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Detection and Classification of Pulmonary Nodules Using Convolutional Neural Networks: A Survey

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ABSTRACT CT screening has been proven to be effective for diagnosing lung cancer at its early manifestation in the form of pulmonary nodules, thus decreasing the mortality. However, the exponential increase of image data makes their accurate assessment a very challenging task given that the number of radiologists is limited and they have been overworked. Recently, numerous methods, especially ones based on deep learning with convolutional neural network (CNN), have been developed to automatically detect and classify pulmonary nodules in medical images. In this paper, we present a comprehensive analysis of these methods and their performances. First, we briefly introduce the fundamental knowledge of CNN as well as the reasons for their suitability to medical images analysis. Then, a brief description of various medical images datasets, as well as the environmental setup essential for facilitating lung nodule investigations with CNNs, is presented. Furthermore, comprehensive overviews of recent progress in pulmonary nodule analysis using CNNs are provided. Finally, existing challenges and promising directions for further improving the application of CNN to medical images analysis and pulmonary nodule assessment, in particular, are discussed. It is shown that CNNs have transformed greatly the early diagnosis and management of lung cancer. We believe that this review will provide all the medical research communities with the necessary knowledge to master the concept of CNN so as to utilize it for improving the overall human healthcare system.

INDEX TERMS Lung cancer, deep learning, convolutional neural networks, computed tomography (CT) images, pulmonary nodules, image classification.

I. INTRODUCTION

In 2018, lung cancer is ranked first for both incidence and mortality among all cancer types worldwide; accounting for 11.6% and 18.4% of all cancer cases and all cancer deaths, respectively [1]. It presents very poor general prognosis due to the fact that the disease tends not to be diagnosed until it is at a critical stage [2], [3]. For instance, the generally low (18%) five-year survival rate can be lifted to 56% if it is diagnosed at an early development; the study by Henschke et al. demonstrated that 88% of 412 patients diagnosed with stage I lung cancer had survived 10 years after the diagnosis [4]. Hence, early diagnosis of lung cancer is vital to improve its therapeutic decisions and prognosis.

One of the effective approaches for reducing the mortality rate of lung cancer is screening as it helps the medical experts to diagnose the disease before it presents any signs or related symptoms. Specifically, the National Lung Screening Trial (NLST) had demonstrated that there was a reduction

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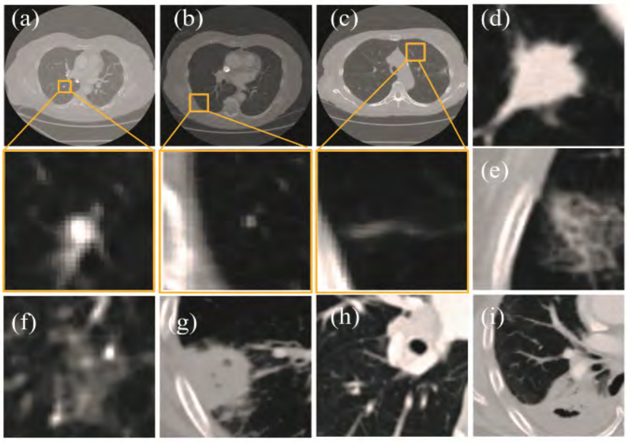

FIGURE 1. Illustration of the great diversity of pulmonary nodules in CT images. (a) Isolated nodule within a single CT slice (> 3.0 mm); (b) Micro-nodule within a single CT slice (<3.0 mm); (c) Non-nodule within a single CT slice (>3.0 mm); (d) Isolated solid nodule; (e) Ground glass nodule; (f)Partly solid nodule; (g) Juxta-pleural nodule; (h) Juxta-vascular nodules; (i) Nodule immersed in pleural effusion.

of over 20% of the mortality rate in patients who underwent low-dose computed tomography (LDCT) screening [5]. Lung screening enables the accurate depiction of pulmonary nodules which constitute the critical indicators of the early development of lung cancer.

In CT images, pulmonary nodules can be referred to as round or oval tissue masses of lung with diameter less than 30 millimeters. They present large variations in sizes, density, location and surrounding. As shown in Fig. 1(a) and 1(b), pulmonary nodules usually have a diameter large than 3 mm and those with diameter smaller than 3 mm are called micro-nodules. Non-nodules including bronchi walls and blood vessels present similar appearances as nodules and may cause false positive during the process of detection (Fig. 1(c)). According to the density, pulmonary nodules can be categorized into solid nodules, ground glass nodules and partly solid nodules (Fig. 1(d, e, f)) [6], [7]. In term of location, nodules can be isolated, juxta-pleural or juxta-vascular (Fig. 1(d, g, h)). In many cases, the pleural effusion makes the delineation of nodule contour challenging (Fig. 1(i)). In summary, these diversities of pulmonary nodules substantially increase the difficulty of achieving accurate detection and diagnosis.

Furthermore, the speedy development of CT screening of lung cancer has led to an exponential increase of images data to be examined by doctors, which significantly increases their workload resulting in erroneous diagnosis causing unnecessary anxiety for the patients or decreasing the chances to be cured. Bechtold et al. demonstrated that the error rate susceptible to occur in 20 CT images analysis conducted by a radiologist per day ranges from $7 - 15\%$ [8]. Therefore, with the aim of reducing the radiologists workload and improving the early detection of lung cancer, numerous methods and systems have been proposed for automatic medical images analysis.

Deep learning, especially convolutional neural network (CNN), has been remarkably utilized in various medical imaging tasks due to the outstanding performances. For the applications on analysis of lung, breast, prostate and brain cancers, several excellent reviews had been published recently [9]–[11]. On the other hand, there exist other survey studies mainly dedicated to CNNs and their applications to radiological tasks [12]–[14]. Although these papers have comprehensively described the applications of artificial intelligence (with special regard to deep learning) to medical imaging tasks, no specific review has been devoted to the detection and classification of pulmonary nodules by CNNs.

In this paper, we aim at illustrating some recent advanced deep learning techniques applied to the analysis of pulmonary nodules. Specifically, a summary of various CNNs based approaches developed in 2018 for the detection and classification of pulmonary nodules is presented. We did not consider studies whose methodology are based on other deep learning models such as recurrent neural networks (RNNs) and auto-encoders (AEs) due to their higher computational complexity and lower recognition performance as compared with CNNs. Moreover, we limited the works reported here to those of 2018 to avoid overlapping with existing reviews. With this review, we intend to:

- *Demonstrate that CNNs stand out of other deep learning models and they have amazingly contributed to the early diagnosis and treatment of lung cancer.*
- *Provide researchers with available medical image datasets as well as environmental (hardware and software) requirement needed for lung cancer studies using deep learning.*
- *Point out the crucial obstacles to successfully applying CNNs to medical image analyses as well as prospective solutions for overcoming them.*

This investigation is structured in the following way. First, fundamental knowledge of CNNs is described as well as the advantages of their usage in pulmonary nodules analysis. Second, an overview of various medical images datasets as well as the environmental setup necessary for conducting lung nodules studies is presented. Third, a comprehensive analysis of the recent studies on the detection and classification of pulmonary nodules is conducted. Finally, the existing challenges of deep learning based approaches for lung nodules analysis are pointed out followed by the identification of some prospective directions.

II. CNN AND ITS DISTINCT CHARACTERISTICS

A. CNNS OVERVIEW

CNN algorithms, also known as deep learning models, are referred to as a class of machine learning techniques; which are all subfields of artificial neural networks. CNN had known its great advancement in 2012 through the study conducted by Krizhevsky *et al.* [15]. They developed a CNN model namely AlexNet which won the ImageNet Large Scale Visual Recognition Competition (ILSVRC) reducing

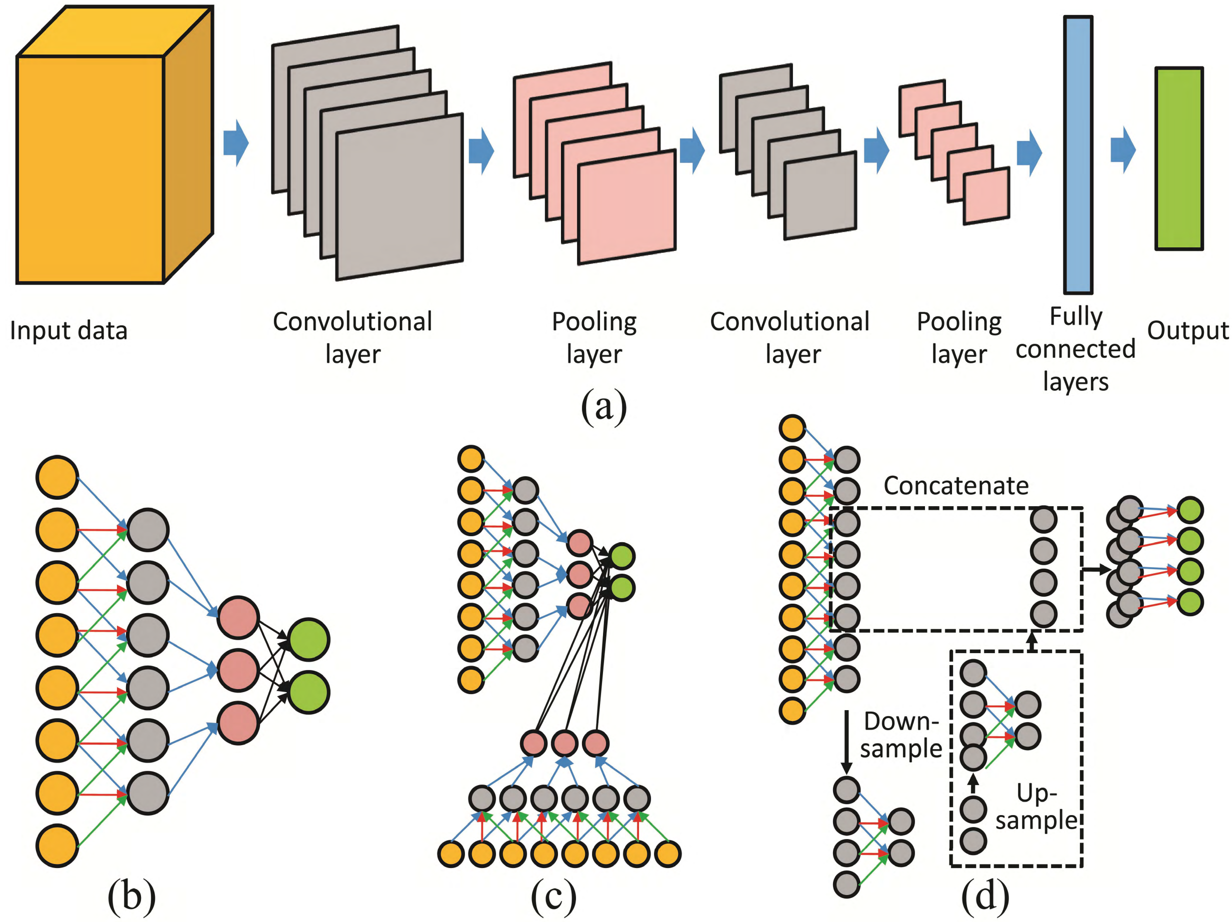

FIGURE 2. CNNs architectures commonly used in medical imaging. (a) One CNN with 2 convolutional layers, 2 pooling layers, and a fully connected layer; (b) Node graph of 1D representation of a classical CNN structure; (c) Node graph of 1D representation of a multi-stream CNN structure; (d) Node graph of 1D representation of structure of a CNN for segmentation (U-NET with only one down-sampling stage).

the classification error record with a margin greater than 10%. Thereafter, new CNN models with more layers have been put forward including VGG-Net [16], ResNet [17], [18], GoogLeNet [19], SENet [20], etc.

Generally, convolutional neural networks consist of a stack of various convolutional layers which are learned accordingly with the aim of automatically extracting useful information from the input data without involving any preprocessing or features engineering procedures. Crucial components of CNNs include convolutional layer, pooling layer, fully-connected and Softmax layers (Figure 2(a)). The main process for achieving the features discovery in CNNs is convolution; which is performed through the convolutional layers. It consists of applying a "dot product" mathematical operation of matrices of weights across the entire content of every sample of the input data (images, videos, etc.) resulting in the generation of the feature maps. Another essential operation in CNNs is pooling. It is often applied after the convolution process. Applying pooling helps in reducing the dimensionality of the output which will consequently result in the preservation of more important essential features. In addition, it is worth mentioning that the size of the receptive field is to be chosen carefully as the recognition performance of a designed CNN architecture can be significantly influenced by the amount of relevant information included in the network input data. For instance, if the surrounding environments of the objects of interest contain much unnecessary details such as noises and artifacts or if they do not enclose enough contextual information of the target objects, the CNN model would be susceptible to yield very poor detection performance. Furthermore, according to the dimensions of the convolutional filters, convolutional neural networks can be classified into 2D-CNN whose kernels are of dimensions of two and 3D-CNN whose kernels are of dimensions of three.

B. CNN ARCHITECTURES COMMONLY USED IN MEDICAL IMAGING

Based on the structures of the CNN models utilized in existing clinical decision-support systems, CNNs can be categorized into classical classification structures, multi-stream structures and segmentation structures [21].

Classical CNN models are those networks built up by stacking multiple layers in a linear way and which are

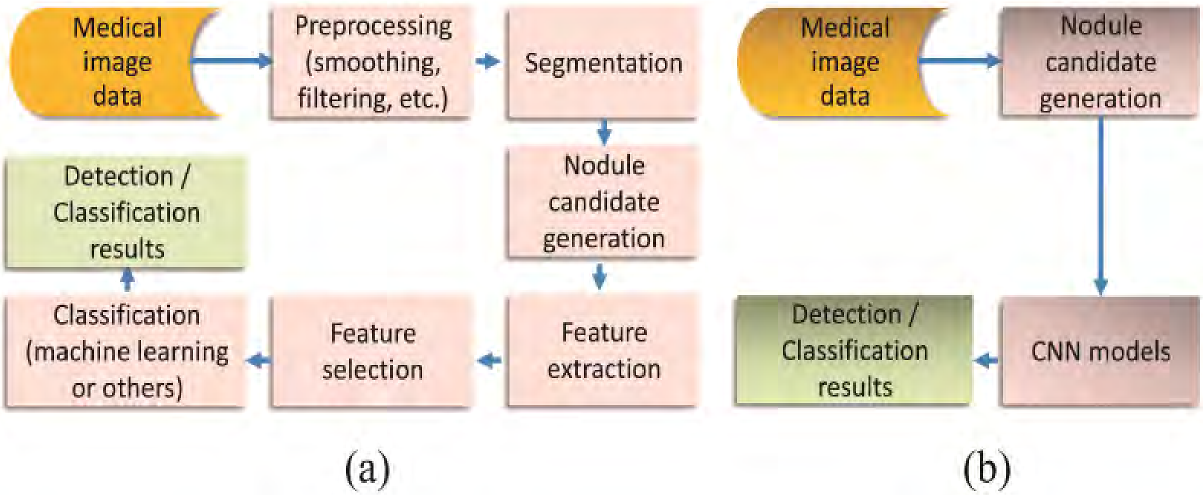

FIGURE 3. **The workflow diagrams of the two categories of methods for pulmonary nodule analysis. (a) Conventional methods; (b) CNNs based methods.**

generally aimed to perform classification tasks (Fig. 2(b)). AlexNet [15] and VGG [16] are the most frequently used networks of this category.

With regard to the fact that the amount of contextual information is of great significance for detecting abnormalities from images and given that the fusion of multiple sources of image information may improve the detection performance, multi-stream CNN models also known as multiple path networks have been proposed (Fig. 2(c)). This concept of multiple paths originated from the idea of extracting the essential features contained in adjacent images of the volumetric medical data without increasing the amount of network parameters and computational cost. Investigating multiple path networks has resulted in the development of multi-scale image analysis and 2.5D image classification frameworks achieving great detection results [24]–[26].

Segmentation CNN models refer to that group of CNNs destined to examine both medical and natural images with the purpose of dividing them into multiple constituents according to the user's need for further analysis. These networks can be fed with images larger than that on which they were trained outputting a likelihood map for every single pixel of the images. They are also known as fully convolutional neural networks (FCNNs); and U-Net and its variants [22], [23] constitute some improved versions of this category as demonstrated by their remarkable performances (Fig. 2(d)).

C. DISTINCT CHARACTERISTICS OF CNNS

In recent years, the crucial role played by the automatic and accurate detection of pulmonary nodules in the early diagnosis and precise management of lung cancer has led to the development of numerous methods. These methods can be categorized into conventional methods and deep learning based methods. Conventional methods are those that are mainly based on traditional image processing techniques and machine learning classifiers [27]–[32] and whose pipelines often include many sub-processes. Whereas, deep learning methods specifically CNNs based methods are those whose implementation does not involve any features engineering steps and they are referred to as end-to-end solutions. The workflow diagrams of these methods are illustrated in Fig. 3.

Several differences between these two kinds of methods are worth noting. First, the pipeline of conventional methods includes many sub-processes; which increases the computational time as well as the error rate. Whereas, CNNs based methods are straightforward systems not involving some computationally costly processes such segmentation and features engineering; which allows them to yield more accurate detection results. Another significant difference is that CNNs based approaches can make full use of the essential information contained in three dimensional images data such as computed tomography (CT) images and Positron Emission Tomography (PET) images. Doing so would definitely result in better diagnostic results. Finally, the great successes of CNNs based methods are often subjective to the amount of samples that comprises the dataset; which limits their application to the analysis of small dataset although they may achieve better results than conventional methods.

III. DATASETS AND EXPERIMENTAL SETUP

Given that the implementation of CNNs requires a huge amount of parameters to be estimated, some hardware and software requirements need to be specified. Some commonly used datasets as well as the environmental setup for automatic detection and classification of pulmonary nodules are given below.

A. DATASETS OF LUNG CANCER CT IMAGES

1) LIDC/IDRI DATASET

LIDC/IDRI stands for Lung Image Database Consortium and Image Database Resource Initiative [33]. It is a database of thoracic CT scans owing its successful creation to three research organizations including the NCI (National Cancer Institute), the FNIH (Foundation for the National Institutes of Health) and the FDA (Food and Drug Administration). LIDC/IDRI dataset consists of a total of $1,018$ cases. In effect, there are only $1,010$ different CT scans due to the fact that there are eight cases that were inadvertently reproduced while gathering the CT scans. All the gathered image data are stored in DICOM format and with uniform size of 512×512. The images thickness ranges from 0.5 to 5 mm where the most recurrent image thicknesses include 1 mm, 1.25 mm, and 2.5 mm. It is worth noting that more than 50% of the recent studies on lung cancer diagnosis have made use of the LIDC/IDRI dataset.

Every case of the LIDC/IDRI dataset consists of hundreds of images plus an XML file which contains the details of the identified lung lesions. Making use of electronic calipers, the diameter of each of the detected lung lesions was assessed resulting in their classification into three main groups including nodules (3-30 mm of diameter), non-nodules (diameter $>$ or equal to 3 mm) and micro-nodules (diameter $<$ 3 mm).

2) LUNA 16 DATASET

This dataset is a subset of the publicly accessible LIDC/IDRI dataset. It consists of a total of 888 thoracic CT scans collected in the basis that the lesions contained in every case have been marked by at least three of the four medical experts having taken part in the annotation processes [34]. Considering this inclusion agreement, only nodules with 3 mm $<$ diameter were considered as positive samples meanwhile all the remaining lesions were referred to as negative samples.

3) NLST DATASET

It is a dataset collected in 2009 by the National Lung Screening Trial (NLST); which was a project that aimed at comparing the lung cancer diagnosis accuracy through low-dose CT screening with that of the chest radiography screening. The whole screening project was performed in 33 American medical institutions and comprised a total of $53,454$ participants. These patients were aged between 55 and 74 years and with a smoking history of at least 30 packs per year. This dataset is made up of both low-dose CT images and chest radiographs. For more details, kindly refer to [5].

4) KAGGLE DATA SCIENCE BOWL (KDSB) DATASET

This dataset was generated from 2101 patients and every patient's file includes between 100 and 400 images [35]. All the images have been annotated in the following manner: label 0 and label 1 were assigned to patient without cancer and patient with cancer, respectively.

5) ELCAP DATASET

ELCAP stands for Early Lung Cancer Action Program. It is a dataset made up of 50 low-dose CT cases [36]. The images slice thickness is equal to 1.25 mm and the diameters of the majority of the identified nodules range from 2 to 5 mm. It is worthy to be mentioned that all the annotated lesions of this dataset are nodules and no non-nodules were marked by the medical experts.

B. CNN SOFTWARE PLATFORMS AND HARDWARE EQUIPMENT

The major programming language utilized for the implementation of deep learning models is python. Besides, there is also Matlab which is a high level programming language and numerical analysis environment conceived for performing engineering and scientific works such as computational finance, image and signal processing, matrix calculations, data analysis, system simulation, etc. [37]. Moreover, there exist many platforms based on python language which have been proposed to facilitate the CNNs models implementation. These platforms include Keras, Caffe, Chainer, TensorFlow, Torch, etc. Caffe provides interfaces for both python and C++; it was introduced by graduate students from the University of California Berkeley. Torch is a relatively easy and efficient computing framework that provides its potential users with an excellent C interface via LuaJIT.

CNNs constitute a class of deep learning techniques; which makes their implementation dependent on great amount of experimental data as well as a huge number of parameters to be estimated. Thus, the great technological advancements have led to the creation of sophisticated computers equipped with graphical processing unit (GPU) and compute unified device architecture (CUDA) supported by NVIDIA.

IV. PULMONARY NODULE DETECTION AND FALSE POSITIVE REDUCTION

Pulmonary nodule detection and false positive reduction constitute the two most essential mechanisms for the early diagnosis and precise management of lung cancer. Thus, extensive research works are being conducted with the aim of improving the early and automatic detection of pulmonary nodules. These research works have led to the development of various methods and systems which are summarized in Table 1 and whose details are presented below.

A. ADVANCED OFF-THE-SHELF CNNS

There exist many well-known CNN models for their remarkable performances in various recognition tasks; which are also known as off-the-shelf CNNs. However, designing a great CNN model depends on the problem at hand and requires a certain level of computer science expertise; which constitutes a very challenging task for researchers due to their diversified background. Therefore, exploiting the advantages of reinforcement learning, region proposal network (RPN), Faster Region based CNN, etc.; advanced CNN models have been designed for lung nodule detection.

1) REINFORCEMENT LEARNING

Ali *et al.* exploited CNN to build up a reinforcement learning framework for detecting pulmonary nodules in CT images [38]. This system constitutes a pioneer work as regarding reinforcement learning applied to medical image

TABLE 1. Recent studies on pulmonary nodule detection and false positive reduction using CNNs.

Years	Authors	Models	Datasets	Key Points
2018	Ali *et al.* [38]	3D CNN	LUNA16	First application of reinforcement learning (RL) to pulmonary nodules detection.
2018	Qin *et al.* [39]	3D U-Net and 3D DenseNet	LUNA16	3D U-Net based Regional Proposal Network (RPN) is employed for nodule candidates'generation and 3D DenseNet is designed for false positives reduction.
2018	Tang *et al.* [40]	3D Faster R-CNN and 3D DCNN	Tianchi AI competition	Two-phase framework utilizing 3D U-Net-inspired Faster R-CNN and 3D DCNN for false positives reduction.
2018	Winkels *et al.* [41]	3D G-CNN	NLST and LIDC/IDRI	False positive reduction using 3D G-CNN (group convolutional neural network).
2018	Silva *et al.* [42]	2D CNN based PSO	LIDC/IDRI	PSO (particle swarm optimization) algorithm is employed to replace the manual search of network hyper-parameters.
2018	Monkam *et al.* [43]	2D CNN	LIDC/IDRI	Automated detection of pulmonary nodule is expanded to micro-nodules (diameter < 3 mm). Effects of CNN depth and receptive field size on the detection performance are clarified.
2018	Liu *et al.* [44]	2D CNN	LIDC/IDRI and ELCAP	2D CNNs are trained with dataset including images with multiple scales generated from multiple views to accurately identify the nodule types.
2018	Jia *et al.* [45]	2D U-Net, GLCM, RF and XGBoost	Tianchi AI competition	An ensemble of RF and XGBoost is used to classify nodules features resulted from applying K-means clustering, median filtering, morphological operations and U-Net.
2018	Pezeshk *et al.* [46]	3D FCN and 3D CNN	LUNA16	3D FCN is used for generating the nodule candidates and averaging is performed to fuse the outputs of four identical 3D CNN for reducing the false positive rate.
2018	Jung *et al.* [48]	Ensemble of 3D CNN	LIDC/IDRI	3D DCNN with shortcut connections and 3D DCNN with dense connections are designed, checkpoint ensemble approach is proposed to boost the networks performance.
2018	Monkam *et al.* [49]	Ensemble of 3D CNN	LIDC/IDRI	ELM is employed to integrate five 3D CNN with five different input sizes for distinguishing between micro-nodules and non-nodules.

analysis tasks. Moreover, it presented excellent detection performance yielding a sensitivity, specificity, accuracy, PPV and NPV above 99%, respectively.

2) REGION PROPOSAL NETWORK

Employing 3D U-Net, 3D DenseNet and RPN (region proposal network), Qin *et al.* developed a system for automatically detecting pulmonary nodule in CT images [39]. The overall system training process was performed utilizing Multi-task residual learning and online hard negative example mining approaches. The proposed methodology included two main modules which are: nodule candidates' generation based on 3D U-Net and decrease of false positives utilizing a 3D DenseNet. It achieved a sensitivity of 96.7% and CPM score of 0.834 on LUNA16 dataset.

3) U-NET-INSPIRED 3D FASTER R-CNN

Tang *et al.* proposed a two-phase framework for pulmonary nodules identification and false positive reduction [40]. First, a U-Net-like 3D Faster RCNN model is employed to generate the nodule samples. Then, a 3D deep convolutional neural network is built to identify the true nodule candidates. The developed system was trained based on hard negative mining approach yielding a CPM score of 0.815.

4) 3D G-CNN

Generally, successful implementation of CNNs necessitates great amount of experimental data which are usually unavailable in medical area. Thus, Winkels *et al.* proposed a system based on 3D G-CNNs which achieved the same performance with that of a normal CNN model requiring ten times more data when applied to the reduction of false positive in automated pulmonary identification [41]. The implementation of the proposed framework includes two main processes which are filter transformation and spatial convolution. It yielded a CPM score of 0.856 on 3000 nodule samples acquired from the NLST and LIDC/IDRI datasets; which is almost equal to the performance (CPM = 0.869) of a normal CNN model trained with ten times more data (30000 nodule samples).

B. CNNS WITH ADVANCED IMPLEMENTATION TECHNIQUES

The detection performance of a designed CNN model is strongly dependent on its implementation procedure as well as the size of the images constituting the dataset. To this purpose, few solutions for improving the implementation of CNNs have been proposed.

1) PARTICLE SWARM OPTIMIZATION

With the aim of facilitating the parameters optimization which is regarded as a crucial step in the implementation of CNN models, Silva *et al*. proposed a framework in which particle swarm optimization (PSO) approach is utilized to automatically select the best network hyper-parameters [42]. The proposed framework was implemented on 12, 157 pulmonary nodule samples including 3, 415 nodules and 8, 742 non-nodules generated from the LIDC-IDRI dataset. It achieved an accuracy, sensitivity, specificity and AUC of 97.62%, 92.20%, 98.64% and 0.955, respectively.

2) CNN RECEPTIVE FIELD AND IDENTIFICATION OF MICRO-NODULE

Although great number of systems have been developed to accurately and precisely identify pulmonary nodules in medical images, very few of them can differentiate micro-nodules from other lung lesions such non-nodules; which increases the amount of false positives. To this purpose, Monkam *et al*. extended lung nodules analysis to automatic identification of micro-nodules [43]. Through examination of the whole LIDC-IDRI dataset, they built up an experimental dataset consisting of 13, 179 micro-nodules and 21, 315 non-nodules. Considering the small sizes of both micro-nodules and non-nodules, they investigated the performance of three CNN models with different depths as well as their recognition ability when fed with samples of different sizes. The three CNN structures included one, two and four convolutional layers, respectively. Whereas, the different image patches sizes consisted of 16×16, 32×32 and 64×64, respectively. The best classification performances were yielded by CNN model with two convolutional layers trained with image patches of 32×32.

C. CNN+

Herein the term of CNN+ refers to those systems whose framework includes both CNNs and some conventional image processing and objects detection techniques. Combining CNNs with other techniques such as linear interpolation, icosahedron divided sphere algorithm, thresholding, K-means, median filtering, morphological operations, Gabor wavelet transform and gray level co-occurrence matrix (GLCM), new systems for classifying lung nodules have been developed. A schematic representation of these systems is displayed in Fig. 4(a).

1) 2D CNN+ (LINEAR INTERPOLATION, ICOSAHEDRON BASED NORMALIZATION AND THRESHOLDING)

Liu *et al*. developed a novel framework that includes 2D CNNs with multiple views and whose pipeline comprises four main phases [44].They aimed at demonstrating the effectiveness of convolutional neural networks to accurately identify the nodules type based on their internal characteristics. They employed linear interpolation, icosahedron divided sphere algorithm and thresholding approach for raw CT images preprocessing, volume of interest detection and generation and selection of views at different scales, respectively. Then, the suitable views chosen at all scales were used to train the 2D CNN model with the aim of classifying the nodule candidates into G (ground glass optical), W (well- circumscribed), V (vascularized), J (juxta-pleural) and P (pleural-tail) and N (non-nodule), respectively. This system achieved an overall accurate of 92.1% and 90.3% on the nodules acquired from the LIDC-IDRI dataset and ELCAP dataset, respectively.

2) 2D U-Net + (K-MEANS, MEDIAN FILTERING, GABOR TRANSFORM, GLCM, XGBOOST AND RF)

In an investigation by Jia *et al*., K-means algorithm, median filtering, some morphological operations, Gabor wavelet transform and gray level co-occurrence matrix (GLCM) were integrated with convolutional neural networks and XGBoost and Random Forest (RF) classifiers to improve the automated identification of lung nodules in CT images [45]. They put forward a system whose pipeline comprises lung parenchyma segmentation, nodule candidates' generation, features engineering and classification of the nodule candidates. First, K-means algorithm, median filtering and morphological operations were applied on the raw CT scans to obtain the whole lung parenchyma. Whereas, a 2D U-Net model was employed to locate the nodule candidates in the delineated lung parenchyma. Then, features engineering was conducted based on various techniques including Gabor wavelet transform, gray level co-occurrence matrix (GLCM), etc. Finally, an ensemble learners consisting of XGBoost and Random Forest (RF) classifiers was trained to obtain the final prediction results. This system achieved an AUC of 0.93 on the 800 cases of the Tianchi medical AI competition dataset.

D. ENSEMBLE LEARNERS OF MULTIPLE CNNS

Ensembling refers to an approach for integrating multiple learners into a single framework with the aim of increasing the overall performance of the system. Generally, lung nodules present large variations in shapes, sizes, internal characteristics, etc. Moreover, different convolutional neural network learners may yield different prediction results. Hence, to the end of improving the accuracy of clinical decision-support systems, various CNNs based ensemble systems have been proposed. Their implementation process is shown in Fig. 4(b).

To alleviate the poor performance of three-dimensional CNNs in medical imaging data analysis due to limited amount of dataset and data classes' imbalance, Pezeshk *et al*. proposed an automatic two-phase 3D CNNs based system for pulmonary nodules detection named DeepMed [46]. First, they employed a 3D FCN (fully convolutional network) to identify and generate the nodule samples. Then, averaging was utilized to fuse the outputs of many CNN models

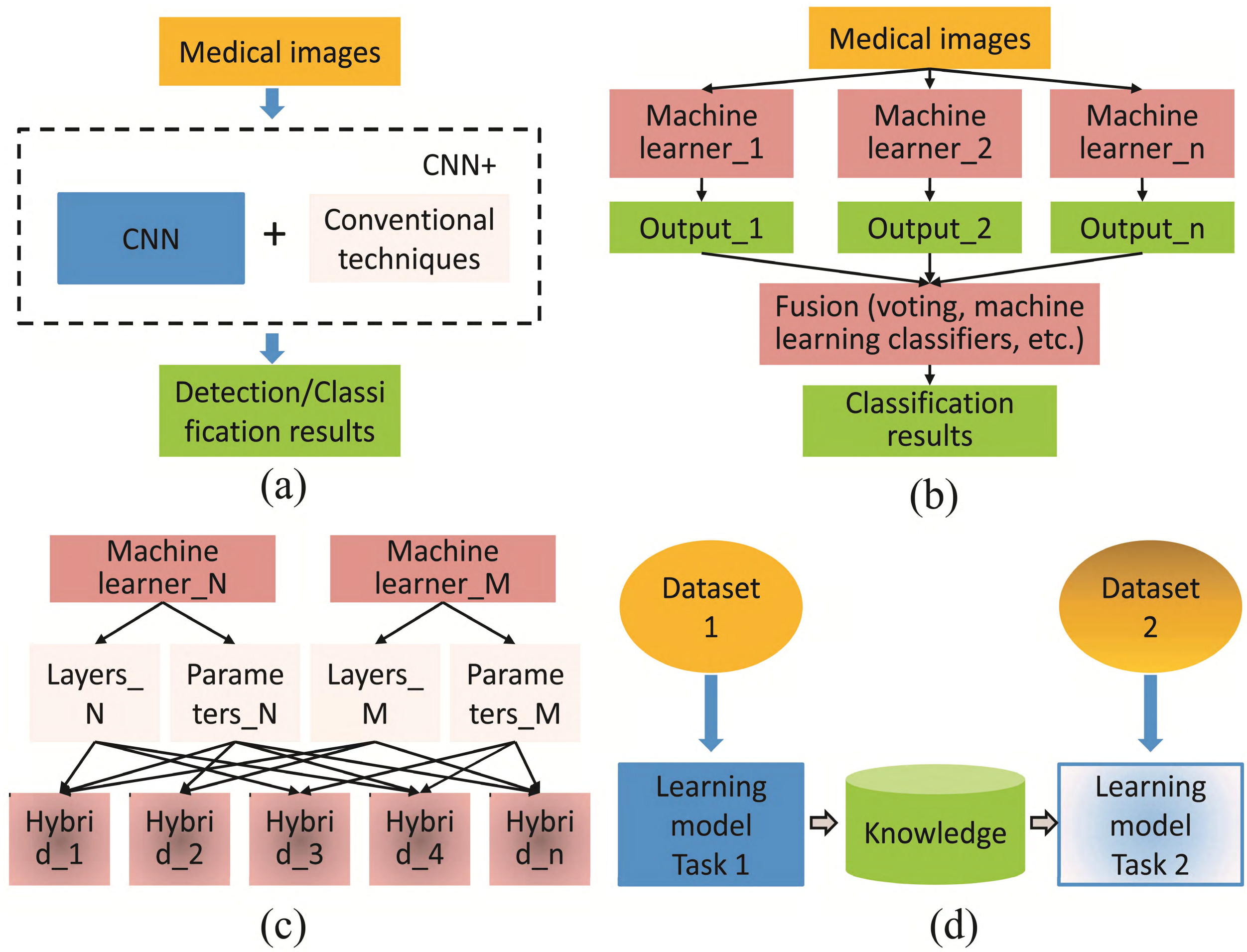

FIGURE 4. Different categories of pulmonary nodule analysis systems. (a) CNN+ system. (b) Ensemble learners system. (c) Hybrid system. (d) Transfer learning system.

yielding the final detection results. To overcome the data imbalance and insufficiency of the training samples, they put forward a new strategy for increasing the amount of the training samples. This augmentation method; which can expand every sample 28 times, is derived from one of their previous studies [47]. The proposed system outperformed various state-of-the-art methods implemented on the LUNA dataset.

Employing 3D deep CNN models with shortcut connections and with dense connections, respectively; a new ensemble system namely checkpoint ensemble method was proposed by Monkam *et al.* [48]. They investigated the performance of ensemble models based on 3Dshortcut connection DCNNs and 3D dense connection DCNNs separately. On the other hand, they also explored the dependence of the performance of these methods on the receptive field sizes. It was found that single deep CNN model with larger receptive field size ($64 \times 64 \times 64$) yielded better classification results. Whereas, shortcut connection DCNN model outperformed dense connection DCNN regardless of the network input size. Furthermore, performing the checkpoint ensemble strategy resulted in the overall system performance improvement yielding a CPM score of 0.910.

Even though, micro-nodules are seen as earliest development of pulmonary nodules, less attention has been paid to improving their detection; which considerably contributes to the high false positives rate in automated pulmonary nodules detection systems. Moreover, the full use of information contained in adjacent images of volumetric imaging data such as MRI and CT may result in more accurate and precise detection performances. Thus, Monkam *et al.* proposed an ensemble learning of multiple 3D CNNs for identifying pulmonary micro-nodules in CT images [49]. They designed 3D CNN models trained with image patches of sizes $20 \times 20 \times 3$, $16 \times 16 \times 3$, $12 \times 12 \times 3$, $8 \times 8 \times 3$ and $4 \times 4 \times 3$, respectively. They explored different approaches to integrate multiple deep learning learners including, majority voting, ELM (extreme learning machine), logical operator AND, averaging and autoencoder (AE). The experimental results indicated that ELM is the most suitable approach for fusing multiple learners that aim to identify micro-nodules in volumetric CT images.

V. CLASSIFICATION BETWEEN CANCEROUS AND NON-CANCEROUS PULMONARY NODULES

Significant successes have been achieved in the automated differentiation of pulmonary nodules from other lung lesions such as non-nodules. However, it is still quite challenging to determine the status of the identified nodules. Moreover, not all lung nodules turn out to be a cancer. Thus, given the great number of images to be analyzed and the criticalness of the task, many systems have been proposed to help the physicians in the process of distinguishing between benign and malignant pulmonary nodules. The recently developed systems for classifying pulmonary nodules into cancerous and non-cancerous are briefly illustrated in Table 2 and introduced in details in the following subsections.

A. CNNS WITH ADVANCED IMPLEMENTATION TECHNIQUES

1) NODULEX (CNN FEATURES + QIF FEATURES)

In a study by Causey *et al.*, a hybrid features based system was developed [50]. The developed framework namely NoduleX, makes use of the features discovered by the CNN model and those of the radiological QIF (quantitative image features) to accurately differentiate malignant nodules patterns from benign nodules patterns. Its capability of predicting malignancy in pulmonary nodules is quite equal to that of expert physicians (AUC = 0.99).

2) DENSEBTNET (CENTER-CROP OPERATION)

In another investigation, Liu *et al.* incorporated a center-crop process into the conventional DenseNet to build up an improved network with a structure in form of binary tree namely DenseBTNet [51]. The introduction of the center-crop process helps in discovering multi-scale features from the nodule candidates; which will consequently contribute to overcoming the influence of the great variations of their sizes, shapes and internal characteristics on the classification performance. The experimental results demonstrated that this new dense network model significantly outperforms the conventional DenseNet as well as numerous existing systems validated on the same dataset.

3) 3D DILATED CONVOLUTION

Zhang *et al.* attempted to differentiate benign pulmonary nodules from malignant pulmonary nodules employing a new CNN structure in which the pooling operation is replaced by a 3D dilated convolution operation [52]. In effect, they made the following contributions to the area of applications of CNN to medical images analysis. First, instead of including pooling layers in the network architecture, they included a 3D dilated convolution layer; which keeps the image quality unchanged and helps retain much smaller image information. Second, they considered different receptive field sizes for the dilated convolutions resulting in the discovery of multi-scale features; which would consequently increase the discrimination ability of the system leading to more accurate and precise diagnostic results regardless of the diversity of the nodules' characteristics.

4) PN-SAMP (MULTIPLE WINDOW WIDTHS AND WINDOW CENTERS)

Wu *et al.* proposed a 3D CNN based framework that takes advantage of multiple window widths and window centers and the multi-task learning concept to accurately identify the nodules areas, to extract semantic information from the detected nodules and to predict the nodules malignancy [53]. This method could be of significant help to the physicians for not only differentiating malignant from benign nodules, but also for assessing the malignancy level of the tumors; which will greatly improve the treatment planning of lung cancer.

5) DUAL-PATH 3D CNN AND MULTI-OUTPUT NETWORK

Dey *et al.* conducted a comparative study aiming to find the most appropriate dual-path 3D CNN model for distinguishing between malignant and benign pulmonary nodules [54]. They investigated the discrimination capability of four 3D deep learning models including an ordinary 3D CNN, a 3D DenseNet, multi-output 3D DenseNet and an augmented 3D DenseNet with multi-outputs. The performances of these networks were assessed on nodule candidates of the publicly accessible LIDC/IDRI dataset and the obtained results indicated that the multi-output 3D DenseNet (MoDenseNet) is the most suitable network model achieving an accuracy of 90.40%.

6) LOCAL AND GLOBAL CONTEXTUAL FEATURES WITH TRIPLE-PATH CNN

Considering both the local and global contextual features is of great significance for accurately assessing the malignancy of lung nodules. To this purpose, Sori*et al.* proposed a multi-path CNN model that can simultaneously learn local and global contextual features from nodule candidates to classify them into cancerous and non-cancerous [55]. To the end of identifying the suspicious nodules, they designed a network derived from the commonly used segmentation CNN model U-Net. Next, the collected nodules were fed into a deep CNN model comprising three different paths wherein the sizes of the receptive field are different. Later on, the essential features discovered by each path were concatenated to build up a much diversified vector features. The validation of this system on the KDSB (Kaggle Data Science Bowl) 2017 dataset yielded an accuracy, a recall and specificity of 87.8%, 87.4% and 89.1%, respectively.

B. CNN+

1) 2D CNN+ (OTSU ALGORITHM, PHYLOGENETIC DIVERSITY INDEX)

Filho *et al.* built a framework employing image processing, pattern recognition and deep learning techniques [56]. In their methodology, with the aim of extracting qualitative information from the internal regions of the identified nodules, they utilized Otsu algorithm to segment the

TABLE 2. Recent studies on the prediction of nodule malignancy using CNNs.

Years	Authors	Models	Datasets	Key Points
2018	Zhao *et al.* [60]	2D LeNet + 2D AlexNet	LIDC/IDRI	Layer settings of LeNet are combined with the parameter settings of AlexNet to build up a CNN model for malignancy prediction.
2018	Filho *et al.* [56]	Otsu algorithm, 2D CNN	LIDC/IDRI	Otsu algorithm is employed for extracting and analyzing the ROI. New indexes of phylogenetic diversity based on topology is proposed for features engineering and selection. 2D CNN is fed with the obtained features.
2018	Causey *et al.* [50]	3D CNN	LIDC/IDRI and LUNA16	3D CNN model is trained and the output features are collected. Then, these features are combined with the radiological QIF and fed into another 3D CNN for malignancy classification.
2018	Xie *et al.* [59]	MV ResNet-50 and KBC	LIDC/IDRI	Nine KBC models based on ResNet-50are built corresponding to the nine views of every 3D nodule. An adaptive weighting scheme is employed to fuse the outputs of the KBC models.
2018	Gupta *et al.* [57]	SRCNN, CNN, SVM, SVR	LUNA16	SRCNN is used for nodules detection, features are engineered from the obtained nodules using a 2D CNN model. Then, the collected features are fed into a SVM and a SVR for malignancy prediction and malignancy score assessment, respectively.
2018	Liu *et al.* [51]	3D CNN	LIDC/IDRI	Introduction of center-crop process into 3D DenseNet resulting in a DenseNet with the form of binary tree (DenseBTNet).
2018	Zhang *et al.* [52]	3D CNN	LIDC/IDRI	3D dilated convolution operation is put forward in replacement of the pooling operation.
2018	Wu *et al.* [53]	3D CNN	LIDC/IDRI	Window widths, window centers and multi-task learning concept are exploited to build up a 3D CNN model.
2018	Dey *et al.* [54]	3D CNN and 3D DenseNet	LIDC/IDRI	Performance comparison between basic 3D DCNN and some variants of 3D DenseNet.
2018	Zhu *et al.* [58]	3D Faster R-CNN, 3D CNN, GBM	LIDC/IDRI	3D Faster R-CNN is designed for nodules detection. GBM and 3D dual path CNN are applied for malignancy prediction.
2018	Sori *et al.* [55]	2D U-Net and 2D CNN	KDSB 2017	2D U-Net is used to detect nodule candidates considering both local and global contextual features. Three paths 2D CNN with three different input sizes is designed for the classification task.
2018	Nobrega *et al.* [61]	2D CNNs, SVM, MLP, KNN, RF, Naive Bayes	LIDC/IDRI	Eleven popularly used 2D DCNN models are employed as features extractors. SVM, MLP, KNN, RF, Naive Bayes are trained separately with the collected features.
2018	Paula *et al.* [62]	2D CNN, VGG-s, RF	NLST	Three ensemble CNN models based on averaging, majority voting and median probability, are built to classify the learned features.
2018	Nishio *et al.* [63]	VGG-16	LIDC/IDRI and private dataset	Performance comparison between DCNN model, features engineering based model and transfer learning model.

nodules into three sections. Then, they designed a new indices of phylogenetic diversity based on topology to explore and select the essential features of pulmonary nodules. Finally, a CNN model was built and fed with the extracted nodules characteristics to produce the final classification results. This system was validated on a dataset consisting of 394 malignant candidates and 1, 011 benign candidates. It achieved an accuracy value of, a sensitivity value of and a specificity value of 92.63%, 90.7% and 93.47%, respectively.

2) 2D CNN+ (SINGLE IMAGE SUPER-RESOLUTION, SVM, SVR)

Gupta *et al*. investigated the malignancy prediction as well as the level of malignancy of the tumor [57]. With the aim of overcoming the influence of low resolution on the diagnostic performance, they made use of the Single Image Super-Resolution approach to preprocess the imaging data. Then, the enhanced images were fed into a CNN model to identify the positive nodule samples. Subsequently, essential features were extracted from the detected real nodules utilizing the previously designed CNN model. Lastly, an SVM classifier was designed to train the generated features vector producing the diagnostic results. Furthermore, the malignancy level was predicted by training the features vector with a SVR (Support Vector Regression) model. This system presented quite satisfactory classification capability, yielding an accuracy of 85.7% on nodule candidates acquired from the LUNA16 dataset.

3) DEEPLUNG (DUAL-PATH 3D DCNN+ (3D FASTER R-CNN, GRADIENT BOOSTING MACHINE))

To the end of automatically detecting and classifying pulmonary nodules in volumetric CT images, Zhu *et al*. employed 3D CNN to build up a dual path networks based system [58].First, a 3D Faster R-CNN model was designed to locate the nodule candidates. Then, they exploited a deep 3D dual path network, gradient boosting machine (GBM) algorithm and some detected nodules characteristics such as size and shape to achieve the final classification results. The proposed system's performances were assessed through tenfold cross-validation experiments conducted on the 888 CT scans of the LUNA16 dataset. It achieved an accuracy of 90.44% demonstrating the great advantages of considering deep 3-D dual path network features.

C. ENSEMBLE LEARNERS OF MULTIPLE CNNS

Xie *et al*. built a MV-KBC (multi-view knowledge-based collaborative) framework for distinguishing malignant from benign pulmonary nodules [59]. The proposed system achieves the malignancy prediction in the following manner. First, every nodule candidate was split into nine views. Then, each view was utilized to build up a KBC model in which three pre-trained ResNet-50 with three different receptive field sizes were fine-tuned. Finally, the outputs of the nine KBC models were combined using an adaptive weighting based strategy to generate the final prediction results. This study constitutes a pioneer work as it has expanded the concept of domain knowledge to convolutional neural networks with application to pulmonary nodules malignancy prediction.

D. HYBRID SYSTEMS

This group of clinical decision-support systems are those whose frameworks comprise networks resulted from combining two or more layers or/and parameters of different other network models. It could also be referred to as the class of systems whose methodology contains different types of networks. Fig. 4(c) presents a brief overview of hybrid model.

Agile CNN (LeNet+AlexNet): A hybrid convolutional neural network model resulted from combining the layers of LeNet and the network parameters of AlexNet for differentiating benign pulmonary nodules from malignant pulmonary nodules in CT images was developed by Nóbrega *et al* [60].The implementation of the proposed model on only 743 nodule candidates yielded an accuracy and an AUC of 82.2% and 0.877, respectively. The obtained results demonstrated that this hybrid CNN model could be considered as a promising alternative for applying deep learning to the analysis of small amount of medical image data. They also investigated the influence of some network hyper-parameters such as kernel size, weight initialization, learning rate and training batch size on the CNN classification performance.

E. TRANSFER LEARNING BASED SYSTEMS

Transfer learning refers to an approach wherein the stored knowledge resulted from learning a model while solving a specific task can be applied to solving a different task of a related problem. Deep convolutional neural networks have achieved impressive recognition performances in natural images analysis. However, such great performances are highly dependent on great amount of datasets. On the other hand, medical imaging data are very limited; which makes the application of deep CNN models to their analysis quite challenging. Thus, with the aim of mitigating the poor performance of deep CNN due to small amount of medical images, transfer learning has been adopted as a reliable alternative for analyzing pulmonary nodules in medical images using deep CNN models. The concept of transfer learning is illustrated in Fig. 4(d).

Nobrega *et al*. employed transfer learning to learn quantitative features from nodule candidates of the LIDC/IDRI dataset; which were later utilized to classify them into benign and malignant [61]. The scenario of their framework is as follows. First, they utilized eleven deep CNN models previously trained on the ILSVRC (ImageNet Large Scale Visual Recognition Challenge). These models include Xception,VGG16,Inception-ResNet-V2, VGG19, DenseNet201, MobileNet, InceptionV3, DenseNet169, ResNet50, NASNetLarge and NASNetMobile. Then, each set of obtained features was fed into five classifiers including MLP (Multilayer Perceptron), Naive Bayes, (SVM) Support Vector Machine, KNN (K-Nearest Neighbor) and RF (Random Forest), to produce the diagnostic results. The experimental results demonstrated that the combination of ResNet-50 for features extraction and SVM-RBF for classification is the most suitable approach for predicting malignancy in nodule candidates based on pre-trained deep CNN models. This combination yielded an ACC, an AUC, an F-score, a TPR and a PPV of 88.41%, 93.19%, 78.83%, 85.38% and 73.48%, respectively.

A methodology employing radiomics features, transfer learning generated features and ensemble learning for nodules malignancy prediction was proposed by Nishio *et al*. [62]. First, they utilized the pre-trained VGG-s for features extraction. Second, they built up three different CNN models including an ordinary CNN with two convolutional layers, a CNN-LSTM model and a CNN with a cascaded architecture. Then, 219 radiomics features were acquired and the useful ones were chosen using image segmentation and Random Forest algorithms, respectively. Finally, they designed three ensemble models using as fusion strategy averaging, majority voting and median probability, respectively. Utilizing averaging as the fusion strategy allows the third ensemble model to achieve the best AUC value of 0.96. Whereas, the highest accuracy value of 89.45% was yielded by the same model utilizing majority voting as the fusion approach.

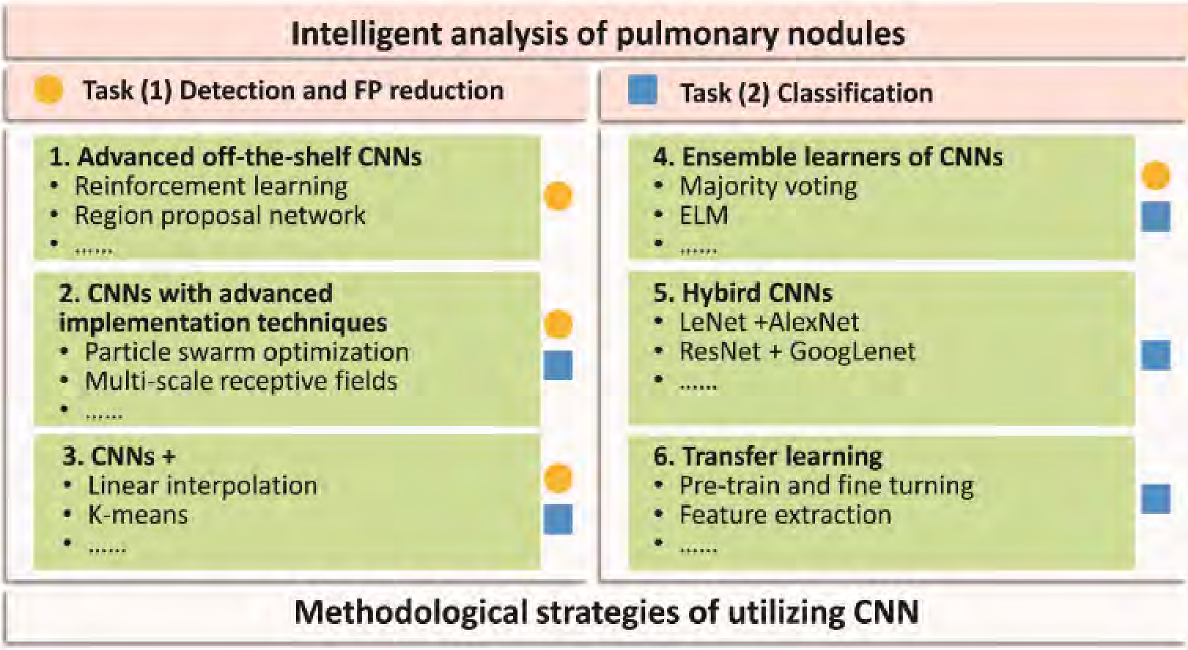

FIGURE 5. Summary of the different categories of CNN methodologies for pulmonary nodule analysis.

With the purpose of classifying nodule candidates into benign, primary cancer and metastatic cancer, Nishio *et al.* investigated the following problems [63]: the recognition performance of deep CNN model as compared with that of features engineering based methods, the importance of utilizing transfer learning and the effect of the receptive field size on the deep CNN classification performance. They implemented the VGG-16 model and made some modifications to it to fit their datasets. Later on, they designed a transfer learning model based on the pre-trained VGG-16 model. Both deep CNN models (without and with transfer learning) were trained with image patches of sizes 56×56, 112×112, and 224×224, respectively. The deep CNN model trained from scratch yielded a validation accuracy of 60.2%, 62.4% and 58.9% for image patches of sizes 56, 112, and 224, respectively. Whereas, the pre-trained model achieved a validation accuracy of 60.7% when fed with images of 56×56; 64.7% when fed with images of 112×112 and 68.0% when fed with images of 224×224.

VI. TRENDS, CHALLENGES, PROSPECTIVE DIRECTIONS AND SUGGESTIONS

From the comprehensive analyses of existing clinical decision-support systems presented above, it is observed that recently, the applications of convolutional neural networks to the early diagnosis of lung cancer have known astonishing progresses. Specifically, great advancements have been achieved in the automated nodules identification, false positive reduction, classification of nodules into cancerous and non-cancerous, etc. However, there is still room for improvements due to existing challenges which are pointed out below as well as some proposals for future investigations.

A. METHODOLOGICAL TRENDS

Convolutional neural network has been the leading method for the detection and classification of pulmonary nodules using deep learning. Using "lung nodules" and "lung nodules and deep learning" as keywords, the statistics during the period of 2015 to 2018 retrieved from the IEEEXplore and PubMed databases show that the studies using CNNs account for 93.8% and 60.5% of the overall publications, respectively. In addition, it is found that the number of studies using CNNs has remarkably increased by 153.3% and 50% from 2017 to 2018 for the two abovementioned datasets, respectively. The study by Litjens *et al.* also supported this trend [21].

As illustrated in Sections IV and V, CNN methodologies for pulmonary nodule analysis can be categorized into six groups including (a) Advanced off-the-shelf CNNs; (b) CNNs with advanced implementation techniques; (c) CNNs+; (d) Ensemble learners of CNNs; (e) Hybrid CNNs and (f) Transfer learning (Fig. 5). The methods of (a), (b), (c) and (d) are utilized for the pulmonary nodule detection and false positive reduction. In our survey, the ratio of the number of publications in 2018 using these four different categories of methods is 4:2:2:3 (see Table 1); indicating that all these categories have been developed evenly and none of them is at dominant position. The category of "Advanced off-the-shelf CNNs" outperforms the other three categories and three of the four studies of this category achieved an accuracy and sensitivity greater than 95%. This could be due to the fact that "Advanced off-the-shelf CNNs" make use of more sophisticated and newer algorithms such reinforcement learning, Faster R-CNN, group convolution, etc.

Five categories of CNN methodologies consisting of (b), (c), (d), (e) and (f) have been employed for pulmonary nodule classification. The ratio of the number of publications in 2018 in the current survey using these five categories of methods is 6:3:1:1:3. It can be seen that more studies prefer to design CNN frameworks with advanced implementation techniques; meanwhile CNN+ and Transfer learning methodologies are also the prior choices. The category of "CNNs with advanced implementation techniques" achieved better performance than the other categories. For instance, the sensitivity of four of the six studies referred in our survey is higher than 95%. Such performances might originate from their ability of learning greater amount and more diversified semantic and radiomics features from the nodule candidates employing newly proposed convolution processes such as center-crop operation, 3D dilated convolution, etc.

B. EXISTING CHALLENGES

1) INSUFFICIENCY OF WELL-LABELED MEDICAL DATASETS WITH GREAT NUMBER OF CASES

It is noted that most of the great successes of deep learning techniques in general and convolutional neural networks in particular, have been achieved on huge amounts of data. However, gathering such datasets in medical imaging is still very challenging due to many factors such as the tediousness of the annotation tasks for the physicians, privacy and ethical requirements, etc. Thus, the lack of datasets with large number of samples constitutes a crucial obstacle to the application of deep learning to the analysis of medical data [12].

2) GENERALIZABILITY CAPABILITY ISSUES

Numerous deep learning based models have been proposed to solve various diagnostic tasks in medicine achieving outstanding performances. However, in most of the cases, a proposed model which performed very well on a specific task may not be valid for other tasks no matter how slight their difference maybe [64].

3) POOR INTERPRETABILITY AND EXPLICATION OF THE DETECTION RESULTS

Nowadays, priority and emphasis are given to performance improvements over understandability and interpretability. However, better interpretability could be helpful in anticipating on the failures of computer-aided detection systems; which would result in the reduction of false positive or late diagnosis. Moreover, increasing the interpretability of deep learning based detection systems will be of great significance not only in figuring out how the predictions are generated, but also in clearly understanding how the outcome of a specific patient is obtained [65]. This may lead to the definition of more accurate and reliable clinical decision guidelines as well as to the formulation of new hypotheses.

4) SHORTAGE OF ACCURATE CLINICAL DECISION TOOLS

Despite the great successes of deep learning in lung cancer screening, predicting the nature of identified pulmonary nodules still constitutes a critical issue as very few of these nodules turn out to be cancerous. For instance, in the National Lung Screening Trial (NLST), less than 5% of the detected nodules were malignant [5]. Moreover, the study by Patz *et al.* had demonstrated that over 18% of this very limited number of cancerous lesions seemed to be indolent [66]. Thus, the research community lacks robust and efficient approaches and tools for determining whether identified pulmonary nodules are malignant or benign and aggressive or indolent.

C. PROSPECTIVE DIRECTIONS

To tackle the abovementioned challenges, the following ideas are put forward for future investigations.

First, one of the crucial obstacles to the application of CNNs to the analysis of pulmonary nodules is the lack of datasets with large number of samples. This issue can be mitigated by developing some new approaches for generating synthetic medical images. For instance, Generative Adversary Networks (GANs) could be further investigated as they have been proven to achieve remarkable results in generating both natural and medical synthetic images [67]–[70]. Moreover, the development of more deep learning based methods not involving great amount of data such as in the study by Zhao *et al.* [60] could also be considered as a promising alternative to the insufficiency of labeled medical data. Furthermore, an incredible improvement of the poor performance due to insufficient data may be achieved by designing new CNNs frameworks in which the conventional translational convolutions are substituted by group convolutions as proved in the studies by Tan *et al.* [4], [71].

Second, given that different medical scanners operate under different settings and that there exist various imaging modalities, different datasets are often made up of images presenting heterogeneous characteristics. These heterogeneities constitute one of the major factors of the low generalizability capability of CNN models. Therefore, we recommend the investigation of the influence of the scanners settings such as reconstruction techniques and parameters as several studies have demonstrated their impact on the radiomics features [72]–[75]. In addition, the generalizability issues could also be alleviated through developing some methods that can be validated on images of different types i.e. Computer Tomography (CT), Magnetic Resonance Imaging (MRI), etc. Furthermore, to adapt other approaches such as knowledge transfer can significantly mitigate the problems of radiological heterogeneity of medical scanners and lung nodules diversity [76]; which will potentially enhance the generalizability of clinical-decision support systems.

Third, the training processes of CNN models often face the problems of overfitting, convergence and high computational time. Thus, there are urgent needs of designing novel clinical decision-support systems whose frameworks include two or more of the newly developed CNN architectures to address these problems; which will consequently contribute to further improving the early diagnosis of lung cancer. For instance, recently, Li *et al*. proposed a hybrid network namely H-DenseUNet resulted from combining DenseNet and U-Net [77]. Other CNN models with such architecture though Unet-Vnet-Fast-R-CNN, Mask-R-CNN are worthy to be investigated.

Fourth, new approaches for both radiomics and semantic features analysis in screening data should be developed to reduce over-diagnosis and improve the early identification of lung cancer. For instance, one could integrate CNNs with other machine learning and image processing algorithms to include the information of the lung parenchyma; which will significantly enhance the extraction of the radiomics and semantic features from the lesions as done in the study by Xu *et al*. [78]. In addition, the crucial utility of semantic and radiomics features in the lung cancer prognosis has been demonstrated by many studies [79]–[81].

Fifth, expert-in-the-loop or doctor-in-the-loop systems should be developed to facilitate both the understanding and explanation of how the predictions yielded by deep learning systems are generated. These systems can be referred to as those resulted from getting both the clinical experts and artificial intelligence experts involved in their building and functioning processes [65]. There already exist some examples of such system [82], [83]. Doing so would definitely increase the interpretability of the predictions; which will lead to the identification of biomarkers and help improve both the diagnosis and prognosis.

D. POTENTIAL SUGGESTIONS

To improve the early diagnosis and management of lung cancer, which will potentially reduce its critical death rate; researchers can develop new methodologies for pulmonary nodule analysis based and centered on CNNs. The potential strategies can consist of:

- *Designing CNNs with completely new architectures specifically for nodule analysis.*
- *Adapting the proposed "advanced off-the-shelf CNNs" to other tasks.*
- *Adding the advanced techniques into the implementations of CNNs.*
- *Integrating CNNs with other machine learning algorithms, hand-crafted features, imaging processing techniques.*
- *Generating ensemble learners of multiple CNNs.*
- *Building hybrid CNNs inheriting great characteristics from their parents.*
- *Using transfer learning from various levels (instance, feature, and knowledge).*

From the comprehensive analyses conducted in this survey, we suggest that to adapt the "advanced off-the-shelf CNNs" might yield competitive performance for pulmonary nodule detection, while "CNNs with advanced implementation techniques" are more suitable for nodule classification.

To initiate multi-center clinical trials is suggested for it is urgently required to verify the value of CNNs based automatic classification for improving the outcomes of lung cancer patients. Beyond the detection and classification, CNNs analysis of pulmonary nodule will inevitably be expanded to the patient stratification or subtyping, the prediction of outcomes (e.g., treatment response, survival), the analysis of the multi-omics correlations (e.g., radiomics, pathomics, genomics), and the understanding of the mechanisms underlying lung cancer. In addition, more attention should be paid to micro-nodules given that apart from the expansion in diameter of pulmonary nodules, their growth in attenuation and density has been proven to be associated with an increase in malignancy risk [6].

VII. CONCLUSION

The precise and accurate detection and examination of pulmonary nodules is one of the best approaches to decrease the lung cancer-related deaths. To this purpose, numerous CNNs based methods and systems have been proposed for analyzing pulmonary nodules in medical images. A comprehensive analysis of these methods has been provided in this paper. We have focused mainly on the remarkable works published in 2018 and whose frameworks include convolutional neural networks. A brief overview of convolutional neural networks as well as their advantages and rationale for applying them to pulmonary nodules analysis were reviewed. Then, we analyzed the recently developed CNNs based systems for nodules classification with main focus on their methodologies, the datasets used for validation as well as their detection results.

It was observed that applying CNNs to the detection of pulmonary nodules as well as their classification into malignant and benign have yielded remarkable performances; which makes them a promising approach to improving the early diagnosis, treatment and management of lung cancer. However, there is still room for improvement as these existing methods present some challenges whose overcoming is of urgent need. We believe that the detailed description of CNNs, their advantages and limitations in medical imaging as well as prospective directions as presented in this paper, will be of great help not only in the diagnosis and treatment of severe diseases such as lung cancer, but also in various areas of radiology.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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