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Review Article

Application of artificial intelligence in respiratory medicine

Chunxi Zhang[1,2,3], Weijin Wu[4], Jia Yang[4], Jiayuan Sun[*,1,3]

[1] Department of Respiratory Endoscopy, Department of Respiratory and Critical Care Medicine, Shanghai Chest Hospital, Shanghai Jiao Tong University, Shanghai 200030, China
[2] Shanghai Jiao Tong University School of Medicine, Shanghai 200001, China
[3] Shanghai Engineering Research Center of Respiratory Endoscopy, Shanghai 200030, China
[4] Shanghai Jingying Information Technology Co., Ltd., Shanghai 200336, China

*Correspondence: xkyyjysun@163.com

Abstract: In recent years, thanks to the dawn of big data, the substantial improvement in computing power, and breakthroughs in algorithm research, artificial intelligence has developed rapidly, and remarkable progress has also been made in its application in medicine. In the field of respiratory medicine, the auxiliary diagnosis of lung cancer is currently the topic on which medical artificial intelligence is the most studied. Therefore, this paper mainly focuses on the diagnosis procedure of lung cancer, and comprehensively summarizes the application of artificial intelligence in the segmentation and detection of pulmonary nodules, classification of benign/malignant pulmonary nodules and intrathoracic lymph nodes, classification of lung cancer pathological images, and lung cancer prognosis analysis. In addition, the application of artificial intelligence in other respiratory diseases such as COVID-19, pneumothorax and pleural effusion is briefly introduced. In summary, artificial intelligence is widely used in the auxiliary diagnosis of respiratory diseases, and has a great potential to become a valuable assistant to respiratory physicians in the near future.

Keywords: artificial intelligence, computer-aided diagnosis, lung cancer, pulmonary nodule, respiratory disease

1. Introduction

Artificial intelligence refers to the use of machines to simulate human consciousness and thinking, and the use of machine learning, deep learning and data analysis to create machines with human-like capabilities. Artificial intelligence has been attracting attention since it was proposed in 1956. In the 2020s, the dawn of big data, the substantial improvement in computing power, and breakthroughs in algorithm research have heralded an age of rapid development and widespread applications of artificial intelligence. Artificial intelligence has resulted in comprehensive changes in various industries, including the medical industry. In recent years, the medical artificial intelligence industry has undergone rapid development, and great advances have been made in medical imaging [1], auxiliary diagnosis and treatment [2], drug discovery [3], disease risk assessment [4], quality control of electronic medical records [5], health management [6], and hospital management [7]. Medical imaging has

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become the most successful direction in the application of medical artificial intelligence. It is currently a popular subject of investment, and rapid product implementation is expected in the near future. Artificial intelligence has achieved good results in the radiologic diagnosis of pulmonary nodules [8], diabetic fundus [9], breast cancer [10], and cervical cancer [11].

Lung cancer is the most common malignancy in China and globally, and is mainly divided into small cell lung cancer and non-small cell lung cancer according to the pathology. Its morbidity and mortality rates are the highest amongst all malignancies. In 2015, around 787,000 patients were newly diagnosed with lung cancer in China, accounting for 20.0% of all malignancies, and 631,000 deaths were caused by lung cancer, accounting for 26.99% of all malignancy-related deaths [12]. Early-stage lung cancer usually has no obvious symptoms, so most patients are diagnosed at an advanced stage. Therefore, the mortality rate of lung cancer has remained high. The five-year survival rate of lung cancer is only 16%, but the five-year survival rate of early-stage lung cancer is 70%–90% [13]. Therefore, effective diagnosis of lung cancer at an early stage is vital to reducing the mortality rate of lung cancer. The early presentation of lung cancer is the presence of pulmonary nodules. Using auxiliary imaging to screen for pulmonary nodules is the most common diagnostic method for lung cancer. However, pulmonary nodules can exhibit diverse morphologies, different sizes, and non-uniform distributions. Inexperienced physicians typically find it difficult to determine the nature of pulmonary nodules and are unable to make accurate diagnoses, resulting in missed diagnoses. In addition, tens of thousands of radiologic images are usually generated by pulmonary nodule screening, and manual analysis of these images is an immense burden to radiologists. Artificial intelligence can help physicians interpret radiologic images, which can increase the diagnostic rate of lung cancer while greatly decreasing the workload of physicians.

This paper aims to briefly summarize the application of artificial intelligence in respiratory medicine. Since the auxiliary diagnosis of lung cancer is currently the field in which medical artificial intelligence is the most studied and widely used, this paper mainly reviews the application of artificial intelligence in the auxiliary diagnosis of lung cancer, including the segmentation and detection of pulmonary nodules, classification of benign/malignant pulmonary nodules and intrathoracic lymph nodes, classification of lung cancer pathological images, and lung cancer prognosis analysis. In addition, the application of artificial intelligence in other respiratory diseases is also briefly introduced.

2. Data and Methods

PubMed, the Web of Science, the Cochrane Library, EMBASE and CNKI were searched for the relevant articles in the last five years with the search terms, “artificial intelligence, deep learning, neural network, algorithm, computer-aided, lung cancer, pulmonary nodule, respiratory disease”. Inclusion criteria: 1) originality and innovation; 2) reliable argument and evidence; 3) high authority. Exclusion criteria: old and irrelevant literature. Literature was selected by two independent authors, and the selected literature was read by all authors and discussed to extract useful information.

3. Results

3.1 Application of artificial intelligence in the diagnosis of lung cancer

3.1.1 Artificial intelligence-based pulmonary nodule segmentation

In computed tomography (CT) examinations, pulmonary nodules have similar morphological characteristics and pixel values to those of surrounding blood vessels and tissues. Therefore, pulmonary nodule candidate regions must be extracted from lung parenchyma for subsequent pulmonary nodule detection and identification. Zhang et al. [14] combined the U-Net network and deep residual structure to construct a new ResUnet and used this network for image segmentation of lung CT images from the LUNA16 dataset to extract the pulmonary nodule regions. After 113 iterations, they achieved 35.02% precision and 97.68% recall. Ni et al. [15] proposed a coarse-to-fine 2-stage framework for pulmonary nodule segmentation in CT scans. In the first stage, a 3D multiscale U-Net was designed for location. In the second stage, a 2.5D multiscale separable U-Net was used for segmentation refinement. The proposed method achieved a Dice similarity coefficient (DSC) of 83.04% and an overlapping error rate of 27.47% on the dataset. Ren et al. [16] proposed a region growing-based semi-automated pulmonary nodule segmentation algorithm (ReGANS) based on CT images. The probability rand index (PRI), global consistency error (GCE) and variation of information (VOI) from a comparison between the algorithm and the radiologist’s manual results were 93%, 6% and 30% for the boundary range, and 86%, 6% and 30% for the precise range, respectively.

3.1.2 Artificial intelligence-based pulmonary nodule detection

Ciompi et al. [17] proposed a multi-stream multi-scale convolutional network deep learning system that can automatically classify all 3300 nodule types related to nodule examination. They tested 639 nodules from 468 subjects and found that the mean accuracy of classification by the deep learning system and humans was 72.9% and 69.6%, respectively. In other words, the overall classification performance was comparable between the deep learning system and humans, so the results of the deep learning system were satisfactory.

Cui et al. [18] constructed a ResNet-based deep learning model for the detection of pulmonary nodules in low-dose CT (LDCT). The training set and validation set were composed of 11,840,536 and 134,985 LDCT images, respectively. The deep learning model achieved an area under the curve (AUC) of 86%, which was better than the AUC of 73% achieved by radiologists ($p < 0.001$), and the deep learning model required significantly less time for the same detection task ($p < 0.05$).

Trajanovski et al. [19] created a two-stage deep learning model. In the first stage, a nodule detector was used. In the second stage, the image context around nodules and nodule features was used as the input for a neural network to assess the malignancy of nodules. When 8466 CT images were screened, 86% to 94% accuracy was achieved.

Zheng et al. [20] proposed a framework using convolutional neural network (CNN) based on maximum intensity projection for automatic pulmonary nodule detection in CT scans, which achieved a sensitivity of 92.7% with 1 false positive per scan and a sensitivity of 94.2% with 2 false positives per scan for lung nodule detection on the publicly available LIDC-IDRI dataset.

Tan et al. [21] proposed a two-stage framework for pulmonary nodule detection based on CT scans. The framework consisted of a segmentation-based three-dimensional CNN (3D CNN) which was designed to segment nodules and three classification-based 3D CNNs which were employed to reduce false positives. This method achieved a sensitivity of 97.5% on the LIDC-IDRI dataset.

Tang et al. [22] retrieved 5300 CT images from the Lung Image Database Consortium (LIDC) to form a dataset, employed Faster R-CNN to detect pulmonary nodule candidate regions, carried out multi-angle feature fusion to remove false positive nodules, and used a CNN to provide performance optimization. They finally obtained a pulmonary nodule detection and identification accuracy rate of 98.1%.

Li et al. [23] introduced inception V3 containing asymmetric convolution kernels into YOLO V2 to construct a new deep network for the detection of pulmonary nodules in CT images. They used CT images from 1010 patients in the LIDC-IDRI dataset for training the model and testing the performance of the model. Finally, they achieved a detection sensitivity of 94.25% and a false positive rate of 8.5% for pulmonary nodules greater than 3 mm.

3.1.3 Artificial intelligence-based classification of benign/malignant pulmonary nodules

SR et al. [24] used a probabilistic neural network (PNN) for the inspection of lung CT images and proposed chaotic crow search algorithm (CSSA)-based feature selection, which provided 90% accuracy.

Massion et al. [25] carried out CT image training and developed and validated a lung cancer prediction- CNN (LCP-CNN). Compared with traditional risk models, this deep learning algorithm can accurately reclassify pulmonary nodules into low-risk and high-risk types in more than a third of cancers and benign nodules, thereby decreasing the number of unnecessary invasive surgeries and delayed diagnoses.

Wang et al. [26] used Gabor wavelets to extract the texture features of solitary pulmonary nodules from a frequency angle and deep belief networks to perform benignancy/malignancy classification of pulmonary nodules. This combination of methods ultimately achieved an accuracy of 83.75% and a test set AUC of 78%. Although the accuracy was increased by only 0.56% compared with traditional support vector machine models, the associated time and cost were halved.

Xu et al. [27] proposed a method called MSCS-DeepLN for evaluating pulmonary nodule malignancy. MSCS-DeepLN consisted of three light models based on 3D CNNs, which were employed to extract the pulmonary nodule features from CT images and preserve spatial heterogeneity. The proposed method achieved a recall of 85.58%, a precision of 90.39%, a specificity of 95.87% and an AUC of 94%.

To solve the problem that the classification effect of pulmonary nodules in CT images is biased due to blurred edges and unobvious features, Guo et al. [28] proposed a multi-model fusion method (MSMA-Net) embedded in the attention mechanism. This method can well extract the position information and the edge features of pulmonary nodules, and achieved a sensitivity of 96.72%, a specificity of 96.17% and an accuracy of 96.28%.

3.1.4 Artificial intelligence-based classification of benign/malignant intrathoracic lymph nodes

Intrathoracic lymph node enlargement can be caused by tumor metastasis, inflammation and other reasons. Correct benign/malignant classification is very important for TNM staging of lung cancer. Wang et al. [29] employed four mainstream machine learning methods (random forest, support vector machine, AdaBoost, and backpropagation neural network) to determine the benignancy/malignancy of mediastinal lymph nodes in non-small cell lung cancer in PET/CT images. The results showed that the sensitivity of these four methods was 77%–84%, which was higher than the 66% sensitivity of human experts ($p < 0.001$).

Li et al. [30] constructed unimodal and multimodal deep learning models to determine the benignancy/malignancy of intrathoracic lymph nodes in convex probe endobronchial ultrasound (CP-EBUS) images. CP-EBUS images of 294 lymph nodes in 267 patients were analyzed.

The ENet and EBUSNet architectures were trained. The study showed that the accuracy of the EBUSNet multimodal architecture in which three models were used was 88.57% and the AUC was 95.47%, which were better than the results of unimodal ENet, and also better than the 80.82% accuracy and 86.96% AUC of human experts ($p < 0.001$). EBUSNet was more consistent than human experts (kappa: 0.7605 vs. 0.5800). The EBUSNet multimodal architecture has huge potential in intrathoracic lymph node diagnosis, higher diagnostic efficiency and consistency than human experts, and important application value in clinical practice.

3.1.5 Artificial intelligence-based classification of lung cancer pathological images

In lung cancer screening, CT and other radiologic methods can only provide preliminary examination and evaluation. Lung cancer diagnosis confirmation and subtype determination require pathologists to observe microscopic information from biopsy sections to draw a conclusion, so the diagnosis process is time-consuming. Artificial intelligence can assist pathologists in the classification of lung cancer pathological images to improve diagnostic accuracy, and decrease diagnosis time. Coudray et al. [31] trained a deep CNN that can automatically classify adenocarcinoma and squamous cell carcinoma as well as normal lung tissues. They also trained the network to predict common mutated genes, and its performance was comparable to that of pathologists with a mean AUC of 97%. Ning et al. [32] used scanned images of lung cancer pathological sections collected from Jiangsu Cancer Hospital and obtained 350 lung adenocarcinoma, small cell carcinoma, and squamous cell carcinoma images that were 6000–9000 pixels in width and length. These images were divided into a training set, a validation set, and a test set according to a 6:2:2 ratio before a six-layered CNN was trained. The final classification accuracies of lung cancer pathological images were 95%, 75%, and 88% for small cell carcinoma, squamous cell carcinoma, and adenocarcinoma, respectively. The overall accuracy of the model was 86%, so the classification results were good. Bi et al. [33] developed a deep learning algorithm based on YOLO V3 and Inception V3 for analyzing pathological sections of lung tissue and providing real-time auxiliary diagnosis. The results show that there were no significant differences between the pathologists who were assisted by the algorithm and who were not in the accuracy of benign and malignant differentiation (100% vs 99.47%, $p > 0.05$) or classification of pathological subtypes (96.84% vs 93.68%, $p > 0.05$). However, it took significantly less time for the pathologists to diagnose with the algorithm ($p < 0.01$).

Biopsy is the gold standard for confirmation of cancer type, but invasive operation may lead to complications. Chaunzwa et al. [34] proposed a radiomics method to predict the histology of non-small cell lung cancer from non-invasive standard CT data. They trained and validated a CNN in a dataset consisting of the two most common histological types: adenocarcinoma and squamous cell carcinoma. The CNN could predict tumor tissue histology with an AUC of 71% ($p = 0.018$). Deep learning-based radiomics can identify the histological subtype of lung cancer. This method has the potential to change existing methods and assist diagnosticians.

3.1.6 Artificial intelligence-based analysis of lung cancer prognosis

The analysis and prediction of the survival of lung cancer patients based on the characteristics of lung cancer cells and the formulation of targeted treatment regimens based on these characteristics are extremely important for improving lung cancer survival rates. Xu et al. [35] employed transfer learning in CNN and recurrent neural network to develop a model. Clinical outcomes were evaluated and predicted by analyzing the time series CT images of locally advanced non-small cell lung cancer patients. Studies have found that deep learning models of time series scans can significantly predict survival rate and cancer-specific results (progression, distal metastasis, and locoregional recurrence). The model divides patients into low mortality rate and high mortality rate risk groups, and these risk groups are significantly correlated with overall survival ($p < 0.001$). This model has predictive capabilities comparable with obtaining tumor volume by time-consuming manual contour extraction. Non-invasive tracking of tumor phenotype can predict survival, prognosis, and pathological responses, and this may have potential clinical significance for adaptive and personalized treatment. A retrospective multi-cohort radiomics study [36] found that the CNN predictions were significantly associated with 2-year overall survival from the start of respective treatment for radiotherapy (AUC = 70%, $p < 0.001$) and surgery (AUC = 71%, $p < 0.001$) patients. Additionally, the CNN was also able to significantly stratify patients into low and high mortality risk groups in both the radiotherapy ($p < 0.001$) and surgery ($p = 0.03$) datasets.

Pan et al. [37] proposed a pathological image-based survival analysis method for lung cancer patients. They employed deep learning for automatic detection of lung cancer cells in pathological images and then carried out topological feature extraction of these cells. These features were used as predictors, and the Cox-Lasso method was used for survival prediction and analysis of lung cancer patients. The results demonstrate that this method has excellent performance in the prediction and analysis of the survival of lung cancer patients.

3.2 Application of artificial intelligence in other respiratory diseases

The outbreak of coronavirus disease 2019 (COVID-19) poses a severe threat to global health. As of 13 March 2022, over 455 million confirmed cases and over 6 million deaths have been reported globally [38]. Rapid and accurate screening of a large number of suspected pneumonia cases to select suitable quarantine and treatment measures has become the focus of pandemic control. X-ray and CT play a crucial role in testing COVID-19 cases. However, millions of images are generated from tens of thousands of patients, so manual screening of these images is a huge burden. Computer-assisted COVID-19 screening may help.

Zoabi et al. [39] generated a machine learning model trained on data from 51831 tested individuals in Israel. This model achieved an AUC of 90% using only eight binary features: sex, age ≥ 60 years, known contact with an infected individual, and the appearance of five initial clinical symptoms.

Ardakani et al. [40] used ten well-known CNN models to distinguish infection of COVID-19 from non-COVID-19 groups: AlexNet, VGG-16, VGG-19, SqueezeNet, GoogleNet, MobileNet-V2, ResNet-18, ResNet-50, ResNet-101, and Xception. The dataset consisted of 1020 image patches including 510 COVID-19 and 510 non-COVID-19. Among all networks, the best performance was achieved by ResNet-101, which obtained a sensitivity of 100%, a specificity of 99.02%, an accuracy of 99.51% and an AUC of 99.4%.

Nayak et al. [41] comprehensively summarized and compared the eight most efficient pre-trained CNN models, namely, VGG-16, Inception-V3, ResNet-34, MobileNetV2, AlexNet, GoogleNet, ResNet-50, and SqueezeNet, which can automatically analyze X-ray images and identify patients with COVID-19. The models have been validated on publicly available chest X-ray images, and the best performance is obtained by ResNet-34 with an accuracy of 98.33%.

Since there are many patients, it is necessary to determine the treatment priority by the severity of patients' symptoms. However, some patients with mild symptoms may get worse quickly. In order to identify these patients, Fang et al. [42] developed an early-warning system with deep learning techniques to predict COVID-19 malignant progression. The proposed system achieved an AUC of 92% in the single-center study and an average AUC of 87.4% in the multicenter study.

Furthermore, many companies, such as Yitu Healthcare and Wuhan EndoAngel Medical Technology, have developed artificial intelligence-assisted CT screening technologies to assist with COVID-19 diagnosis. CT-angel [43] developed by Wuhan EndoAngel Medical Technology (Figure 1) was built on the top of UNet++. It can identify COVID-19 patients in CT images, and achieved an accuracy of 95.24% in internal retrospective dataset, and an accuracy of 96% in external dataset. With the assistance of the CT-angel, the reading time of radiologists was greatly decreased by 65%. The AI-CT rating system [44-46] constructed by Yitu Healthcare (Figure 2) can not only identify COVID-19 patients, but also quantify the severity of pneumonia. Studies show that the deep learning-based quantification for COVID-19 had a good correlation with the conventional CT scoring ($p < 0.001$).

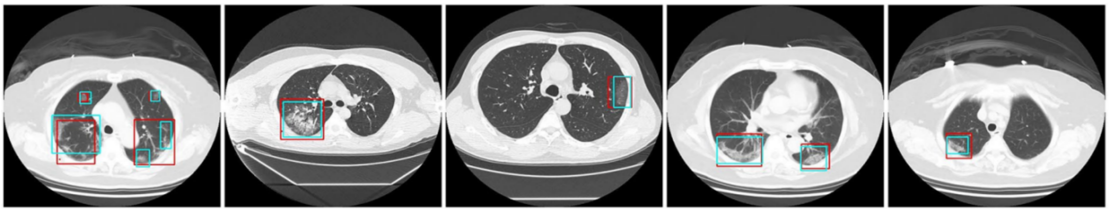

Figure 1. Representative images of CT-angel's predictions.
Green boxes, labels from radiologists; red boxes, labels from CT-angel.

Source: Author's illustration quoted from [43]

Artificial intelligence is also helpful in detecting pneumothorax and pleural effusion based on chest X-ray images. For pneumothorax detection, Critical Care Suite developed by GE Medical Systems achieved a sensitivity of 84.3%, a specificity of 93.5%, and an AUC of 96.07% [47]. HealthPNX developed by Zebra Medical Vision achieved a sensitivity of 93%, a specificity of 93%, and an AUC of 98.3% [47]. For pleural effusion detection, HealthCXR developed by Zebra Medical Vision achieved a sensitivity of 96.74%, a specificity of 93.17%, and an AUC of 98.85% [47]. All the products mentioned above have received the Food and Drug Administration (FDA) approval.

Artificial intelligence is also used in other respiratory diseases. Spathis and Vlamos [48] used machine learning to diagnose chronic obstructive pulmonary disease and asthma. Their results indicated that random forest achieved accuracies of 97.7% and 80.3% for chronic obstructive pulmonary disease and asthma, respectively.

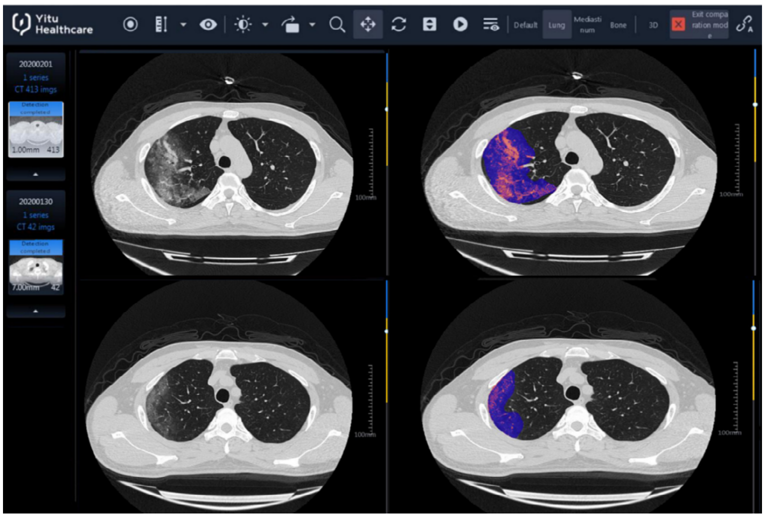

Figure 2. AI-CT rating system constructed by Yitu Healthcare.
The lesions were automatically segmented and color-coded from cold to warm color with the increase of the density.

Source: Author's illustration quoted from [46]

4. Summary

This paper comprehensively summarizes the application of artificial intelligence in respiratory medicine, especially in the field of lung cancer, and visually presents the functions and performance of main algorithms in Table 1.

In summary, artificial intelligence is widely used in the auxiliary diagnosis of respiratory diseases, particularly in the radiologic diagnosis of lung cancer. Artificial intelligence can increase the diagnostic rate of respiratory diseases and greatly decrease the workload of physicians. Enabling computers to learn professional medical information and analyze large numbers of historical images and cases allows for the construction of smart diagnosis systems, which may change the current medical model. More and more artificial intelligence technologies will be used in clinical practice to solve pain points and hot topics in clinical practice. Artificial intelligence will become a valuable assistant to respiratory physicians in the future.

However, there are still a number of challenges that must be overcome before artificial intelligence can be widely used in routine clinical practice. First, further optimizing the algorithm and improving the performance of the algorithm is the premise. Additionally, most of the existing studies are based on small-scale single-center databases, and the ability to generalize to databases from other centers needs to be tested. Besides, the characterization of the performance is very diverse, and essential performance indicators are missing in many studies. Therefore, it is critical to build large-scale multicenter databases to evaluate the performance of algorithms, and comprehensive performance indicators should be used according to the purpose and significance of the study. What's more, CNNs and other complex machine learning algorithms lack interpretability, which reduces the confidence of clinicians and patients in computer-aided diagnosis.

Thus, medical artificial intelligence development requires the collaborative effort of experts in various fields including medicine, artificial intelligence technical algorithms, Internet application technical systems, and services and operations management systems. Furthermore, cooperation among patients, physicians, regulatory institutions, medical device companies, and manufacturers will be required to facilitate widespread clinical adoption with positive outcomes.

Author Contributions

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Conflict of interest statement

All authors declare that there is no conflict of interest.

Table 1. Diagnostic performance of AI models

Reference	AI test model	Diagnostic performance				Value
		Sensitivity (%)	Specificity (%)	Accuracy (%)	AUC (%)	
Ciompi [17]	Multi-stream multi-scale convolutional network	-	-	72.9	-	Detection of pulmonary nodules
Cui [18]	ResNet	73	85	-	86	Detection of pulmonary nodules
Trajanovski [19]	PanCan risk model	-	-	86-94	-	Detection of pulmonary nodules
Zheng [20]	CNN	92.7-94.2	-	-	-	Detection of pulmonary nodules
Tan [21]	Hybrid two-stage 3D CNN	97.5	-	-	-	Detection of pulmonary nodules
Tang [22]	Faster R-CNN	-	-	98.1	-	Detection of pulmonary nodules
Li [23]	YOLO V2 and Inception V3	94.25	91.5	-	-	Detection of pulmonary nodules
SR [24]	PNN	95	85	90	-	Classification of benign/ malignant pulmonary nodules
Massion [25]	CNN	-	-	-	92.1	Classification of benign/ malignant pulmonary nodules
Wang [26]	Gabor wavelets and DBN	-	-	83.75	78	Classification of benign/ malignant pulmonary nodules
Xu [27]	3D CNN	85.58	95.87	-	94	Classification of benign/ malignant pulmonary nodules
Guo [28]	Multi-model fusion method	96.72	96.17	96.28	-	Classification of benign/ malignant pulmonary nodules
Wang [29]	Random forest; SVM; AdaBoost; backpropagation neural network	77-84	-	-	-	Classification of benign/ malignant intrathoracic lymph nodes
Li [30]	EBUSNet	-	-	88.57	95.47	Classification of benign/ malignant intrathoracic lymph nodes
Coudray [31]	Inception V3	-	-	-	97	Histological prediction of lung cancer
Ning [32]	CNN	-	-	86	-	Histological prediction of lung cancer
Bi [33]	YOLO V3 and Inception V3	-	-	96.84	-	Histological prediction of lung cancer
Chaunzwa [34]	CNN	37.5	82.9	68.6	71	Histological prediction of lung cancer
Xu [35]	Transfer learning development model of CNN and RNN	-	-	-	74	Prediction of survival rate and cancer-specific outcomes
Zoabi [39]	GBDT	-	-	-	90	COVID-19 screening
Ardakani [40]	CNN	100	99.02	99.51	99.4	COVID-19 screening
Nayak [41]	CNN	-	-	98.33	-	COVID-19 screening
Fang [42]	LSTM	-	-	-	87.4	COVID-19 malignant progression prediction

*CNN: convolutional neural network; 3D CNN: three-dimensional convolutional neural network; R-CNN: region-based convolutional neural network; RNN: recurrent neural network; PNN: probabilistic neural network; DBN: deep belief network; SVM: support vector machine; LSTM: long short-term memory; GBDT: gradient boosting decision tree.

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