Consolidation describes increased lung attenuation sufficient to obscure bronchial walls and blood vessels (on non-enhanced CT). Patent airways can be identified by the endoluminal gas as an air bronchogram. Consolidation can be caused by any process that evacuates alveolar air such as pneumonia, when air is replaced by inflammatory exudate, or tumor, when air is replaced by tumor cells [3].

On radiographs, consolidation appears as air bronchograms within opacity which is otherwise homogeneous.

Pathology

Etiology

The opacification is caused by fluid or solid material within the airways that causes a difference in the relative attenuation of the lung:

- blood, e.g. pulmonary hemorrhage
- cells, e.g. adenocarcinoma
- fat, e.g. lipoid pneumonia
- gastric contents, e.g. aspiration pneumonia
- protein, e.g. alveolar proteinosis
- pus, e.g. bacterial pneumonia
- transudate, e.g. pulmonary edema secondary to heart failure
- water, e.g. drowning

When considering the likely causes of airspace opacification, it is useful to determine chronicity (by reviewing previous radiographs) and considering laterality.

Additionally, the presence of mediastinal or hilar lymphadenopathy further refines the massive list of differentials:

- acute unilateral air space opacification
- acute bilateral air space opacification
- acute airspace opacification with lymphadenopathy
- chronic unilateral airspace opacification
- chronic bilateral airspace opacification

Patterns of disease

On chest radiography a number of patterns are recognized:

- lobar consolidation
    - right upper lobe consolidation
    - right middle lobe consolidation
    - right lower lobe consolidation

    - left upper lobe consolidation
    - left lower lobe consolidation
- bronchopneumonia
- lobar lung collapse
    - right upper lobe collapse
    - right middle lobe collapse
    - right lower lobe collapse
    - left upper lobe collapse
    - left lower lobe collapse
- We conducted a retrospective analysis to evaluate the volume of the lungs and determine the presence of infiltration and consolidation. To accurately interpret anisotropies and voxel spacings and to maintain resilience even when dealing with unbalanced class distributions, we used nnU-Net with quantitative and qualitative assessments to detect Lung infiltration. Utilizing TCGA-LUAD data (Lung Adenocarcinoma) and TCGA-LUSC (Lung Squamous cell carcinoma) this retrospective study on segmentation for volumetric and consolidation assessments are conducted. Chest OMX is a diagnostic tool that can assess lung volume, which in turn enables various applications such as monitoring recurrence from the changes in Lung volume; identifying infiltration and response to the treatment from Lung Volume and lobes, and detecting abnormalities in the lung from Consolidation. By providing quantitative score values, it assists in tracking changes over time and facilitating decision-making in clinical diagnosis.

Methods

- We used nnU-Net, a popular deep-learning framework designed for medical image segmentation tasks. By analyzing the volume, infiltration, and consolidation characteristics of a lung carcinoma on CT scans, we can assess the tumor's behavior and response to treatment. From regional lung segmentation invasion, the burden is calculated. Additionally, measurements of discovered lung lesions and dedication to the relevant lung lobe are performed, along with fully automated lung lobe segmentation. Lobe 3D uses a deep learning system to measure the volume of the five lobes of the lung. HAA is also analyzed towards the end. Patient cases are selected irrespective of their ages from the TCGA cohort group. The primary outcome was the assessment of lung volume and the extent of the infiltration.

Results

- Table: 1250P. Chest OMX: Generated diagnosis report for the case TCGA-LUSC

Left lung (LL) cm^3	1429.50
Right lung (RL) cm^3	1516.38

Left upper lobe (LUL) cm^3	807.24
Left lower lobe (LLL) cm^3	603.17
Right upper lobe (RUL) cm^3	618.34
Right middle lobe (RML) cm^3	276.84
Right lower lobe (RLL) cm^3	611.89
Left upper lobe (HAA) cm^3	170.16
Left lower lobe (HAA) cm^3	378.00
Right upper lobe (HAA) cm^3	128.18
Right middle lobe (HAA) cm^3	59.05
Right lower lobe (HAA) cm^3	394.12
Volume (LUL, LLL, RUL, RML, RLL) cm^3	(807.24, 603.17, 618.34, 276.84, 611.89)
Involvement (LUL, LLL, RUL, RML, RLL) cm^3	(378.00, 128.18, 59.05, 394.12)
Infiltration percentage (LUL, LLL, RUL, RML, RLL) %	(21.08, 62.67, 20.73, 21.33, 64.41)

- ## Conclusions
- The diagnostic tool, Chest OMX can analyze the lung tissue from CT scans to determine the volume, consolidation and extent of infiltration by cancerous cells.

Abstract

A viral outbreak with a lower respiratory tract febrile illness causes pulmonary syndrome named COVID-19. Pulmonary consolidations developed in the lungs of the patients are imperative factors during prognosis and diagnosis. Existing Deep Learning techniques demonstrate promising results in analyzing X-ray images when employed with Transfer Learning. However, Transfer Learning has its inherent limitations, which can be prevaricated by employing the Progressive Resizing technique. The Progressive Resizing technique reuses old computations while learning new ones in Convolution Neural Networks (CNN), enabling it to incorporate prior knowledge of the feature hierarchy. The proposed classification model can classify pulmonary consolidation into normal, pneumonia, and SARS-CoV-2 classes by analyzing X-rays images. The method exhibits substantial enhancement in classification results when the Transfer Learning technique is applied in consultation with the Progressive Resizing technique on EfficientNet CNN. The customized VGG-19 model attained benchmark scores in all evaluation criteria over the baseline VGG-19 model. GradCam based feature interpretation, coupled with X-ray visual analysis, facilitates

improved assimilation of the scores. The model highlights its strength to assist medical experts in the COVID-19 identification during the prognosis and subsequently for diagnosis. Clinical implications exist in peripheral and remotely located health centers with the paucity of trained human resources to interpret radiological investigations' findings.

1. Introduction

World Health Organization (WHO) reported viral emergences over numerous occurrences, which epitomizes a severe concern for public health. In the last two decades, viral epidemics like Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV), H1N1 influenza, and the Middle East Respiratory Syndrome CoronaVirus (MERS-CoV) have drawn significant attention. In November 2019, a similar viral outbreak with a lower respiratory tract febrile illness was reported in China. Bronchoalveolar lavage (BAL) test analysis highlighted an unfamiliar coronavirus strain responsible for the outbreak. The World Health Organization named the pulmonary syndrome "COronaVIrus Disease 2019" (COVID-19) or severe acute respiratory syndrome coronavirus2 (SARS-CoV-2). The cumulative number of confirmed cases crossed 14,79,168 globally, with approximately 87,987 virus-related deaths as of April 09, 2020, with a significant spread worldwide [1].

Etiological tests, Reverse-Transcription Polymerase chain reaction test, Chest X-rays, and Chest Computed Tomography Scans (CT-Scans) are the tests/techniques which can identify the infection. A nasopharyngeal Exudate swab sample is screened in the RT-PCR test. However, the RTPCR test's reliability with higher turnaround time poses a challenge in diagnosis, especially in developing nations due to limited medical facilities. As the infections in the lungs can be screened with radiographs, the radiographs are being used in the diagnostic workup, check disease progression, and follow-up of the pulmonary consolidations. Since the coronavirus consolidation is dissimilar to bacterial or viral pneumonia consolidation, the radiographs help identify the COVID-19 infection. The chest X-ray findings can improve the diagnosis time-cycle with enhanced screening capability. It also helps to prioritize the treatments of the patients at hospitals. Hence, X-ray analysis is a discriminative element that assists in the timely identification of COVID-19 infections.

Since the etiologic and clinical physiognomies of the illness are analogous to those of SARS and MERS, the experience of these pulmonary syndromes can be helpful during the diagnosis of the COVID-19 [2], [3], [4], [5], [6]. The X-ray images with an exposure of SARS, MERS, pneumonia, and COVID-19 have been taken to develop the X-ray analysis model using Convolution Neural Networks to identify COVID-19 chest infections. The findings are referred to as Ground Glass Patterned areas, which indicate COVID-19 infection. The infections affect both lungs, particularly the lower lobes, especially the posterior segments, with a fundamentally peripheral and subpleural distribution. With visuals of Lesions progression, septal thickening, and formation of Crazy Paving Pattern or Ground Glass Pattern (rounded morphology), the X-ray can indicate the infection [7], [8]. Fig. 1 shows the visual distinction in the same patient's chest X-rays with typical subpleural peripheral opacities developed due to COVID-19 infections.

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Figure 1. The figure shows Chest X-rays from the dataset indicating typical subpleural peripheral Opacities [9].

Our work is motivated by Convolution Neural Network models' convincing performance and the prevailing need for an alternate screening methodology for an efficient healthcare ecosystem for timely detection of COVID-19. We carried out studies on the work published by various research groups. We have carried out a comparative analysis, which brings out the dataset insights, a number of classes, type of Deep Learning models, and performance of these experiments, and details are covered in Table 1. Most of the work has been done on small-sized datasets due to the inadequate availability of annotated Chest X-Rays. However, some of these research groups have used augmented/selective Chest X-Ray images. We also studied data augmentation techniques used in different variants of the investigation.

Table 1. The table illustrates essential aspects of the existing literature for detection of COVID-19 consolidation are shown in the table, which uses various approaches. (Abbreviations: CNN-Convolution Neural Network, SVM- Support Vector Machine, VGG- Visual Geometry Group, and Acc-Accuracy.)

The majority of the published work incorporates two or three-class classification with binary classification. We have analyzed various CNN models by studying their performance scores and the methodology. Since the Convolution Neural Networks (CNN) do not have predefined kernels and learn locally from connected neurons representing data-specific kernels, the CNN filters can be applied repeatedly to the images to classify the X-ray images. We conclude from the study that suitable CNNs can be employed to carry out multi-class classification with an unskewed balanced dataset. We propose the Transfer learning technique's employment on the X-Ray databases. The technique enhances learning new tasks and enables improved classification by transferring learned knowledge from relevant classification datasets. We first train a baseline COnvolution Neural Network on a base dataset with the defined task. After obtaining the weights, we repurpose the learned features by transferring this knowledge to a target (X-ray analysis) model, which will be trained on the X-ray dataset. Transfer Learning helped reduce training time and improve neural network performance. However, this technique also suffers from inherent limitations of negative transfer and overfitting. We propose a novel implementation methodology by amalgamating the Progressive Learning technique with the Transfer Learning technique to circumvent the limitations. The Progressive Resizing technique reuses old computations while learning new ones in Convolution Neural Networks (CNN), which enables it to incorporate prior knowledge of the feature hierarchy [18]. The paper proposes a novel methodology to detect the COVID-19 pulmonary consolidations in X-ray images with a method to interpret the CNN analysis with intuitive Saliency maps (GradCam) Visualisation. Our contributions are listed as follows:

- •

We present a novel Classification Model to detect COVID-19 pulmonary consolidations in chest X-ray, achieving the best specificity and sensitivity score.

- •

We propose a modified VGG-19 architecture that shows promising results over the Baseline VGG-19 model when applied with the Transfer Learning technique.

- •

We demonstrate a comparative analysis of the results generated by CNN models with various techniques.

- •

The classification models classify the X-ray in Pneumonia, SARS-CoV-2, and Normal X-ray with GradCAM Saliency Maps for enhanced assimilation.

2. Datasets

The classification scores are impacted by volumetric data of one class and may skew away from the severity of coronavirus influence while analyzing the radiology images. Hence, the use of multitudinal and multimodal is done while designing a robust AI model [14]. There is a bright possibility of increasing diagnostic results using different clinical data of the same patients, i.e., Electronic Health Record (EHRs), computerized tomography (CT) scans, and Chest X-rays. However, the availability of such a dataset for making an AI model is a challenge. Hence, we have carefully studied the chest X-Rays to formulate our experiments. We used the X-ray Imaging dataset of the COVID-19 patients for the experiments, which was curated by Dr. Joseph Cohen of the University of Montreal, Canada [9]. The dataset incorporates Normal, and COVID-19 infected X-Ray images. We used the COVIDx Dataset of the COVID-Net Team (Vision and Image Processing Research Group), University of Waterloo, and Darwin AI Corp, Canada [19]. The X-Ray imaging dataset consists of 16,756 chest radiography images, including 66 X-ray images of COVID-19. High skewing observed in the quantity of X-ray appertaining to Normal, Pneumonia, and COVID-19 classes may impact the classification scores while training CNNs. Hence, we created a balanced, relevant dataset in consultation with a radiologist to carry out experiments for multi-class classification. The composite dataset has 100 X-rays each in healthy and pneumonia classes and 104 X-ray images of the COVID-19 class.

3. Implementation and methodology

We conducted our experiments on Dr. Joseph Cohen's and amalgamated datasets for binary and multi-class classifications. We conducted the experiments on Convolution Neural Network models, i.e., VGG-19 (baseline) and customized VGG-19 [20], and EfficientNet-B3 Neural Network [21]. To improve the baseline models' results, we incorporated modifications in the final layers of these CNNs. We employed the Transfer Learning technique by transferring pre-trained weights from the ImageNet dataset [22], [23] and then superimposed the Progressive Resizing technique while training the designated CNN models on X-ray imaging datasets. Finally, the classification experiments demonstrated improvements in the results for both datasets. GradCam based Saliency maps facilitate X-ray imaging analysis by highlighting relevant visual information with classification scores. Fig. 2 illustrates the proposed Methodology to detect COVID-19 and Pneumonia in X-ray imaging and generate Saliency Map. We conducted our experiments on Nvidia GTX 2080Ti GPU (4352 CUDA cores). Our experiments and implementation methodology incorporates four stages, i.e., Data Preprocessing, Model Implementation, Training Strategy, and Testing.

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Figure 2. The figure illustrates the implementation methodology and the inference pipeline with the employment of Transfer Learning and Progressive Resizing Techniques on ConvNets to detect COVID-19, Pneumonia consolidations in the X-rays with the saliency maps.

3.1. Data preprocessing

We have employed data augmentation techniques to generate X-ray variations from the available X-ray imaging due to the limited availability of annotated X-ray images of COVID-19 infected patients. The variations were incorporated into the dataset during the training and validation phases.

During data processing phase, we used the value of ϑ = -60 to 60 degrees, α = 1.0 - 1.1, P_A = 0.75 and P_B = 0.5. We used the following techniques to process the data and augment the datasets:

- •

Horizontal Flipping of the X-rays imaging with a probability of P_B.

- •

X-Ray rotations were carried out due to rotational invariance.

- •

Random scaling of α was applied with a probability of P_A.

3.2. Model customization and implementation

COVID-19 Chest X-ray exposes palpable white patches in the lungs – referred to as Ground-Glass-Windows. The proposed CNN approach deliberates on varied patterns like Consolidation, Interstitial, Nodules/masses, and Atelectasis observed in the X-rays. Transfer learning and domain adaptation help to use the knowledge learned in one setting to improve generalization in another setting. During the employment of Transfer Learning, we used pre-trained weights obtained after training the model on a large dataset (i.e., ImageNet) while re-training the model on the COVID-19 datasets. We carefully optimized relevant Hyperparameters, which govern the training process and affect network structure. Learning Rate was optimized after each epoch using an LR finder that identified the optimal learning rate for the subsequent epochs. Various experimental results determined the number of Epochs. We explored various activation functions during the experiments, i.e., ReLU, SoftMax, and TanH. The values of the hyperparameters were optimized during experiments. The Progressive Resizing technique was used repeatedly with a progressive increase of the size of the x-ray images. The methodology facilitated the effective extraction of the features in each iteration, thereby attaining the optimum weights. The same methodology was applied while carrying out multi-class classification on the amalgamated dataset, containing images with pneumonia consolidation.

3.2.1. Customized VGG-19

We used the Baseline VGG-19 model for our experiments on both datasets. We have carried out binary and multi-class classification. We carried out modifications to the baseline VGG-19 model to attain improved results. In VGG-19 baseline model, 'Backbone'- convolution layers analyse the X-ray consolidation features. These layers are dovetailed by culminating linear layers, referred to as 'Head.' 'Head' translates the analyzed features during generating prediction scores for two classes in binary classification. To reduce the learning time and optimize the learning of the CNNs, we employed differential learning rates. We split the head from the rest of the architecture layers and ran the experiments on 'Backbone.' To carry out relevant modifications in VGG-19 architecture, we replaced the 'Head' with the AdaptiveConcatPool layer with Flatten Layer, blocks of Batch Normalization, Dropout, Linear, and ReLU layers. We appended two units with softmax activation as a fully connected layer referenced as - 'Final Classification Layer.' This AdaptiveConcatPool Layer effectively preserves the backbone's feature representations compared to using only the MaxPool Layer or the AveragePool Layer in the 'Head.' Fig. 3 shows a novel modified VGG-19 architecture which demonstrated a substantial upsurge in outcomes.

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Figure 3. The figure illustrates Customized VGG-19 Architecture tailored to detect COVID-19, Pneumonia Consolidation in Chest X-Ray Imaging. The modified 'Head' block in the architecture conserves stability between computational efficiency and representational capacity during binary and multi-class classification.

3.2.2. EfficientNet B3

EfficientNet is a CNN architecture and has several variants. It is a scaling method that uniformly scales all dimensions using a compound coefficient. Since the more extensive networks with greater width, depth, or resolution tend to achieve higher accuracy, we used EfficientNet for carrying out multi-class classification. These models demonstrated enhanced performance during the experiments. Output layers of these CNN variants were suitably modified for classification experiments on both datasets.

3.3. Training strategy

We used pre-trained weights while employing Transfer Learning to train the VGG-19 and Customised VGG-19 CNN models. We experimented with the proposed novel methodology using the Transfer Learning technique followed by the Progressive Resizing while training EfficientNetB3 models. We carried out experiments on the datasets with training to test subsets as 80:20. We used the Discriminative Learning strategy to extract relevant features' information while training the models. We used Weight decay (Wd) to guard against overfitting, which prevents the weights from growing too large. We used Binary Cross Entropy as the loss function. We changed the learning rates iteratively by using the LR Finder [24] on each set of experiments. We used a 1-cycle policy to optimize the learning rates, which helped achieve Super-Convergence with faster training, ensuring optimum regularization [25], [26].

3.3.1. VGG-19 models

The baseline model of Very Deep Convolutional Networks is used in our multi-class classification. It attains a significant accuracy on image classification and localization tasks. Due to its inherent strength in processing X-Ray image recognition, we used it for our experiments. We implemented the Transfer Learning technique on the VGG-19 (baseline) and customized the VGG-19 model during the training on X-Ray datasets. Pre-trained weights of the ImageNet dataset were used. We used discriminative learning rates to preserve the lower-level features and regulate the higher-level features for optimum results.

3.3.2. EfficientNetB3

We conducted our experiments on variants of the EfficientNet, i.e., EfficientNetB0, B1, B2, B3, and B4. The EfficientNet higher variants, i.e., EfficientNet B4, B5, B6, and B7, have extensive width, depth, or resolution. However, the accuracy gain was observed saturating/stable while experimenting with the X-ray datasets. In comparison to the EfficientNet-B3 model, the higher versions do not yield any relevant outcomes. Hence, detailed experiments were undertaken with the EfficientNet B1, EfficientNet B2, and EfficientNet B3 architectures. Due to significant yield accrued while experimenting on the EfficientNet-B3, we carried out binary and multi-class classification on both X-ray datasets. We trained EfficientNet CNN on 64x64 sized X-ray imaging dataset initially to obtain the weights using Progressive resizing technique [27]. These weights were transferred to the resized 128 x 128 Imaging dataset and followed by this; similar iterations were conducted repetitively by gradually increasing X-ray sizes to 256 x 256, 512 x 512. As each larger-scale model incorporated the

weights from the previous iteration, it could extract more relevant features and hence demonstrated improved classification scores. This methodology yields significant results by following the strategy. Fig. 4 illustrates the implementation methodology of Transfer Learning and Progressive resizing techniques on the X-ray Images and applying the obtained weights iteratively to the forthcoming next training model with scaled-up images.

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Figure 4. The figure shows an illustrative representation of the methodology to employ the Transfer Learning technique in consultation with the Progressive Resizing Technique on the EfficientNet-B3 model. Pre-trained weights (ImageNet Dataset) transfer on the EfficientNet-B3 model with (a) (i.e., Imaging input size of 128 x 128 pixels initially), and then carry forward the obtained weights to subsequent models (b) and (c) (i.e., Imaging input size to 256 x 256 pixels and 512x512 pixels respectively).

3.4. Testing

To carry out the testing, resized (H×W) size input images were given to the network to predict the output class. During testing, we used Leave-one-out (LOO) cross-validation method. In LOO-CV, the number of folds equals the number of instances in the data set. Thus, the method applied the learning iteration once for each instance while taking all other instances as its training set. Hence, the method ensured low bias and prevented over-fitting.

4. Discussion

4.1. Evaluation parameters

We carried out the evaluation of the model performance based on the performance metrics. The performance of the model is ascertained by the various scores, i.e., Accuracy (Acc), Precision, Sensitivity (Sens), Specificity (Spec), H-Mean, F1-score, or F-Beta. Accuracy is the overall percentage of correctly identifying COVID-19, Pneumonia, and Normal images. Sensitivity or recall measures the number of correct positive COVID-19 or specific class results to the number of all relevant samples (all positive samples). Specificity shows the ratio of the actual COVID-19 negatives to the correctly predicted as such (i.e., the patients correctly identified as not having COVID-19 consolidations). F1 Score is the Harmonic Mean between precision and recall. Kappa Score [28], [29] is a statistical measure for measuring 'Intra-rater Reliability'. We used the following measures as evaluation criteria (Abbreviations: TP- True Positive, TN- True Negative, FP- False Positive, FN- False Negative):Acc=TP+TNTP+TN+FP+FNPrecision=TPTP+FPSens/Recall=TPTP+FN□□□□F1−Score=2□Precision□RecallPrecision+Recall=2□TP2□TP+FP+FN

4.2. Quantitative results

We discuss the results obtained for binary and multi-class classification in this section. We used VGG-19 (Baseline) for binary classification and customized the VGG-19 model with Transfer Learning with pre-trained weights from Imagenet. Customized VGG-19 results superseded the VGG-19 (Baseline) model (with an accuracy of 89.58%) with a perfect score of 100% under all evaluation criteria. We used Transfer Learning with Progressive resizing on the EfficientNet-B3 model by progressively giving the images in 128x128, 256x256, and 512x512 sizes, and obtained an ideal score of 100% for these experiments. Table 2 illustrates the quantitative scores of the VGG-19 (baseline) viz-a-viz of VGG-19 (Customized) using transfer learning and EfficientNetB3 models' when using Transfer Learning with

Progressive resizing of the X-ray images. The graphs in Fig. 5 show performance comparison under loss functions' values during the training and testing process along with Accuracy, Specificity, Sensitivity, and F1-Scores for binary classification.

Table 2. The table illustrates the results of the implemented models, namely VGG19 (Baseline), VGG-19 (Customized), and EfficientNetB3 with LOO and 5-Fold Cross-validation in terms of evaluations criteria (performance metrics) for Binary COVID-19 Consolidations' predictions.

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Figure 5. The graphs illustrate the performance of the models for Binary classification for VGG-19, Customized VGG-19, and EfficientNetB3 model with (128x128), (256x256), and (512x512) resizing. From left to right, The Loss function convergence while training, and validation phase, with accuracy score shown (a). From left to right, Precision, Specificity, Sensitivity, and F1 Score indicates the enhancements achieved by the Progressive Resizing technique on EfficientNet-B3 model at (b). EfficientNet-B3 (256x256) and Customised VGG19 yield nearly perfect scores on all evaluation criteria, while baseline VGG-19 suffered overfitting.

Significant improvements in results were observed in feature extraction and computation efficiency when progressive resizing was used to carry out multi-class classification. We applied Transfer Learning on VGG-19 Baseline and Customised VGG-19. We experimented on EfficientNet B3 with pre-trained weights and trained them on 256x256, 512x512, and 1024 x 1024 sized progressively. The LOO cross-validation inherent zero randomnesses ensured lower bias which most negligible chances of overestimation in error rate. Hence, the results reflect no overfitting while training. Table 3 highlights the quantitative comparison of the proposed models for multi-class classification wherein the Customised VGG-19 demonstrated substantial improvement over Baseline VGG-19. The EfficientNetB3 (1024x1024) model attained the highest scores progressively and achieved perfect Precision, Recall, F1 Score, and Kappa Score (Fig. 6).

Table 3. The table illustrates the results of the implemented models attained on VGG-19 (Customized) by applying Transfer Learning and EfficientNetB3 by applying the Progressive Resizing Technique with 128x128, 256x256, and 512x512 pixel sized Imaging, in terms of performance scores for Multi-class Consolidations' predictions.

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Figure 6. The graphs illustrate the performance of the models for Multi-class classification for VGG-19, Customized VGG-19, and EfficientNetB3 model with (128x128), (256x256), and (512x512) resizing. From left to right, The Loss function convergence while training, and validation phase, with the accuracy score shown at (a). From left to right, Precision, Recall, F-beta, and Kappa Score indicates the enhancements achieved by the Progressive Resizing technique on EfficientNet-B3 model at (b). The results demonstrated that Customised VGG19 supersedes Baseline VGG-19 and EfficientNet-B3 (256x256) and EfficientNet-B3 (1024x1024) yield nearly perfect scores on all evaluation criteria.

4.3. Clinical implications

Radiographs are non-invasive clinical adjuncts that play an essential role in the preliminary investigation of various pulmonary abnormalities. Especially in the COVID-19 infections, the Chest X-

rays can be helpful in investigations. The exponential rise in pandemic spread makes it challenging for medical experts to carry out RT-PCR / screening tests to complete the diagnosis in time, leading to high morbidity and mortality. Since the studies reveal that the COVID-19 infected patients exhibit distinct multi-focal/bilateral ground-glass opacities and patchy reticular (or reticulonodular) opacities with ground glass patterns, a well trained ConvNet model can act as an alternative screening modality for identifying COVID-19 and validation during diagnosis. The proposed methodology has demonstrated enhancements in identifying COVID-19 consolidations, prioritizing patient care, and allotment of resources.

4.4. Saliency maps

We used Grad-CAM, which uses the gradients of any target class concept, e.g., COVID-19 consolidations, flowing into the final convolutional layer. Finally, it produces a coarse localization map highlighting the important regions in the X-ray image for predicting the class. Gradient-weighted Class Activation Map (Grad-CAM) enhances the assimilation of the results by highlighting the relevant regions from which the results have been predicted [30]. We took the average of all the 1x1x512 channels in Adaptive Average Pooling to generate the Saliency maps, followed by conversion to a tensor of 512. The generated tensor was then multiplied with a matrix of size (512 x no. of classes) to obtain the final visualization output. In our multi-class experiments, the 512 values represented the features extracted in the form of matrices for three different classes. We took the first class's average across every channel to show activated area when the final layer has produced a prediction for any specific class. The activated area is shown with yellow, cyan, and magenta color in decreasing order of values, which contributed to the X-ray image classification. Fig. 7 shows the Grad-CAM activation area for various class inputs by highlighting the relevant features learned from opacities in X-rays.

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Figure 7. The figure illustrates the input Chest X-Ray Imaging with Model generated Gradient-weighted Class Activation Maps below the inputs, respectively. Input X-Ray Imaging and Saliency Map at (a) Predicts in class ‘Normal,’ (b), and (c) show the predictions of Pneumonia, while (d) and (e) show the predictions of COVID-19 consolidations.

5. Conclusion

We proposed a novel methodology to enhance the classification pipeline to identify pneumonia and COVID-19 infections by analyzing pulmonary consolidations in Chest X-rays. Our experiments highlight the novel employment of Progressive Resizing techniques on CNNs to carry out effective medical imaging-based diagnostics. The developed models can act as a second opinion aid in prioritizing the patients' care. The proposed novel approach on Deep Neural Network models enhances the performance significantly. The proposed pipeline starts with the Chest Consolidation recognition stage, where we used VGG-19 (Baseline) and EfficientNet-B3 (Baseline) models to carry out binary and multi-class classifications on both datasets. We modified and fine-tuned the Baseline VGG-19 architecture, demonstrating a significant increase in performance scores in binary classification. In binary and multi-class classification experiments, the Customized VGG-19 and EfficientNet-B3 attained unity scores. Later, we used Transfer Learning and Progressive Resizing techniques on EfficientNet-B3 for multi-class classification, which showed promising results by achieving benchmark scores on X-ray images, i.e., 100% accuracy, 100% precision, 100% recall, 100% specificities, and 100% F-Beta score. The GradCam based visualization, with the help of saliency

maps, extends transparency in correlating model predictions. Clinical implications exist in peripheral health centers with a lack of trained human resources to interpret radiological investigations' for classifying SARS, MERS, pneumonia, and COVID-19.

Abstract

Purpose

To determine whether the percentage of lung involvement at the initial chest computed tomography (CT) is related to the subsequent risk of in-hospital death in patients with coronavirus disease-2019 (Covid-19).

Materials and methods

Using a cohort of 154 laboratory-confirmed Covid-19 pneumonia cases that underwent chest CT between February and April 2020, we performed a volumetric analysis of the lung opacities. The impact of relative lung involvement on outcomes was evaluated using multivariate logistic regression. The primary endpoint was the in-hospital mortality rate. The secondary endpoint was major adverse hospitalization events (intensive care unit admission, use of mechanical ventilation, or death).

Results

The median age of the patients was 65 years: 50.6 % were male, and 36.4 % had a history of smoking. The median relative lung involvement was 28.8 % (interquartile range 9.5–50.3). The overall in-hospital mortality rate was 16.2 %. Thirty-six (26.3 %) patients were intubated. After adjusting for significant clinical factors, there was a 3.6 % increase in the chance of in-hospital mortality (OR 1.036; 95 % confidence interval, 1.010–1.063; P = 0.007) and a 2.5 % increase in major adverse hospital events (OR 1.025; 95 % confidence interval, 1.009–1.042; P = 0.002) per percentage unit of lung involvement. Advanced age (P = 0.013), DNR/DNI status at admission (P < 0.001) and smoking (P = 0.008) also increased in-hospital mortality. Older (P = 0.032) and male patients (P = 0.026) had an increased probability of major adverse hospitalization events.

Conclusions

Among patients hospitalized with Covid-19, more lung consolidation on chest CT increases the risk of in-hospital death, independently of confounding clinical factors.

1. Introduction

Lung consolidations in patients with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection are commonly visualized on radiological exams as ground-glass and diffuse patchy opacities [1], [2], [3]. Due to superior spatial resolution, these changes are usually better visualized by chest computed tomography (CT) instead of simple radiography [4,5].

Previous studies have indicated that imaging findings provide relevant information to establish diagnosis of coronavirus disease-2019 (Covid-19) at multiple stages of the disease [6], [7], [8], [9]. Subsequent reports suggested a qualitative association between diffuse lung involvement and worse clinical outcomes [10], [11], [12], but the magnitude of the increase in the probability given any amount of lung infiltrates at admission is still to be determined.

It is postulated that the reduction in the amount of gas exchange in the consolidation areas, as a result of the combined effect of viral infection and host defense [13], plays a central role in the physiopathology of the Covid-19. In this setting, we hypothesize that by proportionally

reflecting lung parenchyma impairment, the quantity of opacities relative to the total lung volume may be used to predict the need for more intensive medical care and survival. We therefore conducted a study relating the percentage of lung involvement by consolidations at the initial CT to the subsequent risk of adverse clinical outcomes.

2. Materials and methods

2.1. Study population

We screened all consecutive chest CT scans performed between February 1st, 2020, and April 17th, 2020, at two campuses of Michigan State University (Ascension Providence Southfield and Novi, MI, US). Cases with symptoms of viral pneumonia and confirmed by reverse transcription polymerase chain reaction (RT-PCR) for SARS-CoV-2 from nasopharynx swabs were retrospectively selected. Patients who had their first CTs performed after intensive care unit (ICU) admission or intubation (n = 21) were excluded. Finally, four patients transferred to other institutions were excluded (**eFig. 1 in the Supplementary Appendix**). The present study was approved by the Ascension Providence Hospital Institutional Review Board (IRB number 1596627-1). Only retrospective deidentified information was used, and informed consent was waived.

2.2. CT Protocol and volumetric data

Nonenhanced chest CT scans from the lung apex to the bilateral costophrenic angles were performed in the feet-first and supine positions, using a 64-slice scanner (GE LightSpeed Volume CT, General Electric Healthcare, Chicago, Illinois, US). The breathing-hold technique was used. The acquisition was executed with 120 kV (tube voltage) and ~750 mA (Smart mA; tube current), and the image data sets were reconstructed with 1.25-mm slice thickness. There were no specific institutional recommendations regarding the indication for chest CT.

After the case selection stage, the images of the initial CT were transferred from the radiology picture archiving and communication system (PACS) to the radiotherapy treatment planning software (Eclipse Treatment Planning System - Version 15.6; Varian Medical Systems, Palo Alto, CA, US). We choose radiation oncology software due to the enhanced structure delineation capability in three planes (axial, coronal and sagittal), real-time tridimensional reconstruction, and the precision of the volumetric measurement tools. The structure contours (consolidations and lungs) for all cases were performed independently by two radiation oncologists with 5 years and 10 years of experience and familiarity with the contour interface who were blinded to the clinical endpoints. Discordances on final contours were resolved by consensus. The consolidations were analyzed and contoured using the lung window (-1000 to 0 Hounsfield units). Cases with massive peripheral opacities required alternating to the soft tissue window (-125 to 225 Hounsfield units) for better delineation of the lung-chest wall interface. Areas of emphysema and pleural effusion were not included in the normal lung and consolidation contours, respectively. The relative consolidation volume was calculated by dividing the volume of the lung consolidations measured in cubic centimeters by the total bilateral lung volume measured in cubic centimeters (**eTable 1 in the Supplementary Appendix**).

2.3. Statistical Analysis

The primary endpoint was the in-hospital mortality rate. The secondary composite endpoint was major adverse hospitalization events, defined as admission to the ICU, use of mechanical ventilation or in-hospital death. Patients with do-not-resuscitate and do-not-intubate status (DNR/DNI) at admission were included in the primary analysis but excluded from the composite

outcome analysis. The study period encompassed the first two months of the pandemic in the state of Michigan (US). At that time, the institutional treatment protocol indicated that azithromycin, hydroxychloroquine, systemic corticoids, vitamin C and vitamin D would be offered to all patients admitted if there were no specific contraindications. Since therapy was uniform, treatments were not included as independent variables. Additional details on the patient's treatment are provided in **eTable 2 in the Supplementary Appendix**.

Qualitative variables are presented as absolute and relative frequencies. Quantitative variables are presented as medians and interquartile ranges (IQRs). The previous coexisting diseases analyzed were hypertension, diabetes mellitus, dyslipidemia, chronic obstructive pulmonary disease, asthma/bronchitis, obstructive sleep apnea, coronary artery disease, stroke/transient ischemic attack, chronic kidney disease, cancer, acquired immunodeficiency syndrome, hepatitis B/C, and tuberculosis.

Initially, the possible association between the independent and dependent (outcomes) variables was quantified using the odds ratio estimated by a simple logistic regression model (Table 1 and **eTable 3 in the Supplementary Appendix**). To limit the number of variables in the multivariate model, only the variables with P-values < 0.1 in the simple logistic regression model were selected for the initial multivariate model. The final model was obtained using the backward stepwise method (likelihood ratio). Variables were removed from the model if they were not significant and did not act as confounders (change in β coefficient >20 %). The assumption of linearity was assessed for all continuous variables. No imputation method was used for missing data. The assessment of model significance and performance was performed by means of the Hosmer-Lemeshow goodness-of-fit test, receiver operating characteristics (ROC) curve and c-statistic, which represents the area under the ROC curve (AUC) (e**Fig. 2AB in the Supplementary Appendix**). Continuous variables could be categorized to achieve the model with the best replication potential based on Nagelkerke's R-squared and Hosmer-Lemeshow test. The factors associated with the outcomes at the respective final models were represented in a Cartesian coordinate system with percentage of lung consolidations (X axis) and probability of the outcome (Y axis). The significance level of the tests was fixed at 0.05 (two-sided). All analyses were performed using the MASS, ResourceSelection and pROC packages implemented in R software version 3.5 (R Foundation for Statistical Computing, Vienna, Austria).

Table 1. Characteristics of the Patients in the Study at the Time of the Chest Computed Tomography and Association between the Characteristics and the Subsequent Event of In-Hospital Death. IQR: interquartile range. DNR/DNI: do-not-resuscitate and do-not-intubate status.

Characteristic	**All Patients (N = 154)**	**Discharged Alive (N = 129)**	**Died During Hospitalization (N = 25)**	**Odds Ratio (95 % Confidence Interval)**	**P-Value**
Age - Median (IQR)	65.2 (53.6–74.2)	63.2 (51.1–70.0)	79.6 (76.1–82.6)	1.157 (1.091–1.226)	<0.001
Age - N (%)					
≤65	76 (49.4)	75 (58.1)	1 (4%)	Reference	

Characteristic	All Patients (N = 154)	Discharged Alive (N = 129)	Died During Hospitalization (N = 25)	Odds Ratio (95 % Confidence Interval)	P-Value
>65	78 (50.6)	54 (41.9)	24 (96.0)	33.33 (4.375–253.989)	0.001
Sex - N (%)					
Female	76 (49.4)	66 (51.2)	10 (40.0)	Reference	
Male	78 (50.6)	63 (48.8)	15 (60.0)	1.571 (0.657–3.756)	0.309
Body-mass index - Median (IQR) - kg/m²*	31.1 (26.9–35.7)	31.6 (27.1–37.5)	27.9 (25.7–31.8)	0.928 (0.869–0.992)	0.027
Smoking status - N (%)					
Never	96 (62.3)	89 (69.0)	7 (30.4)	Reference	
Former or current	56 (36.4)	40 (31.0)	16 (69.6)	5.086 (1.941–13.327)	0.001
Unknown	2 (1.3)				
Number of previous coexisting disease - Median (IQR)¶	3.0 (1.0–4.0)	2.0 (1.0–4.0)	4.0 (3.0–5.0)	1.402 (1.096–1.792)	0.007
Symptoms - N (%)					
Fever					
No	72 (46.8)	59 (45.7)	13 (52.0)	Reference	
Yes	82 (53.2)	70 (54.3)	12 (48.0)	0.778 (0.330–1.834)	0.566

Characteristic	All Patients (N = 154)	Discharged Alive (N = 129)	Died During Hospitalization (N = 25)	Odds Ratio (95 % Confidence Interval)	P-Value
Shortness of breath					
No	32 (20.8)	22 (17.1)	10 (40.0)	Reference	
Yes	122 (79.2)	107 (82.9)	15 (60.0)	0.308 (0.123−0.776)	0.012
Altered mental status					
No	137 (89.0)	117 (90.7)	20 (80.0)	Reference	
Yes	17 (11.0)	12 (9.3)	5 (20.0)	2.437 (0.775−7.667)	0.128
DNR/DNI at admission - N (%)					
No	137 (89.0)	124 (96.1)	13 (52.0)	Reference	
Yes	17 (11.0)	5 (3.9)	12 (48.0)	22.892 (6.968−75.211)	<0.001
Pleural effusion - N (%)					
No	148 (96.1)	124 (96.1)	24 (96.0)	Reference	
Yes	6 (3.9)	5 (3.9)	1 (4.0)	1.033 (0.116−9.243)	0.977
Involved lobes - N (%)					
<5	23 (14.9)	22 (17.1)	1 (4.0)	Reference	

Characteristic	All Patients (N = 154)	Discharged Alive (N = 129)	Died During Hospitalization (N = 25)	Odds Ratio (95 % Confidence Interval)	P-Value
5	131 (85.1)	107 (82.9)	24 (96.0)	4.935 (0.634–38.421)	0.127
Total bilateral lung volume - Median (IQR) - cm^3	3034.0 (2491.0–3581.0)	3005.1 (2517–3551)	3215.2 (2083.2–4020.4)	–	–
Absolute normal lung volume - Median (IQR) - cm^3	2081.2 (1323.8–2931.7)	2152.8 (1357.9–2983.7)	1700.5 (1093.1–2584.2)	–	–
Median relative normal lung volume (IQR) - %§	71.2 (49.3–90.9)	72.27 (52.07–92.47)	57.08(40.37–82.11)	–	–
Absolute consolidations volume - Median (IQR) - cm^3	787.5 (304.7–1464.2)	743.8 (267.9–1366.4)	1269.1 (508.2–1878.7)	–	–
Relative consolidations volume - Median (IQR) - %†	28.8 (9.5–50.3)	27.7 (7.6–49)	42.9 (17.9–59.7)	1.017 (1.001–1.034)	0.043

*

The body-mass index = weight in kilograms divided by the square of the height in meters.

¶

From a 13-point scale which includes active or history of: hypertension, diabetes mellitus, dyslipidemia, chronic obstructive pulmonary disease, asthma/bronchitis, obstructive sleep apnea, coronary artery disease, stroke/transient ischemic attack, chronic kidney disease, cancer, acquired immunodeficiency syndrome, hepatitis B/C, and tuberculosis.

§

Median relative normal lung volume = volume of normal lung in cubic centimeters divided by the total bilateral lung volume in cubic centimeters.

†

Median relative lung consolidations volume = volume of the lung consolidations in cubic centimeters divided by the total bilateral lung volume in cubic centimeters.

3. Results

3.1. Characteristics of the patients

One hundred fifty-four patients with laboratory-confirmed diagnoses of SARS-CoV-2 infection who underwent chest CT met the study inclusion criteria. The male-to-female ratio was 1:1. The median age of the patients was 65 years (interquartile range, 53–74), and the median body mass index was 31.1 kg/m^2 (interquartile range, 26.9–35.7). One-third of the patients had a history of smoking or were currently smoking. The median number of comorbidities was 3 (interquartile range, 1–4). Seventeen patients (11.0 %) had DNR/DNI status at admission. Other patient characteristics are presented in the Table 1 and **eTable 2 in the Supplementary Appendix**.

Chest CT scans were obtained within 2 days from admission in 128 (83 %) of the cases. In 26 cases, the exam was performed between 2 days and 1 week (16.8 %) after admission, and in 1 case, the exam was performed on hospitalization day 10. Regarding radiological findings, 85.1 % of the patients had involvement of all five lung lobes, and only six cases (3.9 %) presented with pleural effusion. The median total bilateral lung volume was 3034.0 cubic centimeters (interquartile range, 2491.0–3581.0), and the median absolute consolidation volume was 787.5 cubic centimeters (interquartile range, 304.7–1464.2). The median percentage of consolidations relative to the total lung volume was 28.8 % (interquartile range 9.5–50.3).

3.2. Clinical Outcomes

At the time of analysis, all patients completed the hospitalization and were discharged after recovery of SARS-CoV-2 pneumonia or death. The last patient event (death) occurred 47 days after his initial CT sim, on May 30th, 2020.

Overall, the median hospitalization length from admission was 9 days (interquartile range, 5–14). During the hospital stay, forty-five (32.8 %) required treatment at the ICU, and thirty-six (26.3 %) were intubated to receive mechanical ventilation. The median ICU length was 9 days (interquartile range, 5.5–15.5). Twenty-five patients died, resulting in an overall in-hospital mortality rate of 16.2 %. The in-hospital mortality rate was 28.9 % for the patients admitted to the ICU and 36.1 % if mechanical ventilation was used (Table 2).

Table 2. Clinical Outcomes. CT: computed tomography. IQR: interquartile range. ICU: intensive care unit. DNR/DNI: do-not-resuscitate and do-not-intubate status.

Outcomes	**Values**
Admission to discharge (all) - median (IQR) - days	9.0 (5–14)
Admission to discharge (survivors) - median (IQR) - days	8 (5–14)
Admission to CT - median (IQR) - days	0.0 (0–1)
CT to discharge (all) - median (IQR) - days	8.0 (5–14)

Outcomes	Values
CT to discharge (survivors) - median (IQR) - days	7 (4.5–14)
ICU admission	
no. / no. total (%)	45/137 (32.8)
Median length of stay (IQR) - days	9 (5.5–15.5)
Use of mechanical ventilation (intubation)	
no. / no. total (%)	36/137 (26.3)
no. / no. admitted to ICU (%)	36/45 (80.0)
Median length (IQR) - days	8.5 (4.25–15)
Successful extubation - no. / no. total (%)	23/36 (63.9)
Died in hospital[†]	
Overall - no. / no. total (%)	25/154 (16.2)
Non-ICU patients (excluding DNR/DNI) - no. / no. total (%)	0/92 (0.0)
Non-ICU patients (including DNR/DNI) - no. / no. total (%)	12/109 (11.0)
ICU patients - no. / no. total (%)	13/45 (28.9)
Intubated patients - no. / no. total (%)	13/36 (36.1)
Major adverse hospitalization event[*], [‡]	
no. / no. total (%)	45/137 (32.8)

*

Major adverse hospitalization event (secondary composite end point) included admission to intensive care unit, intubation for mechanical ventilation, or death.

†

primary outcome.

‡

secondary outcome.

3.3. Factors associated with outcomes

The median relative consolidation volumes were 42.9 % for the patients who died and 27.7 % for the patients who survived (OR 1.017 [1.001−1.034]; P = 0.043) (Table 1). In the final multivariate logistic regression model, patients with greater lung involvement (P = 0.007), who were older than 65 years (P = 0.013), who had a smoking history (P = 0.008), or were DNR/DNI status (P < 0.001) had a greater chance of in-hospital death (Table 3). Each unit of percent increase in lung consolidation increased the chance of in-hospital death by 3.6 % (OR 1.036; 95 % confidence interval, 1.010–1.063; P = 0.007). Fig. 1 presents the probability of in-hospital death for four subgroups of full-code patients (older than 65 years of age with and without a smoking history, and younger than 65 years of age with and without a smoking history).

Table 3. Final Multivariate Logistic Regression Models for Primary and Secondary Outcomes. DNR/DNI: do-not-resuscitate and do-not-intubate status.

Death during hospitalization					
Variable	**Category**	**Coefficient**	**SE**	**Odds Ratio (95 % Confidence Interval)**	**P-value**
Age	≤65			Reference	
Empty Cell	>65	2.706	1.085	14.965 (1.785−125.466)	0.013
Smoking status	Never			Reference	
Empty Cell	Former or current	1.699	0.641	5.470 (1.558−19.204)	0.008
DNR/DNI at admission	No			Reference	
Empty Cell	Yes	2.991	0.843	19.907 (3.817−103.830)	<0.001
Relative lung involvement (%)*	Continuous	0.035	0.013	1.036 (1.010−1.063)	0.007
Intercept		−6.526	1.340		0.001
Major adverse hospital events					
Variable	**Category**	**Coefficient**	**SE**	**Odds Ratio (95 % Confidence Interval)**	**P-value**
Age	Continuous	0.033	0.015	1.033 (1.003−1.065)	0.032

Major adverse hospital events					
Variable	**Category**	**Coefficient**	**SE**	**Odds Ratio (95 % Confidence Interval)**	**P-value**
Sex	Female			Reference	
Empty Cell	Male	0.898	0.404	2.455 (1.112−5.419)	0.026
Relative lung involvement (%)*	Continuous	0.025	0.008	1.025 (1.009−1.042)	0.002
Intercept		−4.164	1.118		<0.001

*

Relative lung consolidations volume = volume of the lung consolidations in cubic centimeters divided by the total bilateral lung volume in cubic centimeters.

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Fig. 1. Probability of in-hospital death per unit of percent lung involvement.

Probability of in-hospital death (Y axis) per unit percent lung consolidations (X axis) for full code patients: older than 65 years of age and who were former or current smoker (solid red line); older than 65 years of age and no smoking history (dashed red line); 65 years of age or less and former/current smoker (solid black line); and 65 years of age or less and no smoking history (dashed black line). Primary outcome: Nagelkerke's R^2: 0.524. Hosmer-Lemeshow test: $\chi^2 = 9.213$; df = 8; P = 0.325.

The quantity of lung consolidations relative to the lung volume was also independently associated with major adverse hospitalization events (P = 0.002), with an increase of 2.5 % (OR 1.025; 95 % confidence interval, 1.009–1.042; P = 0.002) in the chance per additional unit of percent lung involvement (Table 3). Other factors associated with an increased risk of major adverse hospital events were advanced age (P = 0.032) and male sex (P = 0.026).

Fig. 2 provides axial images at the level of the carina and the respective tridimensional reconstruction of chest CTs of four cases with different percentages of lung involvement (A/a: 9.2 %; B/b: 29.7 %; C/c: 55.5 %; D/d: 83.1 %). Patients A/a and B/b had no major adverse hospitalization events and were discharged alive. Patient C/c survived after requiring ICU admission (7 days) and mechanical ventilation. Patient D/d did not survive after 47 days at the hospital, 32 days at the ICU, with mechanical ventilation support.

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Fig. 2. Axial Chest CT Images (A-D) and Respective Tridimensional Reconstruction (a-d) of Four Patients with SARS-CoV-2.

Case A/a: 9.2 % lung involvement. 82 years-old female, full-code, former smoker. Estimated Probability of in-hospital death: 14.3 %. Estimated probability of major adverse hospital events: 22.3 %. Discharged after 3 days alive.

Case B/b: 29.7 % lung involvement. 73 years-old male, full-code, former smoker. Estimated Probability of in-hospital death: 25.6 %. Estimated probability of major adverse hospital events: 46.8 %. Discharged after 9 days alive.

Case C/c: 55.5 % lung involvement. 62.5 years-old female, full code, former smoker. Estimated Probability of in-hospital death: 5.4 %. Estimated probability of major adverse hospital events: 32.6 %. Discharged alive after 20 days alive (7 days in the ICU, 1 day of mechanical ventilation).

Case D/d: 83.1 % lung involvement. 79 years-old male, full-code, never smoker. Estimated Probability of in-hospital death: 29.5 %. Estimated probability of major adverse hospital events: 80.2 %. In-hospital death after 47 days (32 days in the ICU, 31 days of mechanical ventilation).

4. Discussion

Since the initial case in January 2020 [14], more than 18 million individuals have been diagnosed with Covid-19 in the United States [15]. There have been over three hundred thirty thousand deaths, and a higher number of individuals have developed severe disease, requiring escalated medical care involving hospitalization, admission to the ICU, and the use of mechanical ventilation. During the peak phase of the pandemic in the state of Michigan (March-April 2020) [15], medical resources were used towards the maximum, raising the problem of resource allocation in situations of mass critical care demand [[16], [17], [18]]. In this scenario, tools to predict outcomes would be important to better triage patients who require more intensive support. On the other hand, patients who had a limited risk of developing major adverse events could be managed in a lower complexity facility or from home.

The present study indicated a quantitative increase in mortality and major adverse hospital events with more lung consolidations detected by CT in the setting of SARS-CoV-2 pneumonia. Each unit of percentage increase in lung involvement with consolidations increased the chance of in-hospital mortality by 3.6 % and the chance of major adverse hospital events by 2.5 %. Important information to better predict prognosis and guide clinical management can be derived from our findings. For example, a patient who is more than 65 years of age and has a history of smoking has a 15 % risk of dying during hospitalization if 10 % of the lung is involved at the initial assessment. That risk would escalate to 50 % for a similar patient with 60 % of lung involvement.

The clinical outcomes observed in our cohort were in line with experiences from other geographical areas. Eighty percent (36/45) of the cases admitted to the ICU in our series required mechanical ventilation, similar to the experiences from Seattle (US; 75 %, 18/24) [1], Lombardy (Italy; 88 %, 1150/1300) [19], and Wuhan (China; 64 %, 32/50) [20]. The ICU mortality in the present study (28.6 %,13/45) was also at the level found in the Italian data (26 %, 405/1581) [19] but lower than Seattle's experience (50 %, 12/24) [1]. The increased ICU mortality described in Seattle's case series could be related to more severe presentations, including patients with a higher percentage of lungs with opacities and late-stage disease (quantitative data were not provided by the authors). In addition, Seattle's surge occurred before the peak in Michigan's cases, which could explain differences in

management, including the use of systemic corticoid (none versus 97.8 % on the ICU patients in our series) [21,22].

Of note, patients with do-not-resuscitate and do-not-intubate status at admission had twenty times higher chance of in-hospital mortality. It is unclear whether proceeding with mechanical ventilation or resuscitation maneuvers in those patients with low functional reserve would provide greater survival probability. In relation to cardiopulmonary resuscitation (CPR), previous experiences showed that less than 5 % of Covid-19 patients survived CPR after a cardiac arrest event [23,24]. Regarding mechanical ventilation, in the present study, two-thirds of the non-DNR/DNI (full-code) patients who required intubation recovered from respiratory insufficiency and were able to obtain a successful extubation.

Pleural effusions occurred in only 4% of the patients and were not associated to either endpoint. Other groups also reported a low incidence of pleural effusions [2,3], which could be related to exacerbation of other comorbidities instead of SARS-CoV-2 pneumonia. The other radiologic parameters, including absolute quantity of consolidations and the volume of nonaffected lung, were not used concomitantly as independent variables in the models due to their intrinsic relation with the percentage of lung involvement. Notwithstanding, a group from Piacenza (Italy) [25] indicated that cases with less well-aerated lung parenchyma on admission chest CT (< 73 % vs. > / = 73 %), per visual and software assessments, were associated with increased ICU use or death.

Our study limitations include the effect of changes in the total lung volume during respiratory cycle, which could interfere with the denominator of the percent lung involvement calculation. This source of uncertainty was partially controlled by instructing the patient to hold his or her breath during the CT scan acquisition, which also reduced the artifacts in the area of the lung-diaphragm interface. Further maneuvers such as sustained maximum inspiration would not be possible for dyspneic patients. In addition, alternative models incorporating the absolute consolidation volume as the independent variable confirmed our results (data not shown). Importantly, the model for in-hospital mortality was more accurate in predicting the death event when compared with the model for major adverse hospitalization events (**e**Fig S**2AB**), and both would benefit from external validation to minimize over-fitting bias. Another important limitation is the complexity of the infiltrate contour, which requires trained physicians and significant dedicated time. To illustrate this, videos of the contoured chest CTs of two cases are available online (**Video 1** and **Video 2**). The first presented with 0.2 % relative lung involvement that was contoured in less than ten minutes, and the second presented with 44.9 % relative lung involvement that required three hours to be completed. Further studies creating and validating artificial intelligence systems using neural network algorithms [[26], [27], [28], [29]] could facilitate large scale quantification of percentage lung parenchyma compromised.

5. Conclusions

There is a quantitative relationship between lung involvement with Covid-19 consolidations and clinical outcomes. Per unit percent of lung involved, there was a 3.6 % increase in the chance of in-hospital mortality and a 2.5 % increase in major adverse hospital events. Therefore, this study provides evidence that chest CT is an potential tool in guiding escalation or de-escalation of care in the hospital setting.

Ethical statement

The work described has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans.

The present study was approved by the Ascension Providence Hospital Institutional Review Board (IRB number 1596627−1). Only retrospective deidentified information was used, and informed consent was waived.

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Summary statement

The percentage of lung involvement by consolidations at the initial CT is related to the subsequent risk of in-hospital death, independently of other clinical parameters.

CRediT authorship contribution statement

Lucas G. Sapienza: Conceptualization, Methodology, Data curation, Formal analysis, Writing - original draft, Supervision, Project administration. **Karim Nasra:** Conceptualization, Methodology, Data curation, Writing - review & editing. **Vinícius F. Calsavara:** Conceptualization, Methodology, Formal analysis, Writing - original draft. **Tania B. Little:** Conceptualization, Writing - review & editing. **Vrinda Narayana:** Data curation, Software, Writing - review & editing. **Eyad Abu-Isa:** Conceptualization, Methodology, Data curation, Writing - original draft, Supervision.

Abstract

Objectives

To investigate the value of spectral-detector computed tomography (SDCT) parameters for the quantitative differentiation between atelectasis and pneumonia on contrast-enhanced chest CT.

Material and methods

Sixty-three patients, 22 clinically diagnosed with pneumonia and 41 with atelectasis, underwent contrast-enhanced SDCT scans during the venous phase. CT numbers (Hounsfield Units [HU]) were measured on conventional reconstructions (CON_{120kVp}) and the iodine concentration (C_{iodine}, [mg/ml]), and effective atomic number (Z_{eff}) on spectral reconstructions, using region-of-interest (ROI) analysis. Receiver operating characteristics (ROC) and contrast-to-noise ratios (CNRs) were calculated to assess each reconstruction's potential to differentiate between atelectasis and pneumonia.

Results

On contrast-enhanced SDCT, the difference between atelectasis and pneumonia was significant on CON_{120kVp}, C_{iodine}, and Z_{eff} images ($p < 0.001$). On CON_{120kVp} images, a threshold of 81 HU achieved a sensitivity of 93 % and a specificity of 95 % for identifying pneumonia, while C_{iodine} and Z_{eff} images reached the same sensitivity but lower specificities of 85 % and 83 %. CON_{120kVp} images showed significantly higher CNRs between normal lung and atelectasis or pneumonia with 30.63 and 27.69 compared to C_{iodine} images with 3.54 and 1.27 and Z_{eff} images with 4.22 and 7.63 ($p < 0.001$). None of the parameters could differentiate atelectasis and pneumonia without contrast media.

Conclusions

Contrast-enhanced SDCT can differentiate atelectasis and pneumonia based on the spectral parameters C_{iodine}, and $Z_{eff.}$ However, they had no added value compared to CT number measurement

on CON_{120kVp} images. Furthermore, contrast media is still needed for a differentiation based on quantitative SDCT parameters.

1. Introduction

Pulmonary infections are responsible for significant morbidity and mortality worldwide, and clinical symptoms, laboratory tests, and imaging methods are used for diagnosis and therapy control [1, 2]. The ideal reference diagnosis for pneumonia is the detection of pathogenic agents in the lung parenchyma. However, invasive techniques like bronchoalveolar lavage or lung biopsy cannot be routinely performed for practical reasons.

Computed tomography (CT) can provide a regional and morphological description of lung pathologies and should be considered in patients with an unclear clinical condition or inadequate response to pneumonia therapy [2, 3]. Imaging signs of thoracic infection can be useful, sometimes suggesting a specific diagnosis and often narrowing the differential diagnosis. The consolidated lung is a common imaging sign of pulmonary infection, but it can also reflect atelectasis, a non-infectious lung pathology [4]. Radiological features like volume loss or a positive air bronchogram can help to differentiate pneumonia from atelectasis, but they remain qualitative, non-obligatory observations [4, 5]. In some clinical situations, the diagnosis of pneumonia is not unambiguous, and quantitative CT parameters would be desirable to facilitate a more confident diagnosis. The Hounsfield unit (HU), a relative quantitative measurement of x-ray density, is the most frequently used quantitative CT parameter, but unfortunately, the differences between atelectasis and pneumonia are usually not significant enough to allow a confident diagnosis on non-enhanced images. Here, contrast media administration can help since atelectasis shows a stronger contrast-enhancement than pneumonia [6]. In this context, Edwards *et al.* reported a threshold of 85 HU to diagnose pneumonia which reached a high 97 % sensitivity and 85 % specificity on contrast-enhanced CT pulmonary angiograms [6].

Spectral-detector computed tomography (SDCT) uses an X-ray tube and two different detector layers to selectively absorb different energies from the polychromatic X-ray spectrum [7, 8]. This technical approach allows for the simultaneous measurement of low and high-energy photons at the same spatial and angular location, facilitating dual-energy post-processing in the projection domain, different from other dual-energy techniques [9, 10, 11, 12]. The obtained spectral data set enables the retrospective analysis of the pixel-wise iodine concentration (C_{iodine}) and the calculation of the effective atomic number (Z_{eff}), reflecting the blood supply and the effective atomic number of inorganic materials. In the literature, SDCT parameters were already used to differentiate lung cancer from inflammatory masses and showed benefits when detecting pulmonary embolism and assessing pleural contrast uptake [13, 14, 15]. Due to the significantly different blood supply of atelectasis and pneumonia, we hypothesized that C_{iodine} and Z_{eff} images might have advantages over conventional images since they may offer additional information regarding perfusion properties. Therefore, we conducted this study to investigate if SDCT parameters C_{iodine} and Z_{eff} are beneficial compared to CT number quantification on conventional images for distinguishing atelectasis from pneumonia on contrast-enhanced chest CT.

2. Materials and methods

2.1. Patient cohort

This retrospective study was approved by the institutional ethics committee (S-781/2018), and informed consent for data processing was waived. Database research encompassing the years 08/2017 - 06/2020 identified 3167 patients who underwent venous phase contrast-enhanced or non-

enhanced chest SDCT. CT acquisitions were serially evaluated for inclusion and exclusion criteria. The inclusion criteria were (1) radiologic feature of the consolidated lung, (2) consolidated lung >1 cm^2 in size on four continuous slices, (3) age >18, and (4) absence of motion artifacts. The exclusion criteria were (1) tumor (>1 cm^2), (2) radiologic features of atypical pneumonia, (3) metastatic lung disease, or (4) previous lung surgery.

CT acquisitions were classified as atelectasis or pneumonia based on the presence of a non-radiologic clinical scoring system adapted from Edwards et al. [6]. Clinical criteria were (1) hypoxia, tachypnea, grunting, chest in drawing and/or crackles on auscultation, (2) blood testing (C-reactive protein (CRP) > 5 mg/l or white blood cell count (WBC) >4–10/ml), (3) antibiotic treatment (Abx.) for pneumonia (aminopenicillin and/or after admission in the hospital with a second- or third-generation cephalosporin) or (4) documentation of pneumonia as a discharge diagnosis or clinical suspicion of pneumonia as an indication for chest CT. One point was given for the presence of each criterion. Each case was classified as atelectasis if one or less, and as pneumonia if three or more criteria were met. If two criteria were met, patients with an apparent non-pulmonary infection were also classified as atelectasis, and patients with cough and no other apparent non-pulmonary infections were classified as pneumonia (Figure 1).

Figure 1. Flowchart for patient recruitment. Database research encompassing the years 2017–2020 identified 3167 patients who underwent chest CT. Two hundred twenty-six patients had consolidated lung >1 cm^2 in size on four continuous slices as an imaging feature. Out of these, 123 patients were excluded due to motion artifacts, tumor >1 cm^2, radiologic features of atypical pneumonia, metastatic lung disease, or previous lung surgery. The remaining 103 patients were split up in contrast-enhanced and non-contrast CT. Finally, the patients were classified as atelectasis or pneumonia based on clinical criteria.

2.2. CT acquisition

All SDCT examinations were performed using a 128-slice dual-layer CT system (IQon; Philips GmbH, Hamburg, Germany). All patients were acquired in supine position during an inspirational breath-hold in the craniocaudal direction. The following acquisition parameters were used: collimation 2 × 64 × 0.625 mm; rotation time 0.33–0.75 s; pitch 0.798–1.014; tube current 120 kVp, dose modulation type: DoseRight 3D-DOM with an Dose Right Index (DRI) of 17 (Philips GmbH, Hamburg, Germany). All images were reconstructed in axial orientation using an image matrix of 512 × 512 with a slice thickness of 1-1,5 mm and an increment of 0.75–3 mm using a dedicated spectral reconstruction algorithm (Spectral, Philips GmbH, Hamburg, Germany) and a fixed kernel (B; Philips GmbH, Hamburg, Germany). Conventional 120 kVp (CON_{120kVp}), iodine concentration (C_{iodine}), and effective atomic number (Z_{eff}) images were reconstructed (Table 1).

Table 1. SDCT acquisition parameters.

Protocol	Collimation (mm)	Image matrix	Pitch	Gantry rotation time (s)	Acquisition time (s)	Tube current (kVp)	Tube current-time product (mAs)	Absolute Min (mAs)	Absolute Max (mAs)
Native chest	2 × 64×0.625	512 × 512	1.014	0.75	7.8	120	47	35	230

Protocol	Collimation (mm)	Image matrix	Pitch	Gantry rotation time (s)	Acquisition time (s)	Tube current (kVp)	Tube current-time product (mAs)	Absolute Min (mAs)	Absolute Max (mAs)
Venous chest	2 × 64×0.625	512 × 512	0.984	0.33	3.5	120	93	40	300
Venous body	2 × 64×0.625	512 × 512	0.798	0.5	9.6	120	74	65	300

In all patients who underwent contrast-enhanced CT, the contrast media (350 mg Iohexol/ml; AccupaqueTM 350; GE Healthcare GmbH, Solingen, Germany) was injected via an antecubital vein or a central venous catheter using a power injector. Venous phase imaging was triggered by bolus tracking at the level of the truncus pulmonalis with a threshold of 150 HU and a post-threshold-delay of 35 s. Single bolus contrast-injection was performed for venous chest acquisitions administering 50 ml contrast media followed by a 60 ml saline solution chaser bolus at a 4 ml/s flow rate. Venous body acquisitions used a biphasic contrast-injection protocol consisting of two contrast boli, the first with 50 and the second with 40 ml contrast agent, both followed by a saline solution chaser bolus of 15 and 30 ml, respectively. The interval between both boluses was 30 s, and the flow rate was 3 ml/s. All protocols were slightly adjusted to the patients' body weight.

2.3. Image analysis

Two readers with two and seven years of experience in thoracic imaging analyzed the images, using a picture archiving and communication system (PACS) workstation (Centricity, Version 7.0; General Electrics, New York, USA) and a dedicated post-processing software provided by the SDCT manufacturer (IntelliSpace Portal 10; Philips GmbH, Hamburg, Germany). Images were read in a non-randomized fashion, and the regions of interest (ROIs) were placed in consensus. On conventional images, two standardized oval ROIs of 1 cm^2 and one maximum-sized ROI were placed each in the consolidated lung (pneumonia or atelectasis), the normal lung, and pleural effusion (PE), excluding bronchi and third-order or larger pulmonary vessels. Normal lung regions were chosen by absence of consolidation or ground glass attenuation at the hilum level and at least 1 cm away from the pleura. Singular vessel ROIs were placed in the ascending aorta (AA) and the right pulmonary artery (RPA) at the right proximal pulmonary artery level. ROIs placed on conventional images were automatically transferred to the corresponding position on the iodine concentration (C_{iodine}) and the effective atomic number (Z_{eff}) images. For each ROI, absolute attenuation values in Hounsfield units (HU), iodine concentration (mg/ml) and effective atomic number as well as respective standard deviations (SD) were recorded. Measurements of two ROIs were averaged. According to the definition of van Engen *et al.*, the contrast-to-noise ratio (CNR) between two tissues (1 and 2) was defined as $CNR=|S1-S2|/0.5(\sigma 12+\sigma 22)$ with S being the averaged HU on CON_{120kVp}, iodine concentration (C_{iodine}) or effective atomic number (Z_{eff}) in two homogeneous ROI, and σ being the standard deviation in the same ROIs [16].

2.4. Statistical analysis

All data were recorded in a dedicated spreadsheet (Excel, Microsoft Corp., Redmond, USA), and analyses were performed with SigmaPlot (Systat Software GmbH, Erkrath, Germany) and SPSS (IBM

SPSS Statistics 25, New York; USA). All data are given as mean ± standard deviation (SD). Quantitative imaging parameters results were tested for significant differences with the Mann-Whitney Rank Sum Test for non-paired measurements. An additional analysis using the Bonferroni-Holm method for multiple testing was performed, which did not change the number of significant results. Receiver operating characteristic (ROC) analysis was used to evaluate the performance of conventional (CON_{120kVp}), iodine concentration (C_{iodine}), and effective atomic number (Z_{eff}) images in discriminating between pneumonia and atelectasis. The overall performance was summarized using the area under the curve (AUC). Thresholds were chosen by maximizing the Youden index (J = sensitivity + specificity −1), which treats sensitivity and specificity as equally important and is not weighted by the pre-test probability [17]. Statistical significance was defined as $p \leq 0.05$. CNRs of all three quantitative parameters were compared using one-way analysis of variances (ANOVA) for repeated measures, and post-hoc tests with Bonferroni's correction or Dunn's method as appropriate in case of multiple comparisons. In addition, for each data set a feature vector was composed out of the HU, C_{iodine} and Z_{eff} values of the pneumonia, aorta and atelectasis region. Subsequently, principle component analysis (PCA) implemented in the freely available analysis software PAleontological STatistics (PAST) was performed in a 9 dimensional feature space separately for the data sets with and without contrast enhancement [18, 19].

3. Results

3.1. Patient cohort

In total, 103 patients aged 62.2 ± 16.6 years (range: 19–88 years) could be recruited. Sixty-three patients, 22 clinically diagnosed with pneumonia and 41 with atelectasis, underwent contrast-enhanced SDCT, and 40 patients, 21 clinically diagnosed with pneumonia, and 19 with atelectasis, underwent non-enhanced chest SDCT. There were no significant differences in age (p = 0.574, p = 0.818) or BMI (p = 0.833; p = 0.483), when comparing both groups (Table 2). In both atelectasis groups, 55 % of cases had less than two clinical criteria, which allowed an exact classification. 42 % of cases fulfilled two clinical criteria, but since all of them had an apparent non-pulmonary infection, they were also classified as atelectasis. In both pneumonia groups, 70 % of cases had more than two clinical criteria and were therefore classified as pneumonia. 30 % of cases fulfilled only two clinical criteria, but most of them had a cough, and no other apparent non-pulmonary infection was found; therefore, they were classified as pneumonia (Table 2).

Table 2. Patient demographics and diagnostic criteria for patients with contrast-enhanced and non-enhanced chest CT.

Patient demographics	**Contrast-enhanced**			**Non-enhanced**		
	Atelectasis	**Pneumonia**	**p**	**Atelectasis**	**Pneumonia**	**p**
N	41	22	-	19	21	-
Sex (m/f)	20/21	12/10	-	9/10	13/8	-
Age (y)	64.4 ± 15.1	66.8 ± 14.3	0.574	55.5 ± 20.2	59.3 ± 15.5	0.818

Patient demographics	Contrast-enhanced			Non-enhanced		
	Atelectasis	**Pneumonia**	**p**	**Atelectasis**	**Pneumonia**	**p**
BMI (kg/cm^2)	27.7 ± 5.4	28.9 ± 8.2	0.833	24.5 ± 4.3	28.4 ± 4.1	0.483
Diagnostic criteria						
Fever and/or cough	2 (5 %)	11 (50 %)	-	7 (37 %)	17 (81 %)	-
Leucocytosis and/or CRP	20 (49 %)	11 (50 %)	-	3 (16 %)	6 (29 %)	-
Abx. treatment	25 (61 %)	21 (95 %)	-	11 (58 %)	18 (86 %)	-
Clinical diagnosis of pneumonia	2 (5 %)	22 (100 %)	-	1 (5 %)	21 (100 %)	-
Nonpulmonary septic foci	27 (66 %)	4 (18 %)	-	13 (68 %)	3 (14 %)	-
Total no. criteria present						
0 of 4	12 (29 %)	0 (0 %)	-	7 (37 %)	0 (0 %)	-
1 of 4	11 (27 %)	0 (0 %)	-	3 (16 %)	0 (0 %)	-
2 of 4	18 (39 %)	9 (41 %)	-	9 (47 %)	4 (19 %)	-
3 of 4	0 (0 %)	5 (23 %)	-	0 (0 %)	11 (52 %)	-
4 of 4	0 (0 %)	8 (36 %)	-	0 (0 %)	6 (29 %)	-

Patient characteristics given as median and standard deviation. BMI = body mass index. Distribution of diagnostic criteria with the final clinical diagnosis of atelectasis or pneumonia. Abx indicates antibiotics.

3.2. Influence of ROI sizes and contrast-phase on quantitative CT parameters

Quantitative CT parameters were compared between standardized and maximum-sized ROI, and no significant differences were found in the atelectasis or the pneumonia group (p = 0.953, p = 0.683) (Table 3).

Table 3. Influence of ROI sizes on the quantitative CT parameters.

Empty Cell	**Atelectasis**			**Pneumonia**		
	standardized	**maximum-sized**	**p**	**standardized**	**maximum-sized**	**p**
Region of interest (mm^2)						
Normal lung	10 ± 0	46 ± 12	<0.001	10 ± 0	55.51 ± 16.03	<0.001
Consolidated lung	10 ± 0	19 ± 7	<0.001	10 ± 0	22.01 ± 8.80	<0.001
Pleural effusion	10 ± 0	32 ± 18	<0.001	10 ± 0	15.87 ± 8.74	<0.001
CT numbers measured on CON_{120kVp} (HU)						
Normal lung	-814 ± 57	-797 ± 47	0.055	-810 ± 65	-816.98 ± 52.30	0.953
Consolidated lung	105 ± 21	102 ± 21	0.683	60 ± 13	62.23 ± 13.34	0.869
Pleural effusion	9 ± 8	10 ± 11	0.514	6 ± 11	11.94 ± 14.11	0.536
Iodine concentration measured on C_{iodine} (mg/ml)						
Normal lung	0.71 ± 0.39	0.68 ± 0.20	0.468	0.67 ± 0.39	0.70 ± 0.23	0.230
Consolidated lung	2.65 ± 0.94	2.59 ± 0.92	0.809	1.28 ± 0.39	1.28 ± 0.50	0.824
Pleural effusion	0.06 ± 0.12	0.09 ± 0.17	0.705	0.09 ± 0.08	0.10 ± 0.12	0.569
Effective atomic number measured on Z_{eff}						
Normal lung	9.37 ± 0.57	9.52 ± 0.66	0.356	9.36 ± 0.65	9.42 ± 0.60	0.681
Consolidated lung	8.63 ± 0.39	8.62 ± 0.39	0.937	8.03 ± 0.20	8.03 ± 0.26	0.742
Pleural effusion	7.19 ± 0.17	7.22 ± 0.21	0.350	7.24 ± 0.16	7.26 ± 0.17	0.878

Standardized ROI ($2 \times 1mm^2$) were compared with ROIs of maximum size. Mean ± standard deviation for CT numbers on conventional (CON_{120kVp}) images as well as iodine concentration (C_{iodine}) and effective atomic number (Z_{eff}) on spectral images in the atelectasis and the pneumonia group. Pleural effusion was present in n = 13 patients in the atelectasis, and never in the pneumonia group.

In 63 patients contrast medium was applied intravenously and no significant differences between the atelectasis and pneumonia group were found for volume (ml), duration (sec) and flow rate (ml/s) (p = 0.667, p = 0.527, p = 0.088). ROIs were used to determine the average attenuation in the descending aorta (DA) and the right pulmonary artery (RPA), also showing no significant differences between both groups (p = 0.846, p = 0.941, p = 0.915) (Table 4).

Table 4. Contrast administration protocol and measurements in vessel ROIs on contrast-enhanced chest CT.

Empty Cell	**Atelectasis**	**Pneumonia**	**p**
Contrast administration protocol			
Volume (ml)	86.68 ± 19.19	80.95 ± 22.36	0.667
Duration (s)	28.04 ± 5.85	24.92 ± 5.70	0.527
Flow rate (ml/s)	3.10 ± 0.42	3.22 ± 0.43	0.088
CT numbers in vessel ROIs (HU)			
Descending aorta	193 ± 82	197 ± 83	0.846
Right pulmonary artery	179 ± 83	153 ± 21	0.941
Average of DA and RPA	187 ± 83	178 ± 68	0.915

Contrast media volume, application duration, and flow rate are given for the atelectasis and the pneumonia group. Contrast administration data was missing for 12 patients. The CT number values in Hounsfield units on conventional images are given for the descending aorta (DA) and the right pulmonary artery (RPA). Both measurements were also averaged.

3.3. Contrast media is needed for quantitative discrimination between atelectasis and pneumonia

On non-enhanced SDCT, no significant differences were found between the atelectasis and the pneumonia group, neither on CON_{120kVp} (p = 0.054) nor on Z_{eff} images (p = 0.563) (Figure 2 and Table 5). The AUCs for non-enhanced images were expectedly small, with the largest AUC 0.68 (0.50–0.86) achieved on CON_{120kVp} images with a sensitivity of 56 % and specificity of 52 %. Z_{eff} had an AUC of 0.57 (0.26–0.64) with a slightly higher sensitivity of 61 % and the same specificity.

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Figure 2. Boxplots for quantitative CT measurements. Values are given for the regions of interest on (A, D) conventional (CON_{120kVp}), (B) iodine concentration (C_{iodine}), and (C, F) effective atomic number (Z_{eff}) images for atelectasis and the pneumonia for all patients (N). The cut-off values were calculated using the Youden-Index.

Table 5. Quantitative parameters on non-enhanced chest SDCT.

Empty Cell	**Atelectasis**	**Pneumonia**	**p**
CT numbers measured on CON_{120kVp} (HU)			
Normal lung	-833 ± 58	-835 ± 56	0.789
Consolidated lung	37 ± 15	26 ± 10	0.054
Pleural effusion	1 ± 9	-	-
Effective atomic number measured on Z_{eff}			
Normal lung	7.91 ± 0.49	7.65 ± 0.44	0.076
Consolidated lung	7.24 ± 0.20	7.31 ± 0.12	0.563
Pleural effusion	7.10 ± 0.14	-	-

Mean ± standard deviation for ROIs on conventional (CON_{120kVp}) and effective atomic number (Z_{eff}) images are given for the atelectasis and the pneumonia group. Pleural effusion was present in n = 13 patients in the atelectasis, and never in the pneumonia group.

3.4. Quantitative parameters can discriminate atelectasis from pneumonia with contrast media

On contrast-enhanced SDCT, CT numbers of the consolidated lung were significantly higher in the atelectasis group than in the pneumonia group for CON_{120kVp}, ($p < 0.001$). Correspondingly, C_{iodine}, and Z_{eff} were also significantly higher in the atelectasis group ($p < 0.001$). We found no significant differences for normal lung or pleural effusion measurements between both groups (Figure 2, Figure 3, and Table 6).

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Figure 3. Conventional, iodine concentration, and effective atomic number images of contrast-enhanced chest CT in three different patients. (A, B, C) Bilateral pleura effusion within adjacent homogenous atelectasis (white arrow) in a 45-year-old woman. (D, E, F) Right-sided lobar pneumonia with a positive air bronchogram a 51-year-old woman. (G, H, I) Bilateral pleural effusion with adjacent atelectasis in a 45-year-old man. On the right side is a focal area with hypoperfusion within the atelectasis (white arrow), which is suspicious for a superinfection of the atelectasis. Quantitative CT parameters are shown for atelectasis (square) and pneumonia (circle).

Table 6. Quantitative parameters on contrast-enhanced chest SDCT.

Empty Cell	**Atelectasis**	**Pneumonia**	**p**
CT numbers measured on CON_{120kVp} (HU)			
Normal Lung	-814 ± 57	-810 ± 65	0.971
Consolidated lung	105 ± 21	60 ± 13	<0.001
Pleural effusion	9 ± 8	6 ± 11	0.723
Iodine concentration measured on C_{iodine} (mg/ml)			
Normal lung	0.71 ± 0.39	0.67 ± 0.39	0.498
Consolidated lung	2.65 ± 0.94	1.28 ± 0.39	<0.001
Pleural effusion	0.06 ± 0.12	0.09 ± 0.08	0.077
Effective atomic number measured on Z_{eff}			
Normal lung	9.37 ± 0.57	9.36 ± 0.65	0.943
Consolidated lung	8.63 ± 0.39	8.03 ± 0.20	<0.001
Pleural effusion	7.19 ± 0.17	7.24 ± 0.16	0.180

Mean ± standard deviation for ROIs on conventional (CON_{120kVp}), iodine concentration (C_{iodine}), and effective atomic number (Z_{eff}) images are given for the atelectasis and the pneumonia group. Pleural effusion was present in n = 29 patients in the atelectasis, and in n = 17 patients in the pneumonia group.

3.5. Best contrast-to-noise ratio was achieved on conventional images

On CON_{120kVp} images, significantly higher CNRs were achieved between normal lung and atelectasis or pneumonia compared to the C_{iodine} and Z_{eff} images ($p < 0.001$). On the Z_{eff} images, the highest CNRs were found between the aorta, pleural effusion, and atelectasis or pneumonia ($p < 0.001$) (Table 7).

Table 7. Contrast-to-noise ratios for consolidated lung.

Empty Cell	**CON_{120kVp}**	**C_{iodine}**	**Z_{eff}**	**p**
Atelectasis				
vs. aorta	4.32	6.91	24.83	<0.001
vs. normal lung	30.63	3.54	4.22	<0.001

Empty Cell	**CON_{120kVp}**	**C_{iodine}**	**Z_{eff}**	**p**
vs. pleural effusion	5.21	5.01	23.37	<0.001
Pneumonia				
vs. aorta	7.14	9.79	37.52	<0.001
vs. normal lung	27.69	1.27	7.63	<0.001
vs. pleural effusion	2.98	2.63	7.30	<0.001

Contrast-to-noise ratios between atelectasis or pneumonia and the aorta, normal lung and pleural effusion was calculated using conventional (CON_{120kVp}), iodine concentration (C_{iodine}), and effective atomic number (Z_{eff}) images.

3.6. All quantitative parameters showed comparable diagnostic properties

On contrast-enhanced SDCT, the AUC to differentiate atelectasis from pneumonia on CON_{120kVp} images was 0.98 (CI 0.94–0.99), whereas it was slightly lower for C_{iodine} and Z_{eff} images, with 0.94 (CI 0.87–0.99) and 0.93 (CI 0.87–0.99), respectively. On CON_{120kVp} images, a threshold of 81 HU achieved a sensitivity of 93 % and specificity of 95 % for identifying pneumonia. C_{iodine}, and Z_{eff} images reached comparable sensitivities of 95 % when using a threshold of 1.74 mg/ml and 8.27, but with somewhat lower specificities of 85 % and 83 %, respectively ($p < 0.001$) (Figure 4 and Table 8).

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Figure 4. The area under the curve for diagnosis of pneumonia for quantitative SDCT parameters. Sensitivity and specificity for pneumonia on contrast-enhanced (A) and non-enhanced (B) SDCT for conventional attenuation (CON_{120kVp}), iodine concentration (C_{iodine}), and effective atomic number (Z_{eff}) images.

Table 8. Sensitivity and specificity of quantitative SDCT parameters for discriminating atelectasis from pneumonia.

AUC (95% CI)	**Threshold**	**Sensitivity (%)**	**Specificity (%)**	**p**
CT numbers measured on CON_{120kVp} (HU)				
0.98 (0.94–0.99)	81	93	95	<0.001
Iodine concentration measured on C_{iodine} (mg/ml)				
0.94 (0.87–0.99)	1.74	85	95	<0.001

AUC (95% CI)	Threshold	Sensitivity (%)	Specificity (%)	p
Effective atomic number measured on Z_{eff}				
0.93 (0.87–0.99)	8.27	83	95	<0.001

Sensitivity and specificity as well as area under the curve (AUC) for detecting pneumonia on contrast-enhanced chest SDCT. Thresholds were chosen for conventional (CON_{120kVp}), iodine concentration (C_{iodine}), and effective atomic number (Z_{eff}) images by maximizing the Youden index.

3.7. Diagnosis can be based CT on number measurements

The principal component analysis (PCA) showed the highest variance on the CT number axis, whereas the other parameters only showed little variance, implying that the criterion CT number alone is enough to decide between atelectasis and pneumonia (Figure 5).

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Figure 5. The principal component analysis (PCA). (A) PCA biplot shows both the component scores of pneumonia (dots) and atelectasis (squares). (B) Loadings for conventional (CON_{120kVp}, Hounsfield Units [HU]), iodine concentration (C_{iodine}, [mg/ml]), and effective atomic number (Z_{eff}) for lung, the aorta and pneumonia refer to the Component 3 axis. The graph shows, that the differentiation between atelectasis and pneumonia is almost entirely based on the CT number in HU of pneumonia and to a lesser extent of the CT number in HU of the aorta. The other parameters were irrelevant.

4. Discussion

This study investigated the value of SDCT for quantitative differentiation between atelectasis and pneumonia on contrast-enhanced chest CT. We showed that the quantitative parameters C_{iodine} and Z_{eff} could distinguish atelectasis and pneumonia but without added value compared to CT number measurements on conventional images. As expected, in a negative control group of 40 non-enhanced CT, none of the quantitative parameters could differentiate atelectasis and pneumonia.

CT imaging plays an important role since radiologic findings are considered in the diagnosis. The consolidated lung is a frequent finding in chest CT, in which the air within the affected airspaces is replaced, increasing the pulmonary attenuation and obscuring the margins of adjacent airways and vessels [4]. The radiologist needs to differentiate infectious consolidations caused by pneumonia from non-infectious consolidations caused by atelectasis. Radiological signs suggesting pulmonary infection are the air bronchogram, a volume increase, vessel or airway crowding, adjacent ground glass, or tree-in-bud opacities [4, 5]. However, although radiologic signs may help to assign consolidations to an infectious or non-infectious cause, they remain qualitative non-obligatory observations. Therefore, the diagnosis might be unsure, for example, in patients with underlying chronic disease such as heart failure and pleural effusion, who frequently have basal atelectasis that cannot be reliably distinguished from parenchymal infection [20]. In these cases, quantitative CT parameters would be desirable to facilitate a more confident diagnosis.

Atelectasis and pneumonia differ in tissue density and contrast enhancement which can be detected by quantitative CT parameters. In pneumonia, the volume of the affected lung tissue increases since

the alveolar airspaces are filled with fluid or cells, whereas in atelectasis, the lung volume is reduced by compression, absorption of alveolar air, or impaired pulmonary surfactant production or function [21]. Therefore, the lung tissue density per voxel is higher in atelectasis. The contrast enhancement will be influenced by the number of capillaries per voxel and the complex interaction of pathophysiological mechanisms regulating local perfusion. Atelectasis and pneumonia are causing regional alveolar hypoxia leading to hypoxic pulmonary vasoconstriction and reducing pulmonary perfusion regionally, while active inflammation in pneumonia may increase perfusion [22]. However, the volume effect seems to have a more substantial influence since a higher contrast enhancement can be overserved in atelectasis, represented by higher CT numbers and higher SPCT parameters values.

The CT number is a relative quantitative measurement of x-ray density and the most frequently used quantitative CT parameter. On non-enhanced images, the difference in tissue density alone is usually not significant enough to make a sure distinction between atelectasis and pneumonia, which we confirmed by measuring a non-significant difference of 11°HU ($p = 0.054$). Edwards et al. reported a threshold of 85 HU with a sensitivity of 90 % and a specificity of 92 % for pneumonia by using their contrast-enhanced pulmonary CT angiogram protocol [6]. In our study, the difference between atelectasis and pneumonia was also significant on CON_{120kVp}, achieving a sensitivity of 93 % and specificity of 95 %. However, in our study, the optimal threshold was slightly lower with 81 HU. Nonetheless, we believe that both thresholds are comparable. Edwards *et al.* reported a median value of 119 HU for atelectasis and 62 HU for pneumonia, whereas we determined means of 105 HU and 60 HU, respectively. They also reported higher averaged CT numbers of 252 HU and 278 HU than ours, with 187 HU and 178 HU for the ROIs placed in the ascending aorta and the right pulmonary artery. The higher HU values reported by Edwards *et al.* imply higher concentrations of contrast material and can be explained by their triggered arterial phase CT angiogram protocol with a minimal acquisition delay of around 8–10 s [23]. Our study's venous chest and body protocols had longer acquisition delays of 30–45 s depending on the patient's cardiac output. Furthermore, they administered their contrast material with a higher flow rate of 4–5 ml/s than ours of 1.98–3.92 ml/s. In summary, our data showed that pneumonia could be diagnosed with high sensitivity and specificity on CON_{120kVp}, which is following the existing literature.

SDCT can provide additional material-nonspecific and material-specific energy-dependent information like iodine concentration (C_{iodine}) and the effective atomic number (Z_{eff}). We assumed that these parameters might offer a better differentiation of atelectasis and pneumonia by depicting microvessel density and blood supply. In this context, significant correlations between iodine uptake and perfusion parameters derived from DECT and first-pass dual-input perfusion computed tomography (DIPCT) have been reported [24]. Furthermore, SDCT parameters were already used to differentiate lung cancer from inflammatory masses and to detect pulmonary embolism and pleural contrast uptake [13, 14, 15]. As expected, C_{iodine} and Z_{eff} showed significantly higher values in the atelectasis group ($p < 0.001$), while both parameters showed comparable sensitivities of 95 %, but overall lower specificities of 85 % and 83 %. Therefore, both parameters had no added diagnostic value compared to CT number measurements on conventional images. This conclusion was also strengthened by principal component analysis, which showed that the differentiation between atelectasis and pneumonia could be solely based on CT numbers measurements.

We also investigated whether spectral images have better contrast-to-noise-ratios. The ratio between the contrast of two adjacent structures and the noise level are two major criteria to assess the ability to separate different structures. We calculated the CNR values between the aorta, normal lung, and

pleural effusion vs. atelectasis or pneumonia. CON_{120kVp} images had significantly higher CNRs between consolidated and normal lung than the corresponding C_{iodine} and Z_{eff} images ($p < 0.001$). On spectral images, the noise increases dramatically if the spectral resolution is low [25]. Therefore, the lower CNRs are most likely caused by a higher noise level even though contrast may be enhanced. On Z_{eff} images, significantly higher CNRs were found between the aorta or pleural effusion and atelectasis or pneumonia ($p < 0.001$). The reason for this is because blood and pleural effusion consist mostly of inorganic materials, which is reflected by Z_{eff}. In summary, C_{iodine} and Z_{eff} had no benefit compared to CON_{120kVp} images on non-enhanced chest SDCT with regard to CNR.

There are some technical limitations to our study. First, a validated gold standard is missing, as no histological correlation was performed. Bronchoalveolar lavage or lung biopsy are the reference methods for diagnosing pneumonia but are seldom performed and were not available in a retrospective setting. The clinical criteria we used to assign patients to the pneumonia group have been used slightly modified in other studies [6, 26, 27]. Unfortunately, there were many multimorbid patients in our patient cohort who often had several extrapulmonary infections. A considerable part of the patients had a clinical score of two, which did not clearly assign them to the atelectasis or the pneumonia group. In these cases, individual decisions were made, which was challenging due to the partially overlapping clinical symptoms of atelectasis and pneumonia [28]. Nevertheless, Edwards *et al.* reported comparable results for CT number measurements on CON_{120kVp}, implying that our clinical assignment was adequate enough to allow the assessment of C_{iodine} and Z_{eff} images. Furthermore, we ignored the intra- and inter-individual differences in iodine distribution, which can be seen as another limitation. In the literature, significant differences in iodine concentrations were reported between sexes and age in different parenchymal organs, influencing the obtained quantitative iodine concentration and the applied iodine thresholds [29]. However, even though comparable effects can be expected in the lungs, we argue that our calculated thresholds are still valid since they are based on averaged values, by which the impact of intra- and inter-individual differences are reduced.

5. Conclusion

We showed that the quantitative parameters C_{iodine} and Z_{eff} could distinguish atelectasis and pneumonia in contrast-enhanced SDCT but without added diagnostic value compared to CT number measurements on conventional images. Thus, in every day routine CT contrast material application can add diagnostic value based on quantitative measurements in cases where radiological and clinical diagnosis both are equivocal.

Declarations

Author contribution statement

Philip Konietzke and Mark Oliver Wielpütz: Conceived and designed the experiments; Performed the experiments; Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data; Wrote the paper.

Hauke Helmke Steentoft: Performed the experiments; Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data; Wrote the paper.

Willi Linus Wagner: Contributed reagents, materials, analysis tools or data; Wrote the paper.

Jonas Albers and Christian Dullin: Analyzed and interpreted the data.

Stephan Skornitzke: Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data; Wrote the paper.

Wolfram Stiller and Tim Frederik Weber: Conceived and designed the experiments; Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data; Wrote the paper.

Hans-Ulrich Kauczor: Conceived and designed the experiments; Contributed reagents, materials, analysis tools or data; Wrote the paper.

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Data availability statement

Data included in article/supplementary material/referenced in article.

In most patients presenting with respiratory symptoms, the findings of chest radiography play a key role in the diagnosis, management, and follow-up of the disease. Consolidation is a common term in radiology, which indicates focally increased lung density. When the alveolar structures become filled with pus, fluid, blood cells or protein subsequent to a pulmonary pathological process, it may result in different types of lung opacity in chest radiograph. This study aims at detecting consolidations in chest x-ray radiographs, with a certain precision, using artificial intelligence and especially Deep Convolutional Neural Networks to assist radiologist for better diagnosis.

Methods

Medical image datasets usually are relatively small to be used for training a Deep Convolutional Neural Network (DCNN), so transfer learning technique with well-known DCNNs pre-trained with ImageNet dataset are used to improve the accuracy of the models. ImageNet feature space is different from medical images and in the other side, the well-known DCNNs are designed to achieve the best performance on ImageNet. Therefore, they cannot show their best performance on medical images. To overcome this problem, we designed a problem-based architecture which preserves the information of images for detecting consolidation in Pediatric Chest X-ray dataset. We proposed a three-step pre-processing approach to enhance generalization of the models. To demonstrate the correctness of numerical results, an occlusion test is applied to visualize outputs of the model and localize the detected appropriate area. A different dataset as an extra validation is used in order to investigate the generalization of the proposed model.

Results

The best accuracy to detect consolidation is 94.67% obtained by our problem based architecture for the understudy dataset which outperforms the previous works and the other architectures.

Conclusions

The designed models can be employed as computer aided diagnosis tools in real practice. We critically discussed the datasets and the previous works based on them and show that without some considerations the results of them may be misleading. We believe, the output of AI should be only interpreted as focal consolidation. The clinical significance of the finding can not be interpreted without integration of clinical data.

Introduction

In most patients presenting with respiratory symptoms, the findings of chest radiography play a key role in the diagnosis, management, and follow-up of the disease. Consolidation is a common term in radiology which indicates focally increased lung density. When the alveolar structures become filled with pus, fluid, blood cells or protein subsequent to a pulmonary pathological process, it can reult in different types of lung opacity in chest radiographs [1]. Consolidation is an important radiological finding in a number of diseases and pneumonia can be mentioned as one of the most critical ones. Pneumonia is referred to a lower respiratory tract infection which accounts for the highest rate of mortality among infectious diseases and is the third cause of mortality in overall. It is responsible for more than $17 billion annual cost in the US. Early detection of this condition is crucial, since late diagnosis may lead to increased mortality. However, there is occasionally an inconsistency in the decisive diagnosis of this disease, even among expert clinicians and radiologists [2], [3], [4], [5], [6]. Recently, the application of Artificial Intelligence in detection of pathologies on chest radiographs has been shown useful and become a hot topic in medical research [7].

Currently, deep learning techniques are applied to a range of problems in science, engineering, and medicine [8]. Since 2012, a form of deep learning technique, called Deep Convolutional Neural Network (DCNN), has been widely used [9]. Because of promising results of Deep Convolutional Neural Networks, recently, deep CNNs have been successfully applied in medical fields [10], [11], [12], [13]. Bar et al. investigated the identification of pleural effusion and cardiomegaly on the chest radiography using deep learning technique [14]. Hua et al. proposed a model of the convolutional neural network in the context of nodule classification in computed tomography images [15]. Islam et al. introduced an ensemble model of the convolutional neural network in order to detect and localize the abnormalities in chest X-ray images [16]. Lakhani and Sundarm evaluated three DCNNs such as AlexNet [17], GoogleNet [18] and an ensemble model of AlexNet and GoogleNet for classification of pulmonary tuberculosis in chest X-ray images [19]. Qin et al. published a comprehensive study on applications of artificial intelligence techniques such as DCNNs in detecting diseases on different datasets of chest radiology images [7]. Park et al. investigated the performance and effect of DCNN in medical diagnosis and prediction [20]. Xu et al. proposed and hierarchical deep CNN model to classify images of Chest X-ray14 [21]. Regarding the classification of pneumonia in chest X-ray images, one group using DCNN achieved to the accuracy and AUC of 92.80 and 96.80%, respectively [22].

The well-known DCNNs have many pooling layers which throw away some information of objects in the images [23]. Also, many of the previous works which have extremely promising results reported their performances only according to the numerical metrics [14,21,22,24,25]. A deep convolution neural network such as VGG16 has millions of training parameters, and it is practically infeasible to analyze their values. So, they are called the black box. Recently, Zech et al. [26] proposed a method for classifying chest X-ray as pneumonia and normal images. They reported that confounding variables such as strings on the corner of left and right sides of images can degrade generalization performance of radiological deep learning models, so, it is possible that a deep learning method has promising results on classifying problem according to the inappropriate features. There are other problems in the dataset understudy (Pediatric Chest X-ray) such as different histogram distribution between classes that lead deep leaning model to classify images with promising results according to the difference between histogram of images of classes. In the other hand, in the case of small dataset, choosing the appropriate pre-training dataset is an important issue

Abstract

Primary pulmonary mucosa-associated lymphoid tissue (MALT) lymphoma is extremely rare. MALT lymphoma patients usually show no clinical symptoms or physical signs. Chest

radiograph or computed tomography (CT) may confuse MALT lymphoma with other pulmonary diseases, which would lead to misdiagnosis or a delayed diagnosis. In the present study, a 33-year-old male patient had cough and fever. Chest CT showed consolidation on both sides. Those clinical symptoms disappeared after he had been misdiagnosed and treated for community-acquired pneumonia for three weeks. However, further chest CT still showed the consolidation without any change. Then an ultrasonic guided transthoracic needle biopsy was performed. Morphological changes indicated the diagnosis of extranodal marginal Zone B cell lymphoma of MALT. The patient was then treated with chemotherapy and rituximab. After this line of treatment, the consolidation decreased.

1. Introduction

Primary pulmonary lymphoma accounts for 0.5–1.0% of pulmonary malignancies and ＜1.0% of all lymphomas [1]. It develops both in the normal MALT tissue and in a normal organ or tissue without MALT [2]. Patients with primary pulmonary lymphoma may show no symptoms or physical signs. There are no typical or significant changes in the chest radiograph or CT scan that can distinguish primary pulmonary lymphoma from other pulmonary diseases. Here we present a case of MALT lymphoma with an unchanged consolidation in the chest CT, diagnosed by ultrasonic guided transthoracic needle biopsy.

2. Case report

A 33-year-old male patient who had cough and intermittent for two months was admitted to our clinic. He had experienced fevers, yellow sputum, episodes of minimal hemoptysis and left chest pain recently. He had no history of weight loss, alcohol abuse, or smoking, and didn't expose to tuberculosis. His respiratory examination revealed diminished movement of lower left chest wall. Other general clinical examination results were normal. However, laboratory findings revealed that the white blood cells, C-reactive protein, erythrocyte sedimentation rate (ESR) and procalcitonin (PCT) were all raised. The results of both T-SPOT TB test and tumor markers were negative. Cell immunity and humoral immunity were normal.

His chest CT showed bilateral consolidation in the right upper and middle lobes and the left upper lobes (Fig. 1A). There was a little left pleural effusion. No mediastinal or hilar adenopathy was noted. He was first treated for community-acquired pneumonia for three weeks, and all symptoms were gone. Further blood lab examinations on white blood cells, neutrophil, C-reactive protein, ESR and PCT were all normal. However, the chest CT scan revealed less pleural fluid and an unchanged consolidation (Fig. 1B). Some causes of non-resolving pneumonia should be excluded. We decided to complete other examinations.

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Fig. 1. The chest CT showed bilateral areas of consolidation and little pleural effusion in the left (A). After antibiotic treatment, the chest CT scan revealed less pleural fluid and unchanged consolidation (B).

The bronchoscopy revealed diffuse mucosal swelling in both lobar branches, with neutrophils and some normal bronchial cells, but no malignancies or acid fast bacilli were found; while other tests for microbes showed negative results. Pleural fluid was aspirated from the left hemithorax and identified

as exudative. Cells in the pleural fluid were predominantly lymphocytes, with lactate dehydrogenase (LDH) 299U/L, adenosine deaminase level 45.2U/L. No malignant cells or acid fast bacilli were detected in the pleural fluid. PET-CT indicated intense fluorodeoxyglucose (FDG) uptake in the right upper and middle lobes and left upper lobe (maximum standardized uptake value: 5.66–9.63). There were no signs of disease in other sites.

Then an ultrasonic guided transthoracic needle biopsy of the right upper consolidated area was performed. H&E staining showed that normal alveolar structure had completely disappeared and had been substituted by diffuse lymphoid cells with irregular nucleus. These lymphoid cells included small round lymphoid cells, centrocyte-like cells and monocytoid-resembling lymphocytes (Fig. 2 A). Immuno-histochemistry cell staining showed positive results for CD20, CD79a, PAX-5, LCA, Bcl-2, and ki67 (LI about 10%) (Fig. 2 B, C and D), and negative results for CD5, CD23, CyclinD1, CD10, CD56, TdT, MUM1, CgA, Syn and NSE. These morphological changes match a diagnosis with extranodal marginal Zone B –cell lymphoma of mucosa-associated lymphoid tissue (MALT).

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Fig. 2. H&E staining showed that the normal alveolar structure had completely disappeared, being substituted by diffuse lymphoid cells infiltration. These lymphoid cells included small and round lymphoid cells, centrocyte-like cells and monocytoid-resembling lymphocytes. (Magnification ×40) (A); Immunohistochemical test indicated that the cells were positive for CD20 (B), Bcl-2 (C), CD79a (D).

Furthermore, a bone marrow biopsy was performed and the results showed no neoplastic invasion. Leukemia immunophenotyping was normal. No *Helicobacter pylori* or other infections were found at gastroscopy. Therefore, this young male patient was diagnosed with Primary MALT lymphoma stage IE according to the Ann Arbor classification (Table 1).

Table 1. Clinical Stags of Pulmonary Non-Hodgkin's Lymphoma.

Stage	Extent of Disease
IE	Lung only involved, could be bilateral
II1E	Lung and hilar lymph nodes involved
II2E	Lung and mediastinal lymph nodes involved
II2EW	Lung and adjacent chest wall or diaphragm involved
III	Lung and lymph nodes below the diaphragm
IV	Diffuse disease

A Modified Ann Arbor classification.

The patient was treated with five cycles of chemotherapy, including cyclophosphamide, vincristine, adriamycin and prednisone and rituximab, and complained of no clinical symptoms. He came for clinical and radiological follow-up visits every three months; the consolidation decreased in his CT photograph. There have been no symptoms and no progression since then.

3. Discussion

MALT lymphoma is known as a kind of non-Hodgkin's lymphoma (NHL) and accounts for 7–8% of NHLs. It belongs to the marginal-Zone B cell lymphomas but is different from the nodal and splenic forms. It was originally described at extranodal sites in relation to mucosae or glandular epithelia and usually occurs in the gastrointestinal tract, salivary glands, thyroid, ocular adnexa, kidney, breast, lung and so on [3]. The most common type is gastric MALT lymphoma (about 50% of MALT lymphomas), while the primary lung MALT lymphoma is very rare. MALT lymphoma is considered to have high correlation with chronic antigenic stimulation (especially *Helicobacter pylori* to gastric MALT lymphoma), chronic inflammation and autoimmune disease. It was reported that smoking or autoimmune diseases, such as systemic lupus erythematosus, may be associated with pulmonary MALT lymphomas [4]. The chromosome translocations such as t (11; 18) (q21; q21), t (1; 14) (p22; q32) and t(14; 18) (q32; q21) also take part in the pathogenesis of MALT lymphomas [5].

The primary pulmonary MALT lymphoma is usually observed in patients aged 50–60 years, and is rarely observed in patients aged around 30 years. The incidence is independent of gender. MALT lymphoma is an indolent lymphoma which can last for a long time, with a tendency to disseminate late. It may not even progress for a decade [6]. And the 5-year relative survival of patients with MALT lymphoma is about 89% [7].

Half of the MALT lymphoma patients have no symptoms or physical signs. The patients may have cough, dyspnea, shortness of breath, chest pain, hemoptysis, fever and so on [8]. There are no specific symptoms that are essential for the diagnosis. But it tends to disseminate to other parts of the lung and the mucosa of other organs, such as the stomach and the salivary glands. Results from the common laboratory examination including routine blood tests are usually normal. The bone marrow biopsy is important, and the results may be abnormal when the patient has neoplastic infiltration. There are no typical or significant changes in chest radiograph or CT scan which distinguishes it from other pulmonary lymphomas. It can present as mass or mass-like consolidation and multiple nodules (about 70%). An air bronchogram (about 50%), ground-glass opacities and pleural effusion can also be seen in the case. The characteristics of all the changes are an indolent process, which may not develop for several years. The role of bronchoalveolar lavage (BAL) was unclear. It was reported that lymphocytes of BAL were more than 20% and CD19/20 positivity may suggest MALT lymphoma [9]. Bronchoscopy brushing is only useful when the bronchus is involved.

Histopathologic examination is the gold standard for the diagnosis of MALT lymphoma. Biopsy such as transbronchial biopsy, CT scan-guided or ultrasonic-guided transthoracic biopsy would be necessary. The histology characteristics of MALT lymphoma are centrocyte-like cells, which are small to medium-sized lymphocytes with abundant cytoplasm and small irregular nuclei. Alternatively, the neoplastic cells may resemble monocytoid lymphocytes, which have distinct cell borders, or they may resemble small mature lymphocytes. Infiltration of the epithelium by neoplastic cells can lead to lymphoepithelial lesions. This can also occasionally be seen in inflammation including reactive pulmonary infiltrates. In pulmonary MALT lymphoma, neoplastic cells could infiltrate

lymphatic vessels, spreading along bronchovascular bundles, interlobular septa and pleura and then form pulmonary parenchyma lesions.

No specific immunohistochemical marker has yet been identified for MALT lymphoma. The NCCN Guidelines (Version 2.2016) of Non-Hodgkin's Lymphomas recommend markers for an immunohistochemistry (IHC) panel of Non-gastric MALT Lymphomas, including CD20, CD3, CD5, CD10, CD21 or CD23, CCND1, BcL2. CD5, CD23 and cyclinD1, IHC results are useful to differentiate MALT lymphoma from other low-grade B-cell lymphomas such as small lymphocytic lymphoma, chronic lymphocytic leukemia and mantle cell lymphoma, whereas CD10 and BcL-6 are identified in follicular lymphoma. In this case, the immunohistochemistry showed CD20, CD79a and Bcl-2 were positive, whereas CD5, CD23, CyclinD1, CD10, CD56, CgA, Syn and NSE were negative. A high expression of Ki-67 indicates a large number of cells in the proliferation cycle and correlates positively with the malignant degree of non-Hodgkin's lymphoma [10]. In the end, CgA, Syn and NSE positive were observed in small-cell carcinoma. Detection of Ig gene and chromosome of MALT 1 gene rearrangements would be helpful to the diagnosis [11].

After the diagnosis of pulmonary MALT lymphomas, an evaluation should be given. The following examinations should also be completed: A physical exam with performance status; complete blood count and measurements of serum lactate dehydrogenase; a CT scan of abdomen and pelvis; gastroscopy examination for *Helicobacter pylori* or other infections; and bone marrow biopsy. Hepatitis B testing should be done before immunotherapy and chemotherapy [12]. For clinical pulmonary MALT lymphoma staging, we always use the Ann Arbor classification (see Table 1). The value of the PET scan in the evaluation is controversial. A low-grade lymphoma has little FDG uptake, especially in the stomach [13], whereas some researchers think it may be helpful for initial staging and follow-up of patients [14]. So a PET scan is not used routinely for staging in lymphoma. Nonetheless, the treatment should be done whether there is a result for PET-CT or not [12].

The main treatment modalities for MALT lymphoma include surgery, radiotherapy, chemotherapy and rituximab [15,16], but the most effective course of treatment is still being debated. For patients with limited pulmonary diseases, surgical excision may be an appropriate choice. NCCN recommend that patients with stage I-II non-gastric MALT lymphoma should be given involved-site radiotherapy (ISRT) (24–30 Gy); however, this is unsatisfactory for primary pulmonary MALT lymphoma. Patients with pulmonary MALT lymphoma or extranodal involvement also could be observed [16]. Although chemotherapy is the traditional therapy for MALT lymphomas, which regimens to choose, the long-term effect and other data should be evaluated, especially in a localized disease. Rituximab is a choice for selected patients [17]. In our case, the patient was given chemotherapy regimens, such as cyclophosphamide, vincristine, adriamycin and prednisone, combined with rituximab, and no progression has been observed until now.

In conclusion, primary pulmonary MALT lymphoma is extremely rare and has no typical clinical symptoms or signs. Changes in the chest radiograph or CT scan may confuse it with other pulmonary diseases, which could lead to misdiagnosis or a delay in diagnosis. Histopathologic and genetic examinations contribute to the diagnosis of MALT lymphoma. Therefore, the diagnosing and staging is challenging. Although the disease was indolent and had a favorable prognosis, treatment was tailored to fit the individual patient. When we encounter an unchanged consolidation in chest CT or non-resolving pneumonia, we should keep in mind pulmonary MALT lymphoma, and a biopsy is necessary.

Abstract

Objectives

Despite emerging evidences on the clinical usefulness of lung ultrasound (LUS), international guidelines still do not recommend the use of sonography for the diagnosis of pneumonia. Our study assesses the accuracy of LUS for the diagnosis of lung consolidations when compared to chest computed tomography (CT).

Methods

This was a prospective study on an emergency department population complaining of respiratory symptoms of unexplained origin. All patients who had a chest CT scan performed for clinical reasons were consecutively recruited. LUS was targeted to evaluate lung consolidations with the morphologic characteristics of pneumonia, and then compared to CT.

Results

We analyzed 285 patients. CT was positive for at least one consolidation in 87 patients. LUS was feasible in all patients and in 81 showed at least one consolidation, with a good inter-observer agreement (k = 0.83), sensitivity 82.8% (95% CI 73.2%-90%) and specificity 95.5% (95% CI 91.5%-97.9%). Sensitivity raised to 91.7% (95% CI 61.5%-98.6%) and specificity to 97.4% (95% CI 86.5%-99.6%) in patients complaining of pleuritic chest pain. In a subgroup of 190 patients who underwent also chest radiography (CXR), the sensitivity of LUS (81.4%, 95% CI 70.7%-89.7%) was significantly superior to CXR (64.3%, 95% CI 51.9%-75.4%) (P< .05), whereas specificity remained similar (94.2%, 95% CI 88.4%-97.6% vs. 90%, 95% CI 83.2%-94.7%).

Conclusions

LUS represents a reliable diagnostic tool, alternative to CXR, for the bedside diagnosis of lung consolidations in patients with respiratory complains.

Introduction

Pneumonia is a common disease characterized by an infection that involves alveoli, distal airways, and interstitium, and leads to lung inflammatory consolidations. Chest computed tomography (CT) is considered the gold standard imaging test for the diagnosis of pulmonary consolidations, but its routine application for the diagnosis of pneumonia is limited by concerns about the high radiation exposure and high costs [1], [2]. In clinical practice, the diagnosis of pneumonia is based on clinical signs and supported by the visualization of typical opacities on chest radiography (CXR). However, in patients evaluated in the emergency department (ED), CXR showed a poor sensitivity (43.5%) when compared to CT [3]. Therefore, reliance on CXR to diagnose pneumonia may lead to significant rates of misdiagnosis.

Lung ultrasonography (LUS) is a bedside diagnostic tool that showed high sensitivity for the diagnosis of various pulmonary conditions, including pneumonia [4], [5], [6], [7], [8], [9]. However, an important limitation of some of these previous studies is that not always CT was used as the gold standard to confirm a pulmonary consolidation.

The aim of our study was to define the diagnostic performance of LUS in detecting pulmonary consolidations with the morphologic characteristics of pneumonia, using chest CT as the gold standard.