

Predicting COVID-19 Lung Infiltrate Progression on Chest Radiographs Using Spatio-temporal LSTM based Encoder-Decoder Network

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Abstract

Automated analyses of chest imaging in Coronavirus Disease 2019 (COVID-19) have largely focused on a single timepoint, usually at disease presentation, and have not explicitly taken into account temporal disease manifestations. We present a deep learning-based approach for prediction of imaging progression from serial chest radiographs (CXRs) of COVID-19 patients. Our method first utilizes convolutional neural networks (CNNs) for feature extraction from patches within the concerned lung zone, and also from neighboring areas to enhance the contextual phenotypic information. The framework further incorporates two distinct spatio-temporal Long Short Term Memory (LSTM) modules for effective predictions. The first LSTM module captures spatial dependencies between patches and the second exploits the temporal context of sequential CXR scans. The resulting network focuses on critical image regions that provide relevant information for learning the progression of lung infiltrates without the explicit need for infiltrate segmentation. The second LSTM provides an encoded context vector used as an input to a decoder module to predict future severity grades. Our novel multi-institutional dataset comprises sequential CXR scans from N=100 patients. Specifically, our framework predicts zone-wise disease severity for a patient on the last day by learning representations from the previous temporal CXRs. We design two baseline approaches - one using fine-tuned VGG-16 features and the other using radiomic descriptors. Experimental results demonstrate that our proposed approach outperforms both baselines in average accuracy by 10.33% and 12.16%, respectively, in predicting COVID-19 progression severity.

Keywords: COVID-19, proning, convolutional neural network, chest radiographs, long short term memory, transfer learning

1. Introduction

Coronavirus disease 2019 (COVID-19) has infected 107 million people worldwide and caused over 2 million deaths as of February 2021 (Dong et al., 2020). Currently, chest radiography (CXR) is the primary imaging modality for disease monitoring (American College of Radiology, 2020). Findings of COVID-19 infection on CXR include the presence of infiltrates, opacities, and consolidations (Hui et al., 2020). These findings vary in quantity and location throughout the disease course of COVID-19. Studies have reported that the spatial distribution of these radiographic findings within lung zones is of clinical significance (Hui et al., 2020; Toussie et al., 2020). For instance, the presence of lung findings on CXR in multiple lobes has been shown to be correlated with severe disease (Toussie et al., 2020).

Clinical motivation. Due to their convenience, CXRs can be taken serially for inpatients with COVID-19. Expert interpretation of these serial images can be used to monitor COVID-19 progression. Recent studies have suggested that placing patients in prone position has shown to improve clinical outcomes for patients receiving mechanical ventilation in the setting of other illnesses (Guérin et al., 2013). However, studies have not yet explored whether its effect on disease progression can be appraised on chest radiography (CXR). Figure 1 shows AP (antero-posterior) radiographs of the chest (a-d) from a single patient demonstrating the lung infiltrates burden over the course of four days during prone ventilation. Lung contours have been coloured green. There exist no models currently that can predict the severity of disease, as manifested on imaging on a later time point, based on the trajectory in the first few days of treatment. As an application of our study on serial medical images, we can provide imaging evidence of disease improvement. Radiographic findings on sequential CXR might be analyzed to provide insights into when proning or other treatments should be initiated and for what duration proning is most effective in patients undergoing mechanical ventilation.

Technical motivation. Existing deep learning (DL) based COVID-19 studies primarily utilize single-timepoint radiographic images rather than serial CXRs taken at different timepoints (Bae et al., 2020; Shi et al., 2020). By analyzing sequential CXRs, our work aims to more accurately model disease progression.

Recurrent neural networks (RNNs) have been mainly applied for prediction of time series data in problems related to natural language processing and computer vision. RNNs have been found to be quite successful in a variety of health-care tasks such as disease progression prediction (Wang T, 2018; Chen et al., 2018) and electronic health record analysis (Cheng et al., 2016; Choi et al., 2016b). Previous works have explored the use of gated recurrent units to predict the evolution of tumors (Zhang et al., 2018) and treatment response from serial medical images (Wang et al., 2019b; Xu et al., 2019). In RNNs, the past hidden states of an object are passed through a weighted non-linear function to predict its state at a future timepoint. As a result, relevant past information is stored and used for future predictions. As an extension of RNN, the Long-Short Term Memory (LSTM) (Hochreiter and Schmidhuber, 1997) is specifically designed to capture long-term patterns that are commonly found over a long period of patients' records (Martin et al., 2012). LSTM-based approaches have achieved great success in many applications that involve sequential data, such as video processing. There are quite a few publications that employ LSTM for medical data (Jiang et al., 2018; Lao et al., 2018; Wang et al., 2019a, 2018). However most are based

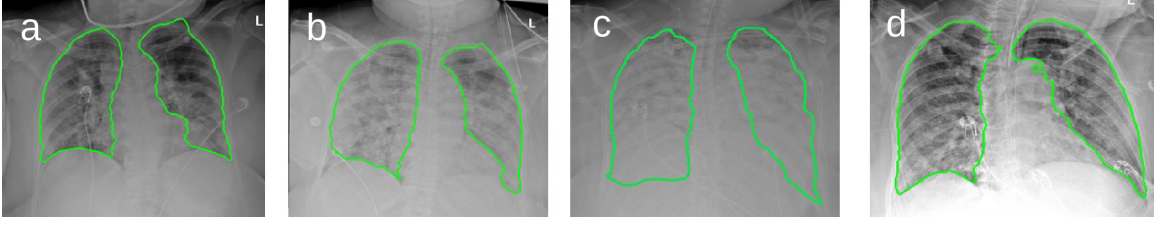


Figure 1: AP (antero-posterior) radiographs of the chest (a-d) from a single patient demonstrating the lung infiltrates burden over the course of four days. (a) Ground glass opacities throughout the left and right lung zones on day 1. (b) Slightly increased opacities throughout the aforementioned lung zones. (c) shows that disease burden has increased to become extensive confluent consolidations in the bilateral middle and lower lung zones. (d) resembles the similar findings seen on day 1.

on clinical measurements (Lipton et al., 2015), although a few use the concept of disease progression modeling (Choi et al., 2016b).

Despite the great success of LSTM, one of its major drawbacks lies in its failure to interpret prediction results. (Choi et al., 2016a) shows that capturing interpretable information is more significant than building a robust deep network in disease progression scenarios. Also, LSTMs do not directly consider irregular time intervals between consecutive events. Previous works have shown that LSTMs are able to correlate features from different image regions (Zuo et al., 2015; Linsley et al., 2018). We incorporate this idea into our framework to generate more discriminative features from the image patches. None of the previous works jointly exploit the spatial distribution within images and the temporal information across timepoints. We use a framework that encodes a combination of spatial and temporal information. Similar models have achieved great success in action prediction from video data. (Liu et al., 2017; Mao et al., 2016; Clark et al., 2017).

Using a unique cohort of multi-institutional serial CXR (N=100 patients), we present a novel two-stage LSTM based encoder-decoder network to predict CXR severity progression. Sequential CXRs taken for a patient are used as inputs to this model to predict imaging severity scores for future CXRs. Our framework learns both temporal and spatial information from CXR images. The first stage, called *LSTM-Spatial*, aggregates spatial information from different locations. This module also takes into account imaging variability in the immediately adjoining lung zones. The second stage, *LSTM-Temporal*, learns to aggregate information from temporal CXRs and unravels the information to predict the severity at a future time point.

1.1. Contributions

- Our work uses a multi-stage spatio-temporal LSTM framework to model the progression of COVID-19 lung infiltrates over multiple timepoints and predict the infiltrate severity at a later time.

- We are the first to use a temporal COVID-19 imaging dataset for severity prediction. Our proposed model has been evaluated on this dataset (N=100 patients, 657 CXRs) and compared against multiple baseline approaches.

2. Method

In this IRB-approved study, temporal sequences of varying number of CXR images were curated for N=100 patients. The number of images for each patient is denoted by D , which ranges from 4 to 13. The images corresponding to D days are represented by $I_{t_1}, I_{t_2}, \dots, I_{t_{D-1}}, I_{t_D}$. The lung fields for both right (R) and left (L) lungs were automatically segmented using a Residual UNet model (Bae et al., 2020). We do not perform any image co-registration. However, to avoid any possible bias from the temporal data, these masks were further subdivided into upper (L_1, R_1), middle (L_2, R_2), and lower (L_3, R_3) lung zones, with each zone comprising approximately one third of the entire lung field. Based on the observed infiltrate patterns, each of these 6 lung zones was independently assigned a severity score $g_0 = 0, g_1 = 1$, or $g_2 = 2$ by three expert readers in consensus, representing mild, moderate, and high disease severity, respectively. The severity grades of the last image I_{t_D} is used as a ground truth for the severity prediction at timepoint t_D .

Our model consists of 6 encoder-decoder frameworks to facilitate zone-wise predictions, represented by F_{L_i}, F_{R_i} , where $i = 1, 2, 3$. Figure 2 shows F_{L_1} framework which considers patches from L_1 zone as input.

2.1. Two-stage encoder LSTM

Capturing spatial dependencies for CXR imaging findings is a critical step in our analysis due to the nature of COVID-19 clinical progression. Recurrent neural networks (RNN) enable the modeling of data sequences, allowing inputs of varying number of patches. However, this method can lead to the problem of vanishing gradients during back-propagation, restricting the model’s capability of handling excessively long contextual temporal information (Bengio et al., 1994). LSTM models address this issue by proposing three gating units: input, output, and forget units (Hochreiter and Schmidhuber, 1997). The gates operate based on the present input and the previous hidden states.

Our framework includes two LSTM modules: 1) *LSTM-Spatial* to learn the patch diversity at different spatial locations of an image, which we refer to as “spatial dependencies” and 2) *LSTM-Temporal* to exploit the “temporal dependencies” between CXR images from multiple days.

The feature representations of all image patches obtained from CNN described below (sub-section 2.3), are fed into *LSTM-Spatial* following the same sequence in which the extracted patches were provided to the CNN. The number of timesteps in *LSTM-Spatial* depends on the number of CNN maps obtained for each zone for each day. Time steps vary from 1 to P for each day, where P refers to the number of patches obtained from a given zone. The output from each timestep is a 1×512 dimension feature vector. Thus, as the output of the *LSTM-Spatial*, we obtained a $P \times 512$ dimension feature vector, where P varies day-wise and, further, patient-wise. It can be seen from Figure 2 that day ‘ t_1 ’ of the particular patient has P input patches which may differ across days $[t_2, \dots, t_{D-1}]$. To construct a holistic feature representation from each of the $D - 1$ days of a particular

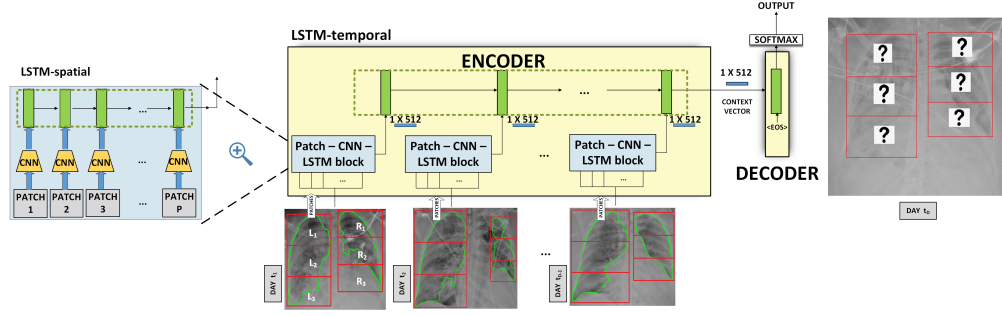


Figure 2: Architecture of the proposed LSTM approach

patient, we obtain a single dimensional feature vector from the last cell state (denoted by LCS in Figure 2) of the *LSTM-Spatial*. This is the global feature of the entire sequence of patches for a particular day, and has dimension 1×512 . We provide these day-wise global features as inputs to each timestep of *LSTM-Temporal*. *LSTM-Temporal* has $D - 1$ timesteps. Finally, from the last cell state of the *LSTM-Temporal*, we obtain the encoder module context vector.

2.2. Patch extraction

A sliding window approach was employed to extract dense patches from each lung zone. The patch dimension used for our framework is 256×256 . The stride length of the window is chosen as 128 pixels. Because segmented masks from CXRs have non-uniform dimensions, the number of patches extracted for a lung zone will vary each day for a particular patient. The patches that had more than 80% background pixels were discarded. In our dataset, a large proportion of image zones are assigned g_1 , making it the majority class. To address the issue of class imbalance, we randomly upsampled the number of patches labelled (g_0, g_2) by 25%. Thus, for an encoder-decoder framework for a particular zone, we achieved a fair proportion of patches with grades g_0, g_1 , and g_2 . Moreover, it has been clinically proven that features from neighboring areas tend to enhance the contextual information of a zone in medical imaging (Toussie et al., 2020). Therefore, in the pool of extracted patches to be used as an input for a zone, we also included an array of patches from the boundary of its adjoining neighboring zones. As an example, for patches from L_2 shown in Figure 2, the closest patch array from adjoining zones L_1 and L_3 have been considered.

2.3. CNN for feature extraction

After patch extraction, for each of the 6 zone-wise encoder-decoder frameworks, a CNN architecture was employed to obtain image feature representations. For each framework, patches from the concerned lung zone were fed as input to this CNN network in a day-wise manner, spanning across $D - 1$ days. The number of days varies for each patient depending on the number of time-points available in the dataset. For example, for the patient in Figure 1, $D = 4$. The output response of the CNN for each patch for each such time-point is a 1×256 dimensional feature vector. The CNN network configuration contains

five convolutional layers, each associated with an operation of max-pooling. The model terminates with a fully connected layer.

2.4. The decoder module

A decoder module is defined to decode the encoded vector representation from *LSTM-Temporal* and predict the grades of t_D^{th} day, for each lung zone. The encoded context vector and start tokenizer (*EOS*) are used as inputs (Bahdanau et al., 2014) to the first timestep of the LSTM module in this section. We then apply a softmax layer to classify the decoder output into g_0, g_1 , or g_2 .

3. Experiments

3.1. Dataset Description

The multi-institutional dataset consists of a unique cohort of AP CXRs from 23 COVID-19 patients at Newark Beth Israel Medical Center (Cowan et al., 2021), and from 77 COVID-19 patients at Stony Brook University Hospital (657 scans in total). CXRs were 3470×4234 pixels in size. The duration (number of days) between the CXRs are variable. For a particular patient, there can be a span of 1 day or even 5 days between two sequential timepoints.

3.2. Implementation Details

A cross entropy loss function was selected for training, which was optimized with an Adam optimizer for both the CNN and the LSTM. The initial and consistent learning rate and maximal number of epochs were set to 0.0001 and 15, respectively. We used pack padded sequence using Pytorch to mask out all losses that surpassed the required sequence length. Thus we could nullify the effect of missing timesteps for a patient in the dataset. For each model, we performed a 5-fold cross validation, with 20 distinct test cases (patients) in each fold. Each time, the 80 remaining cases were randomly divided into 60 training and 20 validation splits.

3.3. Baseline approach

Approach 1. We trained 6 models in this baseline approach for each of the 6 lung zones. The last layer of the VGG-16 network (Simonyan and Zisserman, 2014) was replaced with a mini network of 2 small fully connected layers. The new network was trained after freezing all other pre-trained convolutional weights as shown in Figure 4 of Appendix section.

For our framework, we considered the first $D - 1$ days' images of a patient, that are $I_{t_1}, I_{t_2}, \dots, I_{t_{D-1}}$. Hence for each patient, 64×64 patches were extracted in a sliding window approach from the concerned zone of each I with a stride of 32. Upsampling of minority label patches and inclusion of neighboring patches were adopted, similar to our LSTM approach. Features were extracted from these patches to obtain a $P_L \times 4096$ dimensional feature vector. P_L denotes the number of patches for a particular zone over $D - 1$ days, which may vary across different patients. The output for each patient was averaged into a 1×4096 feature vector.

We trained a 1D neural network with these extracted feature vectors to perform the final classification task. In the testing phase for each patient, the classifier predicted severity scores for each patch. A majority voting approach was then employed on these patch classification scores to obtain a single zone-wise severity score. This score was compared against the ground truth severity grade for $I_{t_D}^{th}$ image to compute the evaluation metrics.

An SGD optimizer with a batch-size of 64 was applied to minimize the objectives. The VGG-16 network, with a learning rate set to 0.0001, was finetuned across 30 epochs. Categorical cross entropy loss was used as a cost function.

Approach 2. We trained 6 different models of this baseline for each of the 6 lung zones. In this approach, 445 texture-based radiomic features (Prasanna et al., 2017; Thawani et al., 2018) were extracted from the patches of the concerned zone of a patient (Griethuysen et al., 2017). Averaging was performed on this feature vector and passed on to a random forest classifier. An approach identical to the previous baseline was used to compute the classification performance.

4. Results

Experimental results were quantitatively evaluated using accuracy (Acc), precision (Pre), and recall (Rec) metrics. Acc was measured zone-wise, whereas Pre and Rec were calculated on a grade level. The results using our approach and the baseline method are illustrated in Tables 1 and 2 for the left and the right lung zones, respectively (standard deviations reported in Appendix D). Notably, the proposed two-stage LSTM network consistently outperforms the designed baseline models. This is likely because our network is able to exploit spatial and temporal dependencies in CXR images; on the other hand, both baseline methods average convolutional and radiomic feature vectors respectively from $I_{t_1}, I_{t_2}, \dots, I_{t_{D-1}}$. We also provide breakdowns of different sub-variants of our configuration in an ablation setup and tested them to analyze the gradual improvement.

Variant-1: This variant used a single stage LSTM in which *LSTM-Spatial* was removed from our framework. A simple averaging of the CNN feature maps to construct the feature vector input for each time-point of *LSTM-Temporal* was used instead.

Variant-2: This variant of our configuration was designed without upsampling the minority label patches and not giving importance to edge patches from the neighboring zones.

The combined two-stage LSTM was incrementally developed from these more fundamental approaches, and was shown to outperform each by a significant margin. For example, in the middle zone of the left lung, the accuracy improved from 69% (in variant 1) and 70% (in variant 2) to 73% achieved through our proposed method. The improved performance of our model as compared to variant 2 also seems to suggest that contextual information from immediate adjoining lung zones plays an important role in the disease trajectory.

We used Cohen’s Kappa score ($\mathcal{K}$) to evaluate the agreement between predictions of each approach and the grades assigned by experts. $\mathcal{K}$ values were computed to be 0.503, 0.41, 0.426, 0.541, 0.362, 0.43 for L_1, L_2, L_3, R_1, R_2 , and R_3 zones, respectively. We noticed that our model prediction has a higher agreement with the radiologists in the upper lung zones. Also, the average $\mathcal{K}$ values for our approach, baseline 1, baseline 2, variant 1, and variant 2 were 0.445, 0.256, 0.219, 0.356, and 0.32 respectively. $\mathcal{K}$ values for other methods were significantly lower than our approach.

Table 1: Quantitative results (Accuracy, Precision, Recall) shown for Left lung zones (Upper, Middle, Lower)

Methods	Left Lung Upper								Left Lung Middle								Left Lung Lower										
	Acc(%)	Pre				Rec				Acc(%)	Pre				Rec				Acc(%)	Pre				Rec			
		0	1	2		0	1	2			0	1	2		0	1	2			0	1	2		0	1	2	
Baseline-1	60 ±4.76	0.55	0.66	0.52	0.51	0.68	0.52		64 ±5.47	0.5	0.71	0.59	0.47	0.74	0.56		58 ±4.89	0.5	0.62	0.56	0.47	0.71	0.48				
Baseline-2	57 ±4.63	0.48	0.67	0.48	0.41	0.64	0.60		61 ±5.80	0.48	0.7	0.56	0.52	0.64	0.60		55 ±4.64	0.5	0.60	0.50	0.52	0.70	0.43				
Variant-1	66 ±4.33	0.57	0.67	0.63	0.56	0.73	0.48		69 ±4.68	0.45	0.72	0.51	0.65	0.74	0.56		64 ±4.87	0.39	0.66	0.74	0.45	0.74	0.70				
Variant-2	68 ±3.51	0.53	0.74	0.41	0.67	0.78	0.63		70 ±2.89	0.43	0.68	0.55	0.47	0.69	0.77		61 ±4.16	0.35	0.57	0.64	0.48	0.81	0.64				
Our Approach	71 ±3.58	0.69	0.75	0.64	0.62	0.77	0.69		73 ±2.56	0.72	0.77	0.6	0.69	0.83	0.52		69 ±3.94	0.61	0.73	0.67	0.52	0.73	0.72				

Table 2: Quantitative results (Accuracy, Precision, Recall) shown for Right lung zones (Upper, Middle, Lower)

Methods	Right Lung Upper								Right Lung Middle								Right Lung Lower							
	Pre				Rec				Pre				Rec				Pre				Rec			
	0 1 2				0 1 2				0 1 2				0 1 2				0 1 2				0 1 2			
Baseline-1	64 $\pm$ 3.23	0.56	0.72	0.52	0.6	0.71	0.5	55 $\pm$ 4.08	0.45	0.60	0.51	0.40	0.63	0.51	58 $\pm$ 3.91	0.54	0.62	0.54	0.42	0.59	0.61			
Baseline-2	67 $\pm$ 3.38	0.63	0.72	0.6	0.7	0.65	0.66	52 $\pm$ 3.29	0.47	0.60	0.39	0.45	0.63	0.37	56 $\pm$ 4.36	0.4	0.65	0.51	0.42	0.63	0.51			
Variant-1	72 $\pm$ 3.09	0.65	0.69	0.52	0.67	0.73	0.62	66 $\pm$ 2.62	0.42	0.56	0.72	0.56	0.62	0.80	63 $\pm$ 3.85	0.50	0.62	0.57	0.60	0.61	0.52			
Variant-2	70 $\pm$ 2.81	0.84	0.62	0.67	0.70	0.64	0.57	62 $\pm$ 1.76	0.59	0.78	0.63	0.57	0.71	0.45	64 $\pm$ 3.27	0.77	0.43	0.66	0.40	0.66	0.66			
Our Approach	76 $\pm$ 2.33	0.68	0.84	0.66	0.73	0.80	0.66	67 $\pm$ 2.72	0.59	0.71	0.65	0.59	0.75	0.58	65 $\pm$ 3.73	0.5	0.67	0.67	0.5	0.65	0.69			

5. Conclusion

Imaging changes post onset of COVID-19 have been studied previously, albeit mostly in CT scans (Liang et al., 2020). Study of imaging evolution using machine learning techniques can complement the understanding of COVID-19 pathogenesis. Portable CXR is a more widely available modality and is an ideal tool to monitor imaging progression (Khullar et al., 2020). Here we present a novel multi-stage LSTM framework for the analysis of serial CXRs to predict changes in imaging severity. Unlike datasets used in other studies (Duchesne et al., 2020), we developed and validated our models on a very unique dataset of sequential CXRs collected over multiple days from two institutions. Unlike generative approaches, our model does not require registration between images from different timepoints. More importantly, our computational approach mirrors the clinical diagnostic interpretation process for medical images by uniquely taking advantage of the temporal evolution and spatial context of COVID-19 manifestation on CXRs. This enables more accurate predictions of the future evolution of the disease as compared to simpler computational models. By predicting future CXR severity scores in COVID-19 patients, our model might enable physicians to modulate the duration and timing of treatments (such as prone ventilation) in order to improve clinical outcomes. Furthermore, the proposed multi-stage LSTM approach can be applied to monitor progression in other diseases in which multiple sequential images are acquired.

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References

- American College of Radiology. ACR recommendations for the use of chest radiography and computed tomography (CT) for suspected COVID-19 infection, 2020. URL <https://www.acr.org/Advocacy-and-Economics/ACR-Position-Statements/Recommendations-for-Chest-Radiography-and-CT-for-Suspected-COVID19-Infection>. Library Catalog: www.acr.org.
- Joseph Bae, Saarthak Kapse, Gagandeep Singh, Tej Phatak, Jeremy Green, Nikhil Madan, and Prateek Prasanna. Predicting mechanical ventilation requirement and mortality in COVID-19 using radiomics and deep learning on chest radiographs: A multi-institutional study. *arXiv preprint arXiv:2007.08028*, 2020. URL <http://arxiv.org/abs/2007.08028>.
- Dzmitry Bahdanau, Kyunghyun Cho, and Yoshua Bengio. Neural machine translation by jointly learning to align and translate. *arXiv preprint arXiv:1409.0473*, 2014.
- Yoshua Bengio, Patrice Simard, and Paolo Frasconi. Learning long-term dependencies with gradient descent is difficult. In *IEEE transactions on neural network*, pages 157–166, 1994.
- L Chen, Z Zhou, D Sher, and et al. Combining many-objective radiomics and 3-dimensional convolutional neural network through evidential reasoning to predict lymph node metastasis in head and neck cancer. *Phys Med Biol.*, 2018.
- Y Cheng, F Wang, P Zhang, and J. Hu. Risk prediction with electronic health records: A deep learning approach. In *Proceedings of the 2016 SIAM International Conference on Data Mining*, pages 432–440, 2016.
- E Choi, M Bahadori, J Sun, J Kulas, A Schuetz, , and W. Stewart. Retain: An interpretable predictive model for healthcare using reverse time attention mechanism. *NIPS*, pages 3504–3512, 2016a.
- E Choi, MT Bahadori, A Schuetz, WF Stewart, and J. Sun. Doctor ai: predicting clinical events via recurrent neural networks. *Machine Learning for Healthcare Conference*, pages 301–318, 2016b.
- R Clark, S Wang, A Markham, N Trigoni, and H. Wen. Vidloc: A deep spatio-temporal model for 6-dof video-clip relocalization. In *Proceedings of the IEEE international conference on computer vision*, pages 6856–6864, 2017.
- Connor Cowan, Joseph Bae, Gagandeep Singh, Rohit Khullar, Shrey Shah, Nikhil Madan, and Prateek Prasanna. Evolution of chest radiograph radiomics and association with respiratory and inflammatory parameters in covid-19 patients undergoing prone ventilation: preliminary findings. In *Medical Imaging 2021: Computer-Aided Diagnosis*, volume 11597, page 1159709. International Society for Optics and Photonics, 2021.
- Ensheng Dong, Hongru Du, and Lauren Gardner. An interactive web-based dashboard to track COVID-19 in real time. *The Lancet Infectious Diseases*, 20(5):533–534, 2020. ISSN

14733099. doi: 10.1016/S1473-3099(20)30120-1. URL <https://linkinghub.elsevier.com/retrieve/pii/S1473309920301201>.
- Simon Duchesne, Daniel Gourdeau, Patrick Archambault, Carl Chartrand-Lefebvre, Louis Dieumegarde, Reza Forghani, Christian Gagne, Alexandre Hains, David Hornstein, Huy Le, et al. Tracking and predicting covid-19 radiological trajectory using deep learning on chest x-rays: Initial accuracy testing. *medRxiv*, 2020.
- Van Griethuysen, J J, A Fedorov, C Parmar, A Hosny, N Aucoin, V Narayan, RG Beets-Tan, JC Fillion-Robin, S Pieper, and HJ. Aerts. Computational radiomics system to decode the radiographic phenotype. *Cancer research*, 77(21):e104—e107, 2017.
- Claude Guérin, Jean Reignier, Jean-Christophe Richard, Pascal Beuret, Arnaud Gacouin, Thierry Boulain, Emmanuelle Mercier, Michel Badet, Alain Mercat, Olivier Baudin, Marc Clavel, Delphine Chatellier, Samir Jaber, Sylvène Rosselli, Jordi Mancebo, Michel Sirodot, Gilles Hilbert, Christian Bengler, Jack Richecoeur, Marc Gainnier, Frédérique Bayle, Gael Bourdin, Véronique Leray, Raphaele Girard, Loredana Baboi, and Louis Ayzac. Prone positioning in severe acute respiratory distress syndrome. *New England Journal of Medicine*, 368(23):2159–2168, 2013. ISSN 0028-4793. doi: 10.1056/NEJMoa1214103. URL <https://doi.org/10.1056/NEJMoa1214103>.
- Sepp Hochreiter and Jürgen Schmidhuber. Long short-term memory. In *Neural computation*, pages 1735–1780, 1997.
- Terrence C. H. Hui, Hau Wei Khoo, Barnaby E. Young, Salahudeen Mohamed Haja Mohideen, Yeong Shyan Lee, Chien Joo Lim, Yee Sin Leo, Gregory J. L. Kaw, David C. Lye, and Cher Heng Tan. Clinical utility of chest radiography for severe COVID-19. *Quantitative Imaging in Medicine and Surgery*, 10(7):1540–1550, 2020. ISSN 2223-4292. doi: 10.21037/qims-20-642. URL <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7358410/>.
- Jiewei Jiang, Xiyang Liu, Lin Liu, Shuai Wang, Erping Long, Haoqing Yang, Fuqiang Yuan, Deying Yu, Kai Zhang, Liming Wang, Zhenzhen Liu, Dongni Wang, Changzun Xi, Zhuoling Lin, Xiaohang Wu, Jiangtao Cui, Mingmin Zhu, and Haotian Lin. Predicting the progression of ophthalmic disease based on slit-lamp images using a deep temporal sequence network. *PloS One*, 13(7):e0201142, 2018. ISSN 1932-6203. doi: 10.1371/journal.pone.0201142.
- Rohit Khullar, Shrey Shah, Gagandeep Singh, Joseph Bae, Rishabh Gattu, Shubham Jain, Jeremy Green, Thiruvengadam Anandarangam, Marc Cohen, Nikhil Madan, et al. Effects of prone ventilation on oxygenation, inflammation, and lung infiltrates in covid-19 related acute respiratory distress syndrome: A retrospective cohort study. *Journal of clinical medicine*, 9(12):4129, 2020.
- Qicheng Lao, Thomas Fevens, and Boyu Wang. Leveraging disease progression learning for medical image recognition. pages 671–675. IEEE Computer Society, December 2018. ISBN 978-1-5386-5488-0. doi: 10.1109/BIBM.2018.8621245. URL <https://www.computer.org/csdl/proceedings-article/bibm/2018/08621245/17D45X0yjUK>.

- Ting Liang, Zhe Liu, Carol C Wu, Chao Jin, Huifang Zhao, Yan Wang, Zekun Wang, Fen Li, Jie Zhou, Shubo Cai, et al. Evolution of ct findings in patients with mild covid-19 pneumonia. *European radiology*, 30(9):4865–4873, 2020.
- Drew Linsley, Junkyung Kim, Vijay Veerabadran, Charles Windolf, and Thomas Serre. Learning long-range spatial dependencies with horizontal gated recurrent units. In *Advances in neural information processing systems*, pages 152–164, 2018.
- Z.C. Lipton, D.C. Kale, C. Elkan, and R. Wetzel. Learning to diagnose with lstm recurrent neural networks. *arXiv preprint arXiv:1511.03677*, 2015.
- S Liu, Z Zhu, N Ye, S Guadarrama, and K. Murphy. Improved image captioning via policy gradient optimization of spider. In *Proceedings of the IEEE international conference on computer vision*, pages 873–881, 2017.
- J Mao, J Huang, A Toshev, O Camburu, AL Yuille, and K. Murphy. Generation and comprehension of unambiguous object descriptions. In *Proceedings of the IEEE international conference on computer vision*, pages 11–20, 2016.
- Sundermeyer Martin, Schluter Ralf, and Ney Hermann. Lstm neural networks for language modeling. *ISCA*, 2012.
- Prateek Prasanna, Jay Patel, Sasan Partovi, Anant Madabhushi, and Pallavi Tiwari. Radiomic features from the peritumoral brain parenchyma on treatment-naïve multi-parametric mr imaging predict long versus short-term survival in glioblastoma multi-forme: preliminary findings. *European radiology*, 27(10):4188–4197, 2017.
- Feng Shi, Jun Wang, Jun Shi, Ziyang Wu, Qian Wang, Zhenyu Tang, Kelei He, Yinghuan Shi, and Dinggang Shen. Review of artificial intelligence techniques in imaging data acquisition, segmentation and diagnosis for COVID-19. *arXiv preprint arXiv:2004.0273*, 2020. URL <http://arxiv.org/abs/2004.02731>.
- Karen Simonyan and Andrew Zisserman. Very deep convolutional networks for large-scale image recognition. In *arXiv preprint arXiv:1409.1556*, 2014.
- Rajat Thawani, Michael McLane, Niha Beig, Soumya Ghose, Prateek Prasanna, Vamsidhar Velcheti, and Anant Madabhushi. Radiomics and radiogenomics in lung cancer: a review for the clinician. *Lung cancer*, 115:34–41, 2018.
- Danielle Toussie, Nicholas Voutsinas, Mark Finkelstein, Mario A. Cedillo, Sayan Manna, Samuel Z. Maron, Adam Jacobi, Michael Chung, Adam Bernheim, Corey Eber, Jose Concepcion, Zahi A. Fayad, and Yogesh Sean Gupta. Clinical and chest radiography features determine patient outcomes in young and middle-aged adults with COVID-19. *Radiology*, 297(1):E197–E206, 2020. ISSN 0033-8419. doi: 10.1148/radiol.2020201754. URL <https://pubs.rsna.org/doi/10.1148/radiol.2020201754>. Publisher: Radiological Society of North America.
- Chuang Wang, Andreas Rimner, Yu-Chi Hu, Neelam Tyagi, Jue Jiang, Ellen Yorke, Sadegh Riyahi, Gig Mageras, Joseph O. Deasy, and Pengpeng Zhang. Toward predicting the

- evolution of lung tumors during radiotherapy observed on a longitudinal MR imaging study via a deep learning algorithm. *Medical Physics*, 46(10):4699–4707, October 2019a. ISSN 2473-4209. doi: 10.1002/mp.13765.
- Chuang Wang, Andreas Rimner, Yu-Chi Hu, Neelam Tyagi, Jue Jiang, Ellen Yorke, Sadegh Riyahi, Gig Mageras, Joseph O. Deasy, and Pengpeng Zhang. Toward predicting the evolution of lung tumors during radiotherapy observed on a longitudinal mr imaging study via a deep learning algorithm. *Medical physics*, 46:4699–4707, September 2019b.
- Tingyan Wang, Robin G. Qiu, and Ming Yu. Predictive Modeling of the Progression of Alzheimer’s Disease with Recurrent Neural Networks. *Scientific Reports*, 8(1):9161, June 2018. ISSN 2045-2322. doi: 10.1038/s41598-018-27337-w. URL <https://www.nature.com/articles/s41598-018-27337-w>. Number: 1 Publisher: Nature Publishing Group.
- Yu M. Wang T, Qiu RG. Predictive modeling of the progression of alzheimer’s disease with recurrent neural networks. *Machine Learning for Healthcare Conference*, 8:1–12, 2018.
- Yiwen Xu, Ahmed Hosny, Roman Zeleznik, Chintan Parmar, Thibaud Coroller, Idalid Franco, Raymond H. Mak, and Hugo JWL Aerts. Deep learning predicts lung cancer treatment response from serial medical imaging. *Clinical Cancer Research*, 25:3266–3275, April 2019.
- L Zhang, L Lu, RM Summers, E Kebebew, and J. Yao. Convolutional invasion and expansion networks for tumor growth prediction. *IEEE Trans Med Imaging*, 37:638–648, 2018.
- Zhen Zuo, Bing Shuai, Gang Wang, Xiao Liu Liu, Xingxing wang, Bing Wang, and Yushi Chen. Convolutional recurrent neural networks: Learning spatial dependencies for image representation. In *Proceedings of the IEEE conference on computer vision and pattern recognition workshops*, pages 18–26, 2015.

Appendix A. Additional experiments

A new baseline (Baseline-3) is formulated as follows: For each of the 100 cases, we have CXRs from at least 4 timepoints. We aim to extract features from the images of the first three timepoints and predict the severity grade on the fourth image. We average the features from the patches at a single timepoint into a 1×4096 feature vector. 3 such feature vectors are extracted from each of 3 timepoints and concatenated into a 3×4096 feature vector. Hence, unlike Baseline - 1, we do not perform averaging across all timepoints but at each timepoint on an individual basis. In this way, we can capture the inherent features relevant to each timepoint within our encoded representation at greater capacity. The 3×4096 feature vector is eventually flattened and provided to 1D-NN classifier for the severity grade prediction.

A new variant (Variant-3) is designed. We have now averaged the feature vectors obtained from the last cell state of spatial LSTM at each timepoint. We provide this averaged feature representation as the context vector to our decoder module. Quantitative results for methods Variant-3 and Baseline-3 are presented in the following tables:

Table 3: Quantitative Results on Left lung zones

Methods	Left Lung Upper							Left Lung Middle							Left Lung Lower						
	Acc(%)	Pre			Rec			Acc(%)	Pre			Rec			Acc(%)	Pre			Rec		
		0	1	2	0	1	2		0	1	2	0	1	2		0	1	2	0	1	2
Baseline-3	54	0.56	0.71	0.45	0.57	0.62	0.48	63	0.42	0.77	0.58	0.54	0.71	0.63	51	0.56	0.66	0.40	0.42	0.63	0.56
Variant-3	65	0.47	0.80	0.45	0.69	0.73	0.66	69	0.52	0.64	0.63	0.49	0.72	0.74	63	0.56	0.52	0.67	0.41	0.79	0.60

Table 4: Quantitative Results on Right lung zones

Methods	Right Lung Upper							Right Lung Middle							Right Lung Lower						
	Acc(%)	Pre			Rec			Acc(%)	Pre			Rec			Acc(%)	Pre			Rec		
		0	1	2	0	1	2		0	1	2	0	1	2		0	1	2	0	1	2
Baseline-3	60	0.49	0.76	0.68	0.63	0.64	0.57	56	0.51	0.64	0.48	0.52	0.60	0.61	60	0.58	0.64	0.51	0.47	0.65	0.63
Variant-3	69	0.72	0.69	0.63	0.66	0.82	0.63	64	0.63	0.75	0.69	0.61	0.75	0.53	59	0.61	0.63	0.58	0.59	0.62	0.75

Appendix B. Plot of severity grade distribution across timepoints

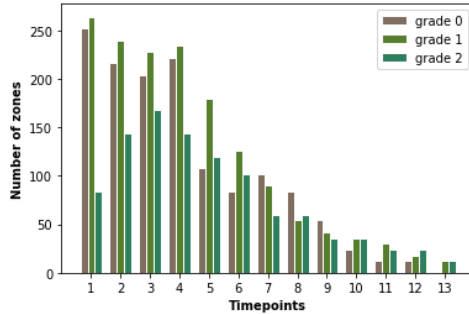


Figure 3: Distribution of severity grades (0,1,2) across 13 timepoints

Appendix C. Network configurations

While designing both *LSTM-Spatial* and *LSTM-Temporal*, we stacked two LSTM layers for better abstraction ability.

Table 5: CNN configuration

Type	Configuration
Input	256 × 256 patches
Convolution Max pooling	filter:8, kernel:5×5, auto-padding kernel:3, stride:2, auto-padding Output size: 8×128×128
Convolution Max pooling (2×)	filter:16, kernel:3×3, auto-padding kernel:3, stride: 2, auto-padding Output size: 16×32×32
Convolution Max pooling (2×)	filter:32, kernel:3×3, auto-padding kernel:3, stride: 2, auto-padding Output size: 32×8×8
Fully connected	256 neurons

Appendix D. Standard deviations

Table 6: Standard deviation of results (Accuracy, Precision, Recall) shown for Left lung zones (Upper, Middle, Lower)

Methods	Left Lung Upper							Left Lung Middle							Left Lung Lower						
	<i>std</i> (Acc)		<i>std</i> (Pre) 0 1 2			<i>std</i> (Rec) 0 1 2		<i>std</i> (Acc)		<i>std</i> (Pre) 0 1 2			<i>std</i> (Rec) 0 1 2		<i>std</i> (Acc)		<i>std</i> (Pre) 0 1 2			<i>std</i> (Rec) 0 1 2	
Baseline-1	4.76	0.032	0.024	0.022	0.025	0.023	0.019	5.47	0.017	0.029	0.031	0.021	0.027	0.03	4.89	0.024	0.022	0.031	0.035	0.017	0.024
Baseline-2	4.63	0.023	0.025	0.029	0.016	0.025	0.031	5.80	0.022	0.017	0.026	0.03	0.014	0.023	4.64	0.034	0.02	0.017	0.013	0.024	0.029
Variant-1	4.33	0.03	0.027	0.022	0.028	0.032	0.02	4.68	0.021	0.016	0.035	0.031	0.023	0.028	4.87	0.018	0.016	0.023	0.02	0.034	0.026
Variant-2	3.51	0.018	0.021	0.017	0.015	0.024	0.027	2.89	0.024	0.016	0.021	0.018	0.015	0.027	4.16	0.019	0.025	0.032	0.023	0.02	0.023
Our Approach	3.58	0.015	0.013	0.02	0.017	0.019	0.022	2.56	0.019	0.021	0.024	0.012	0.014	0.018	3.94	0.012	0.016	0.026	0.021	0.018	0.025

Table 7: Standard deviation of results (Accuracy, Precision, Recall) shown for Right lung zones (Upper, Middle, Lower)

Methods	Right Lung Upper						Right Lung Middle						Right Lung Lower								
	<i>std</i> (Pre)			<i>std</i> (Rec)			<i>std</i> (Pre)			<i>std</i> (Rec)			<i>std</i> (Acc)			<i>std</i> (Pre)			<i>std</i> (Rec)		
	0 1 2			0 1 2			0 1 2			0 1 2						0 1 2			0 1 2		
Baseline-1	3.23	0.034	0.03	0.037	0.025	0.021	0.032	4.08	0.032	0.036	0.021	0.028	0.029	0.035	3.91	0.019	0.027	0.03	0.023	0.028	0.034
Baseline-2	3.38	0.023	0.027	0.02	0.03	0.028	0.035	3.29	0.021	0.024	0.028	0.023	0.03	0.037	4.36	0.026	0.031	0.036	0.031	0.026	0.029
Variant-1	3.09	0.018	0.022	0.027	0.02	0.025	0.032	2.62	0.02	0.028	0.033	0.024	0.018	0.027	3.85	0.024	0.018	0.029	0.022	0.015	0.026
Variant-2	2.81	0.02	0.018	0.023	0.015	0.023	0.026	1.76	0.017	0.026	0.031	0.022	0.025	0.021	3.27	0.018	0.014	0.021	0.019	0.016	0.024
Our Approach	2.33	0.013	0.018	0.021	0.016	0.011	0.024	2.72	0.012	0.021	0.026	0.018	0.013	0.019	3.73	0.02	0.014	0.026	0.013	0.009	0.021

Appendix E. Dataset details

X-rays of 23 patients have been obtained from Newark Beth Israel Medical center. The remaining 77 case X-rays have been obtained from Stony Brook University Hospital. CXRs taken from Stony Brook University Hospital were acquired using the portable DRX Revolution machine developed by Carestream Health with AP image technique. Image acquisition parameters included average kVp of 90 and average mA of 2.8. CXRs taken from Newark Beth Israel Medical Center were acquired using GE Optima XR240 AMX portable machines. Image acquisition parameters included kVp 85 and mAs between 4 to 5 with automatic exposure control.

Appendix F. Baseline Architecture

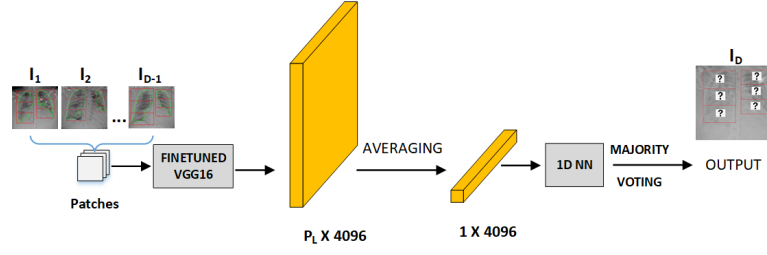


Figure 4: Architecture of the baseline approach