diagnosis of wheezing symptoms in children

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Abstract

The incidence of pediatric wheeze is extremely high. Poor control of wheeze in young children affects lung function in adulthood and is closely associated with the occurrence of chronic obstructive pulmonary disease. Substantial efforts worldwide have been aimed at developing methods to identify the etiology of wheezing symptoms as early as possible to aid in early management strategies. However, the diagnosis of childhood wheeze relies heavily on the clinical experience of pediatricians, most of whom lack sufficient training to accurately diagnose children with wheezing symptoms. Artificial intelligence is an approach that may improve general pediatricians' diagnostic ability for wheezing symptoms by identifying patterns and trends from large and complex clinical datasets. However, few studies have used artificial intelligence to diagnose wheeze in children. Therefore, this review aims to comprehensively assess these studies in this field, analyze their interpretability and limitations, and explore and discuss future research directions in real-world clinical applications.

Keywords: artificial Intelligence, children, wheezing, diagnostic assistant, interpretability

1. INTRODUCTION

Wheeze is one of the most common respiratory symptoms in children [1]. In recent years, the incidence of wheeze in children has steadily increased. Relevant studies have shown that poorly controlled wheeze in children can affect lung function in adulthood and is closely associated with the development of chronic obstructive pulmonary disease (COPD), which can severely affect quality of life, and place a great burden on families and society [2-6]. Given the numerous etiologies of wheeze, identifying the etiology of wheezing symptoms as early as possible is essential to enable early management strategies. However, most general pediatricians in China cannot make an accurate diagnosis because of the lack of standardized training in the diagnosis of wheezing symptoms. Data-driven artificial intelligence (AI) approaches may effectively improve general pediatricians' differential diagnostic ability for wheezing symptoms by identifying patterns and trends from large and complex clinical datasets. However, to date, few studies have used AI to diagnose wheeze in children. Therefore, this review aims to comprehensively summarize published studies on AI approaches to the diagnosis of pediatric wheeze, and discuss future research directions in clinical applications.

2. THE NEED FOR EARLY IDENTIFICATION OF THE ETIOLOGY OF WHEEZE IN CHILDREN

Wheezing symptoms in children occur at very high prevalence, owing to a decrease in the internal diameter of the lower airways and an increase in airway resistance [7]. Approximately 34% of children younger than 3 years of age have at least one episode of wheeze, and 50% of children younger than 6 years have had wheezing [8]. Asthma, one of the major causes of wheezing, had a prevalence among Chinese urban children of 1.09% in 1990 and 1.97% in 2000, and increased to 3.02% by 2010 [9]. The recent 2018 Global Initiative for Asthma has indicated a global prevalence of asthma of 4.4% in preschool aged children and up to 6.4% in primary school children [10]. The World Health Organization has estimated that approximately 235 million people worldwide will have asthma by 2020.

Multiple factors, such as air pollution, chemical or physical stimuli, viral infections, exercise, body mass index, gastroesophageal reflux and sleep-disordered breathing, can lead to wheeze in children [11]. In addition to asthma, common causes of wheezing include acute bronchiolitis due to viral infections, congenital airway maldevelopment, endotracheal tuberculosis, mediastinal lymph nodes or neoplasms compressing the airway, and bronchial foreign bodies [12]. Recurrent wheeze in infancy is also a risk factor closely associated with pediatric pneumonia [13]. Wheezing can cause shortness of breath, respiratory distress, and even hypoxia and death in children in its acute phase. Recurrent wheeze can lead to chronic airway inflammation that causes airway remodeling and impairs children's airway development. Imaging techniques are important in distinguishing asthma from asthma-like diseases, and chest radiographs are most commonly used for rule-out diagnosis [14]. Chest high-resolution CT and sinus CT are used as further imaging modalities to identify other non-asthmatic causes closely associated with wheezing, such as diffuse bronchiolitis, sinus disease and pneumothorax. The etiologic diagnosis of wheezing symptoms is extremely complex and requires a combination of disease history, physical examination, imaging examination, laboratory tests and diagnostic treatment to establish an effective differential diagnosis. Meanwhile, China has an extreme shortage of pediatricians and pediatric specialty clinics. According to a survey in a white paper on the status of pediatric resources in China [15], the proportion of pediatric specialty clinics among medical providers in urban areas is only 0.5%, whereas that in rural areas is 0%. Furthermore, most pediatricians lack the necessary training and clinical experience to accurately diagnose wheezing symptoms. However, diagnosis of etiology as early as possible is essential for timely intervention, controlling the disease, and preventing its development into asthma and other severe respiratory conditions.

3. ARTIFICIAL INTELLIGENCE PROVIDES NEW SOLUTIONS FOR THE DIAGNOSIS OF WHEEZING SYMPTOMS IN CHILDREN

3.1 AI research on diagnosis of wheezing symptoms in children

AI has already been applied in several medical fields and yielded excellent results. By combining the clinical experience of pediatric experts and medical big data, machine learning (ML) techniques are being used to build AI diagnostic models for diagnosis of childhood wheezing, which can effectively improve the diagnostic accuracy of pediatricians with low seniority or primary care clinicians. According to the data modality used for modeling, AI based diagnosis of wheezing can be divided into two categories based on clinical medical records or based on medical images.

3.1.1 Diagnosis of wheezing on the basis of clinical medical records. Clinical medical records include the diagnosis and treatment associated with a patient's onset and development of the disease. These records consist of large amounts of textual information regarding the patient's condition, such as complaints, symptoms, signs and disease history. Clinical medical records are usually in the form of text and tables. The text records the patient's physical examination findings, past medical history and other information, in a strictly standardized form. The tables record the patient's examination data, such as routine blood test results. Existing AI techniques for medical records usually use traditional ML algorithms such as linear models, Bayesian networks, and decision trees with structured data, which are interpretable to a certain extent. Himes et al. [16] have extracted demographic information and disease data from clinical medical records, and explained the correlations and interactions between variables by using a multivariate model of Bayesian networks to explore the clinical factors to predict patients' asthma developing into COPD. Pennington et al. [17] have evaluated the effects of several methods of defining asthma in medical records on the estimation of the onset of asthma in children 3 years of age and also determined the validity of defining early asthma for the prediction of pediatric asthma. Afzal et al. [18] have proposed a method that can automatically extract information from extensive clinical records and identify children with asthma. Xi et al. [19] have developed a retrospective graphical analysis method to identify informative fields in medical records, extract their correlation with asthma and develop a method for asthma diagnosis through serial combinations of Boolean operators. Quinto et al. [20] have developed a multiple logistic regression model based on information extracted from medical records to establish the relationship between asthma and the severity of obesity in children. In addition, ML has been successfully used to interpret pulmonary function tests associated with the differential diagnosis of obstructive pulmonary disease, and has also shown promising results in other diagnostic examinations, such as breath analysis, lung sound analysis and telemedicine, although those findings were based on limited sample sizes [21]. Nonetheless, transforming existing AI methods from research to real-world practical applications requires interpretability of the diagnostic algorithms, which is currently lacking in the existing literature.

3.1.2 Diagnosis of wheezing on the basis of medical images. Medical imaging, one of the most common diagnostic tools used by physicians, plays an important role in observing lesions and understanding the cause of diseases. For example, three-dimensional volume rendering imaging of airways by using multi-row spiral CT can visualize airway lesions more intuitively and clearly especially when observing their shape and spatial relationship. By proposing a mathematical function that constructs a three-dimensional spatial model of the airway, Tgavalekos et al. [22] have effectively measured the airway width, which not only matched the size and location of ventilation defects, but also identified the causes of inhomogeneous ventilation in asthma. Amaral et al. [23] have used ML methods such as random forest and AdaBoost with a decision tree to improve the accuracy of the diagnosis of airway obstruction in asthma. Schilham et al. [24] have studied an ML-based algorithm for lung nodule detection through finding local maxima in multi-scale Gaussian space to identify candidate boxes of images; identify pixel edge points from large to small to detect the boundary location of nodules; and classify the features extracted by multi-scale Gaussian filters. Yedururi et al. [25] have analyzed the clinical and imaging manifestations of various common tracheal and bronchial diseases in children to develop a systematic approach for their imaging and classification, which may help physicians accurately and effectively diagnose tracheal and bronchial diseases in children. Recent advances in deep learning techniques, specifically models based on convolutional neural networks (CNN), have been widely used in image data analysis. However, research on image-based AI-assisted diagnosis for the differential diagnosis of wheezing symptoms remains in its infancy. Xu et al. [26] have introduced deep CNN transferred multiple instance learning and proposed identification of COPD from CT images. In this work, a pre-trained CNN model was used as a feature extractor to extract the image features for each view of a CT instance, and KNN was used for classification. González et al. [27] have evaluated the performance of CNNs for COPD detection in chest CT by using statistical analysis. Zhang et al. [28] have detected and classified COPD in chest CT by using CNN models. Bharati et al. [29] have developed a hybrid CNN for COPD and asthma detection from X-ray images.

3.2 Limitations of existing AI research on diagnosis of wheezing symptoms and exploratory research on interpretability

Existing AI technologies, particularly deep learning-based methods, have achieved excellent disease diagnostic performance. However, most of the diagnostic process is performed in an end-to-end "black box" mode, thus hindering primary-level pediatricians' understanding of diagnosis results and detection of diagnosis errors. Interpretability is particularly important for AI clinical diagnosis [30, 31].

3.2.1 Interpretable AI research. In general, two approaches to interpretability are used: model interpretability and inference interpretability. Model interpretability involves understanding how a model behaves, whereas inference interpretability is aimed at demonstrating how the model determines the output for each situation. In both approaches, interpretability can be achieved by displaying symbols (e.g., structured languages or natural language such as logical forms) to explain the model reasoning. Interpretable AI can also be categorized as model-based methods and model-agnostic methods (Table 1). Linear models and Bayesian-based models are typical model-based interpretable models. Model-agnostic models can generally be divided into three types: visual interpretation, agent interpretation and importance ranking interpretation. Visual interpretation explains how the model works by plotting the effect of the prediction results of the model with the numerical changes in features in a certain range. Friedman et al. [32] have proposed partial dependence plots characterizing the marginal effects of features on the model's predicted outcomes. Goldstein et al. [33] have proposed individual conditional expectation plots visualizing dependencies between features and predictions for each instance in the form of lines. Apley [34] has proposed the accumulated local effects plot describing how feature values affect the prediction on average. In agent interpretation, the target model is interpreted on the basis of relatively more interpretable agent models, such as linear models, which are trained to approximate the output of the target model on the same inputs. Ribeiro et al. [35] have proposed the local interpretable model-agnostic explanation method, in which an agent model is trained on a set of sampled instances. The importance ranking interpretation determines the features that dominate the output of the model by calculating their contributions and ranking them. Typical methods include Shapley Additive Explanations and Model Reliance [36, 37]. The interpretability of deep learning-based models for image data analysis has been achieved primarily by visualization of the relationship between input images and model outputs [38-40]. Zeiler et al. [38] have proposed to visualize the characteristics of high-level neurons through a deconvolution network and explained the learning process of the network. Zhou et al. [41] have designed a category activation mapping (CAM) method to visualize categorical features, observe the activation states of neural networks and analyze their decision-making process. Selvaraju et al. [42] have proposed a gradient-based category activation mapping method (grad-CAM) that combines category activation mapping with guided backpropagation and deconvolution to visualize the fine-grained features of images. The study has also explained generation of classification results, thus making the processing flow of the CNN based AI models clearer and more interpretable. Recently, variants of CAM, including Grad-CAM++, XGrad-CAM, AblationCAM and HiResCAM, have become an active area of visualization-based interpretable research [43-49]. Figure 1 shows an example of visualization of Grad-CAM in chest radiograph. Wagner et al. [40] have improved the interpretability of CNN models by investigating the internal working mechanism of neural networks, generating fine-grained visual

Table 1 | Summary of interpretable AI methods

Categorization of interpretable AI methods	Description	References describing applications
Model-based interpretable methods	Linear models and Bayesian-based models are typical model-based interpretable models.	[16, 20]
Model-agnostic interpretable methods	Model-agnostic models can generally be divided into three types: visual interpretation, agent interpretation and importance ranking interpretation.	[32-37, 42-49]
Visual interpretation	Visual interpretation explains how the model works by plotting the effects of the prediction results of the model with the numerical changes in features in a certain range. Typical methods include the following.	[32-34, 42-49]
	Partial dependence plots characterize the marginal effects of features on the model's predicted outcomes.	[32]
	Individual conditional expectation plots visualize dependencies between features and predictions for each instance in the form of lines.	[33]
	Accumulated local effects plots indicate how feature values affect the prediction, on average.	[34]
	Category activation mapping (CAM) and its variants, including Grad-CAM++, XGrad-CAM, AblationCAM and HiResCAM, have become an active area of visualization-based interpretable research.	[42-49]
Agent interpretation	Agent interpretation interprets the target model based on a relatively more interpretable agent model, such as linear models, which are trained to approximate the output of the target model on the same inputs. The local interpretable model-agnostic explanation method is an agent model trained on a set of sampled instances.	[35]
Importance ranking interpretation	The importance ranking interpretation determines the features that dominate the output of the model by calculating their contributions and ranking them. Typical methods include the Shapley Additive Explanations and Model Reliance.	[36, 37]

interpretations in image space, selectively filtering the gradients in the optimization process, and refining the interpretability at the pixel level.

3.2.2 Interpretable AI auxiliary diagnosis in medical and diagnostic research on wheezing. With recent advances in interpretable AI technology, some progress has also been made in interpretable AI in medical and diagnostic research [50-57]. The AI algorithms used in clinical medical records in the current literature mainly reflect their interpretability through traditional ML methods and structured features, whereas the interpretability of the decision-making process of diagnostic algorithms has been poorly explored. Yu et al. [58] have reported a diagnostic method based on information extracted from chief complaints, medical histories and physical examination findings in clinical medical records. Furthermore, they have structured key information extracted from clinical medical records through a rule-based approach and used ML techniques to identify the structured data, thus not only improving the accuracy of identifying asthma in pediatric inpatient setting but also increasing interpretability. Spathis et al. [59] have developed a random forest classifier based diagnostic system for COPD and asthma in 132 representative samples. The model has indicated that the most prominent factors in COPD cases are smoking, forced expiratory volume, age and forced vital capacity, and the most prominent factor in asthma is MEF25–75. Topalovic et al. [60] have developed a decision tree based on pulmonary data to enable automatic interpretation of pulmonary function tests and COPD detection in 968 participants. They have modeled the relationships among indicators (e.g., diffusing capacity for carbon monoxide, forced expiratory volume and forced vital capacity), thus enabling transparency in the decision-making process. In deep learning-based medical image diagnosis, CAM and its variants have been widely used for visual interpretation through generating pixel-level diagnostic models for overall interpretability, thus greatly improving the diagnostic accuracy of AI models [61-65]. Rajaraman et al. [66] have visualized and explained CAM-based deep learning predictions for pneumonia detection in pediatric chest radiographs. Gotkowski et al. [67] have proposed the M3D-CAM method to specifically highlight spatial regions in volumetric medical images.

Recently, multi-modal models that integrate clinical medical records data and medical images have become a focus in clinical diagnosis [68-70]. Through extracting clinical diagnostic information from medical images and

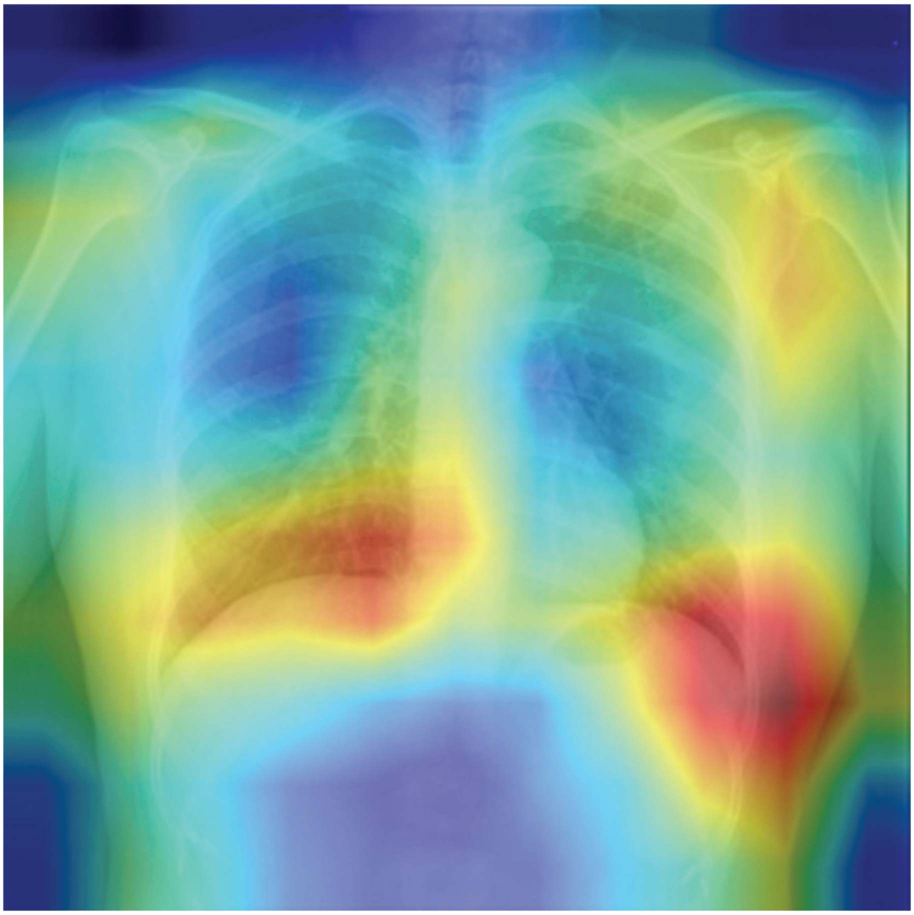

Figure 1 | Visualization of Grad-CAM in a chest radiograph.
The class-discriminative region, i.e., red highlighted area, is concentrated in the lungs, in agreement with clinical experience.

using visual attention to search for disease descriptions associated with these images. Zhang et al. [71] have constructed an MDNet model based on an image module and a language module. Their study has established multi-modal associations between medical images and clinical medical records, and illustrated the model's iterative diagnostic process through an attention mechanism. Yao et al. [72] have applied a logistic regression model for feature selection to clinical data and used a CNN to extract image features from CT images, then established a model by integrating the above two types of features for pulmonary venous obstruction prediction. Yu et al. [73] have proposed a two-stage diagnostic system based on deep learning features extracted from medical records and fine-grained image recognition techniques to identify pediatric respiratory diseases, and achieved excellent results. Furthermore, they have explored a symptom-level interpretability approach to medical record analysis to demonstrate correlations between input and final diagnoses. Yang et al. [74] have explored focal-level interpretability of images and texts by establishing connections between objects and relationships relative to given ground reference representations, and have further used graph convolution to achieve a consistent correspondence in the representation of lesions and text information in images.

3.3 Future development directions in relevant research fields

The demand for readability and reliability are increasing, particularly in the medical field, in which current AI-associated technologies have unsatisfactory interpretability. Therefore, an urgent need exists to explore interpretable implementations for the diagnosis of pediatric wheeze to meet clinical requirements. Several research directions are worthy of exploration in the future.

3.3.1 Improve existing AI algorithms and construct interpretable AI models based on text data. Existing AI diagnosis algorithms based on medical records generally rely on unstructured data, semi-structured data and structured data to capture information and make a disease diagnosis. However, the corresponding algorithms do not explain the cause-and-effect correlations between inputs and outputs, because the interpretability of the AI models has been neglected. Moreover, physicians experience difficulties in understanding the algorithmic diagnostic process from numerous inputs, thus compromising the credibility of AI algorithms. Future studies must improve existing diagnostic algorithms and use gradient-based input and output correlations in the development of interpretable AI models to create a map outlining the relationship between symptoms and diagnostic outcomes.

3.3.2 Investigate an interpretable AI algorithm for diagnosing wheeze in children on the basis of images and correlations between images and text. Medical imaging is a common technical tool with important roles in intuitively understanding disease conditions. The advantage of CNNs in performing image analysis is their use of weighted convolutional kernels to achieve local feature learning and high-level feature extraction by increasing the depth. This process tends to perform analysis from a global perspective, because it hides the joint weighting of local features for diagnostic outcomes. Nonetheless, difficulties arise in explaining the causal relationship between lesions and diagnostic outcomes with image-based complementary diagnostic techniques, and establishing the correlation between image details and diagnostic outcomes. Consequently, low-ranking and primary pediatricians cannot easily directly use the conclusions provided by AI diagnostics. Furthermore, to fully use image information and deeply understand the correlation between changes in the state of an organ for any given location and diagnostic result, AI models interpretable at the level of image pixels are needed to build the mapping relationship between feature maps and images, and to achieve interpretable analysis of overall information.

Therefore, interpretable AI algorithms based on image and text correlations are needed to reveal the reasoning process linking image blocks and diagnostic conclusions, and to provide output understandable to physicians. Visualization methods of feature maps must also be explored to support the interpretability studies and make the data analysis more easier.

3.3.3 Develop personalized wheezing-associated disease predictive or diagnostic models for children by using AI methods from multi-domain candidate predictors. Selecting and evaluating clinical and imaging candidate predictors of wheezing-associated disease in children 3 years of age or younger can facilitate early intervention and management in clinical practice. Future research on wheezing symptoms must develop AI-based predictive or diagnostic models using interpretable methods in sufficiently large cohorts of both general and clinically associated populations, and validate them externally with the measurement of prediction sensitivity, specificity, accuracy and generalizability.

3.3.4 Establish a benchmark database of wheezing-related diseases in children. Rapid development of AI techniques, particularly deep learning-based methods, has benefited from the large amount of available data [75-77]. According to Vapnik-Chervonenkis theory [78], the relationship between the required sample size and the Vapnik-Chervonenkis dimension of the model is defined as a log-like function. However, collecting and labeling large amounts of medical data is very expensive and challenging; consequently, most studies have focused on small sample datasets. More importantly, practical application in clinical practice, in addition to requiring large amounts of data for model training, requires thorough validation in a sufficiently large general and clinically relevant population to ensure the high performance of the AI model in terms of sensitivity, specificity, accuracy and generalizability. Therefore, we believe that the establishment of a publicly available benchmark database of wheezing-associated diseases in children will be an important future direction to promote research on AI for diagnosis of wheezing, which will require collaborations between multiple medical institutions and health administrations, as well as the participation of physicians, software developers, data scientists and policy makers.

4. SUMMARY AND CONCLUSIONS

Wheezing is a very common symptom in children, and its association with multiple diseases and risk factors makes differential diagnosis challenging. AI algorithms are a novel technique in the field of childhood wheezing diagnosis. AI models, compared with conventional methods, can make better use of large complex datasets to develop diagnostic and predictive models for causational analysis of pediatric wheezing symptoms. However, few studies have used AI to diagnose wheeze in children. Moreover, most existing AI research has proposed a "black box" diagnostic process that is difficult to control and interpret. Therefore, interpretable AI technologies must be explored for the assisted diagnosis of wheezing symptoms in children, which reveal the diagnostic decision-making process from the perspective of causality and explain the diagnostic rationale, to balance high-level assisted diagnosis with the risk of misdiagnosis. Interpretable AI technologies can guide decisions to refer high-risk and low-trust cases to high-level pediatric specialists, and ensure primary pediatricians' diagnostic accuracy for common wheeze symptoms in young children.

Improving the reliability and credibility of current AI auxiliary diagnosis models would have high value and clinical significance in decreasing the risk of potential misdiagnosis caused by the limitations of AI algorithms. Moreover, such improvements would help establish a credible interpretable framework enabling mutual monitoring between AI and physicians, to provide a diagnostic basis for individualized, specific, precise interventions to treat wheezing symptoms in children. These improvements will be crucial for the development, application and promotion of AI-assisted diagnostic technologies.

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DECLARATION OF CONFLICTS OF INTEREST

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported herein.

ABBREVIATIONS

COPD: chronic obstructive pulmonary disease
AI: artificial intelligence
ML: machine learning

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