Enhanced Multimodal Timely Prediction of Pulmonary Fibrosis Progression with Uncertainty Estimation from Chest CT Images and Clinical Metadata

Mohamed Dahmane [a]

Computer Research Institute of Montreal (CRIM),
405 Av. Ogilvy #101, Montreal, Quebec, Canada

Keywords: CT Scans, Uncertainty Estimation, Pulmonary Fibrosis, Multimodal Deep Learning, Clinical Metadata.

Abstract: Pulmonary Fibrosis (PF) is a progressive chronic illness in which the lung tissues become increasingly scarred and damaged, leading to irreversible loss of their capacity to oxygenate vital organs. The specific causes of the illness are often unknown in many cases. Assessment of the severity of the lung disease is critical for physicians to diagnose PF early, control disease decline, and manage damage progression. The Forced Vital Capacity (FVC) of the lungs measured by a spirometer, is a good indicator of the severity of the condition of the lungs. In this work, we investigated an approach for early diagnosis of PF and showcased a multimodal architecture that predicts the FVC of patients at different stages of the disease. We propose an anti-Elu intermediate block and an anti-Relu confidence block to predict the pulmonary fibrosis progression. The uncertainty estimation block proved effective in predicting the FVC using data from initial spirometry measurements, clinical meta-data and CT images. Evaluation of the model on the OSIC pulmonary fibrosis progression dataset showed improved performance compared to state-of-the-art methods, with an average modified Laplace log-likelihood score of -6.8227 on a private test set.

1 INTRODUCTION

Pulmonary Fibrosis (PF) is often characterized by difficulty breathing, which can progressively worsen until the lungs are no longer able to supply vital organs with sufficient oxygen. In some cases, this damage can lead to serious health conditions such as Progressive Fibrosis Interstitial Lung Disease (PID) or Idiopathic Pulmonary Fibrosis (IPF). Timely and accurate diagnosis of the stage of pulmonary fibrosis is essential in reducing the burden of morbidity and mortality related to lung diseases. Chest imaging, such as X-ray and high-resolution computed tomography (HRCT), is one means of diagnosing PF, as well as other tests and procedures used by radiologists. However, accurately diagnosing PF, particularly predicting the stage of a progressive disease like PID, can be challenging. Radiological imaging provides a dedicated tool for visually assessing the presence of fibrotic tissue and determining the development of lung scarring.

Several research works propose imaging diagnosis approaches to aid radiologists in diagnosing lung diseases. Various consortiums worldwide, such as the Open Source Imaging Consortium (OSIC), Radiological Society of North America (RSNA), and Society of Thoracic Radiology (STR), bring together clinical researchers and data scientists to improve radiology-based imaging through deep learning and artificial intelligence. These organizations collect extensive datasets of high-resolution CT images and relevant metadata to develop advanced multimodal solutions.

In the literature, many research works have proposed using CT scans as a unimodal source of information to assess the evolution of Idiopathic Pulmonary Fibrosis. However, few studies have explored predicting the disease progression from multimodal data by predicting the Forced Vital Capacity (FVC), which is an important indicator of pulmonary function in IPF (du Bois et al., 2011). Moreover, in this work we enhanced the the uncertainty estimation by introducing a new anti-Relu block. The paper is organized as follows: Section 2 discusses the related works in computer-assisted fibrotic lung disease assessment. In section 3, we investigate the OSIC pulmonary fibrosis data used to evaluate our approach. Section 4 provides a detailed description of the methodology. Sec-

[a] https://orcid.org/0000-0002-2670-1433

tion 5, presents the evaluation and the performance of the proposed approach. Finally, section 6 gives conclusions and some insights on potential direction and future works.

2 RELATED WORK

In recent years, there has been an increasing trend in the prevalence of idiopathic pulmonary fibrosis (IPF) in the USA (Nalysnyk et al., 2012). In a study by (Raghu et al., 2014) on US Medicare patients aged 65 years and older, the authors found that patients with a median age of 79.4±7.2 years had a survival time of 3.8 years. The study also revealed an overall incidence ratio of 93.7 cases per 100k persons. Another study by (Hutchinson et al., 2015) reported an increase in mortality due to pulmonary fibrosis, ranging from 4.64 per 100k for Spain to 8.28 for England and Wales.

The integration of assitive vision and AI in healthcare has become essential due to the abundance of clinical data. CT scans are particularly useful for visually estimating the stage of lung deterioration. A clinical association was found between interstitial lung abnormalities (ILA) judged by high-resolution computed tomography (HRCT) and idiopathic pulmonary fibrosis (IPF), as reported in (Wells and Kokosi, 2016; Scatarige et al., 2003).

Motivated by recent advances in deep learning and computer vision, researchers have investigated various architectures for interstitial lung disease (IDL) detection, segmentation, and classification (Soffer et al., 2022). For instance, in a study by Walsh et al. (Walsh et al., 2018), deep learning was used to classify fibrotic lung diseases from high-resolution CT scans, and the algorithm outperformed 60 out of 91 radiologists with a median accuracy of 73.3% compared to the physicians' accuracy of 70%. In another study, Comelli et al. (Comelli et al., 2020) evaluated the UNet and E-Net segmentation models on 10 patients with idiopathic pulmonary fibrosis (IPF) and achieved a segmentation accuracy of 96% using the dice similarity coefficient without any radiologist intervention.

Kido et al. (Kido et al., 2022) developed a deep neural-network architecture for three-dimensional segmentation of lung nodules for lung cancer diagnosis from CT images. The 3D UNet model's performance was comparable to human experts with a dice similarity coefficient of 84.5% and 82.2%, respectively. The authors found that traditional machine learning techniques such as watershed and graph-cut provided lower accuracy compared to neural-network based models, with only 62.8% and 56.6% dice sim-

ilarity coefficient, respectively. In another study by (Christe et al., 2019), an integrated computer-aided diagnosis system for IPF was developed using deep learning on CT images. The system's performance was similar to that of radiologists under certain evaluation criteria. The study conducted by (Zucker et al., 2020) utilized a DCNN model based on ResNet-18 to predict Brasfield scores, which are indicative of various lung function features such as air trapping, linear markings, nodular cystic lesions, large lesions, and overall severity. The authors reported minimal differences between the model's Brasfield scores and those of the experts, except for the large lesion features, which had an average Spearman correlation of only 32% between the model and the radiologists. However, the correlation rate for large lesion scores showed a higher rate of 80.2%. In (Agarwala et al., 2020), a convolutional neural network was first trained on natural images and then fine-tuned on CT images to automatically segment interstitial lung disease (ILD) patterns such as emphysema, consolidation, and fibrosis. The reported results were acceptable, with a classification rate of 90% for fibrosis pattern segmentation.

Several research studies based their works on the OSIC data (Osic, 2023) to predict the decline in lung function severity which is assessed by measuring the forced vital capacity using a spirometer (Watters et al., 1986; Noth et al., 2021). The best performance was obtained using a bimodal deep learning model to process CT images and a neural net regressor to process patient clinical metadata. The objective function was optimized using a multiple quantile loss function. Efficient-Net was adopted as a backbone to process the images. In their study, (Wong et al., 2021) developed Fibros-Net, an architecture designed to predict fibrosis progression from chest scans. The model used CT images, spirometry measurements, and patient clinical metadata to estimate forced vital capacity (FVC) over a specific time interval from the OSIC data. The model achieved a good Laplace log-likelihood score of -6.8188. In contrast, FVC-Net from (Yadav et al., 2022) represents a different architecture that estimates FVC from derived honeycombing features, CT scans, and metadata of the OSIC dataset. The model showed a higher Laplace log-likelihood coefficient of -6.64. A study by (Mandal et al., 2020) compared the performance of machine learning models with CNN architecture in predicting FVC from CT images and patient metadata. The experiments showcased good results using an Elastic-Net regression method achieving a higher likelihood score of -6.73 on the OSIC dataset.

3 OSIC PULMONARY FIBROSIS PROGRESSION DATA

The data used in this study comprises CSV metadata and CT scans from the OSIC-Pulmonary Fibrosis Progression dataset (Osic, 2023). The CSV file contains metadata information such as age, sex, weeks, smoking status, and FVC percent, which is defined as the percentage of the typical FVC measure for a person with similar characteristics. Each patient has a unique ID, and a baseline chest CT scan is available corresponding to the reference visiting week, i.e., week=0. The FVC of the patient is measured as a function of the week number during the follow-up visits, which span approximately 1 to 2 years. Pre/post visits relating to the reference week are referred to by negative/positive values. Table 1 provides an example of the metadata for a particular patient.

Table 1: FVC ground-truth per week and metadata of patient ID00007637202177411956430.

Patient	Weeks	FVC	Percent	Age	Sex	SmokingStatus
ID00007637202177411956430	-4	2315	58.253649	79	Male	Ex-smoker
ID00007637202177411956430	5	2214	55.712129	79	Male	Ex-smoker
ID00007637202177411956430	7	2061	51.862104	79	Male	Ex-smoker
ID00007637202177411956430	9	2144	53.950679	79	Male	Ex-smoker
ID00007637202177411956430	11	2069	52.063412	79	Male	Ex-smoker

The task at hand is to predict the Forced Vital Capacity of a group of patients for expected weeks. There are 176 unique patients with an average of 9 visits per person, which occur at different weeks throughout the year. Figure 1 presents a histogram of the number of visiting weeks referred to as the number of instances per patient. Figure 2, depicts the distribution of 'smoking status' vs. 'gender' of the patients in the dataset. Male ex-smokers are the most prevalent group, while there are more never-smoked cases among female patients. The proportion of non-smokers is almost equal for both sexes. The figure highlights the importance of smoking as a risk factor for pulmonary diseases such as fibrosis.
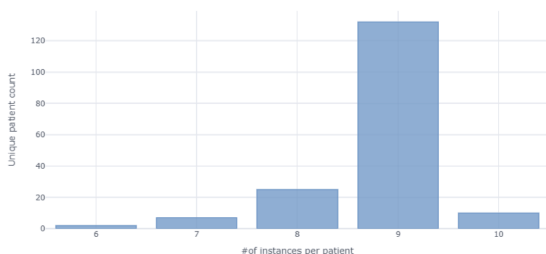

Figure 1: Instance distribution of unique patients.

The majority of the patients are around 67 years old with a roughly equal distribution of males and fe-
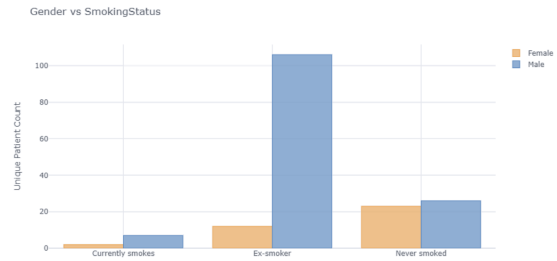

Figure 2: Instance distribution over smoking status and gender.

males as shown in Figure 3. This is consistent with the fact that, like many other diseases, age is a major risk factor for the incidence and prevalence of fibrosis. Patients over 60 years old are more likely to be diagnosed with fibrosis (Raghu et al., 2006).
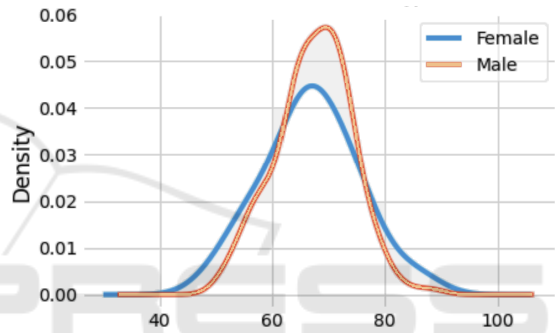

Figure 3: Distribution of the age of the patients by their gender.

In figure 4, the FVC distribution across 'Smoking status' and 'Gender' is shown. The measurements are spread over different intervals, and the average FVC value of male patients is higher than the corresponding female average for each smoking status, which is in line with expectations. Figure 5 depicts 28 slices of the chest Computerized Tomography scan of a particular patient. Notice that he number of images may differ for each person.

In the next section, the methodology is covered, and the predictive models of pulmonary fibrosis progression are described.

4 MULTIPLE QUANTILE REGRESSION-BASED MODELS

To estimate the FVC value, we propose a multi-modal model that incorporates computed tomography scans, demographic, and clinical data, including 'Age', 'FVC percent', 'Sex', 'Week number', and 'Smoking status'. First, $model_{CL}$ a clinical data-based model using only clinical information. Next,
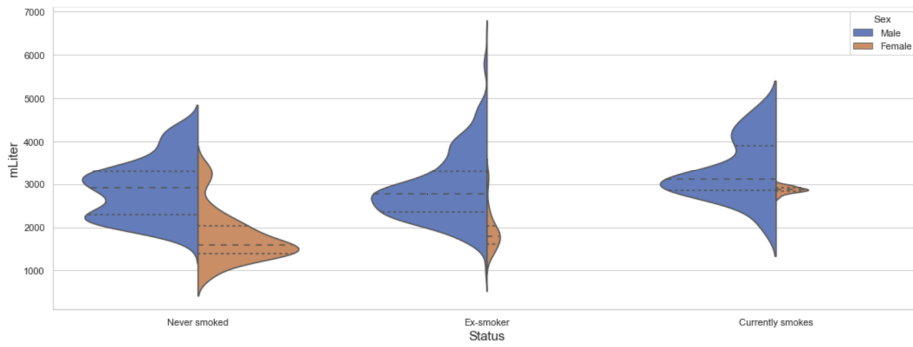
Figure 4: The measured Forced Vital Capacity distribution across smoking-status and gender.
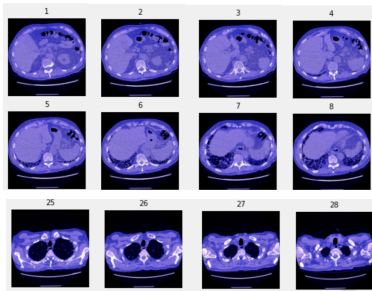

Figure 5: Chest CT-scan from patient ID00007637202177411956430.

the multimodal $model_{CL-CT}$ is trained and evaluated on both clinical and CT images. Finally, $model_{Blend}$ a blended model predicts the final FVC value and the confidence interval for each week of the considered period. The performance of the models is analyzed using the Laplace Log Likelihood (LLL) evaluation metric, which considers the uncertainty when evaluating the accuracy of the predictions. The problem is approached as multiple quantile regression problem.

4.1 Clinical Data-Based Model

The clinical data-based model $model_{CL}$ depends only on the clinical data. We applied our confidence block to the baseline model from (Lhagiimn, 2023). The input variables of the model consist of both continuous and categorical features. The continuous features includes 'Male', 'Female', 'Ex-smoker', 'Never smoked', 'Currently smokes', 'Age', 'Week', 'Base', 'Min percent norm', and 'Age week norm', while the categorical features consist of 'Gender' and 'Smoking status'. The model incorporates four sequential blocks and two input blocks. The categorical input version of the variables 'Gender' and 'Smoking status' are fed to the embedding layer of the preprocessing block for encoding whereas the continuous variables are fed directly to the self-attention block

with the encoded variables. The confidence block is plugged to the bottom component of the model (Fig. 9). As a quantile regressor, the model estimates the quantiles of a dependent variable expressed as the conditional median, low quantile, and high quantile respectively at 50%, 20%, and 80%. Hence, the estimation of the confidence interval is given in general as a concatenation of the outputs of 3 linear layers since the model (Fig. 6) has to predict a confidence range $[FVC_L, FVC_M, FVC_H]$ as in equation 1.
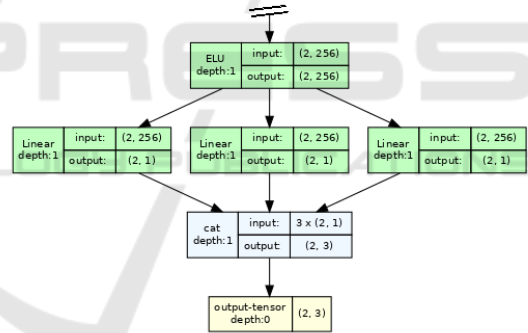

Figure 6: A conventional confidence block.

$$FVC_L = \texttt{Linear}(o_{block\,B})$$
$$FVC_M = \texttt{Linear}(o_{block\,B}) \qquad (1)$$
$$FVC_H = \texttt{Linear}(o_{block\,B})$$

We applied a anti-Elu layer (Eq. 2) to the output of intermediate `block A` (see Fig. 9). That handles both negative and positive activation with doubled output dimension (Fig. 7) compared to the traditional `Elu` layer (Eq. 3).

$$o^- = -\texttt{Elu}(-\texttt{Linear}(o_{block\,A}))$$
$$o^+ = -\texttt{Elu}(\texttt{Linear}(o_{block\,A})) \qquad (2)$$
$$o = \texttt{Concat}(o^-, o^+)$$

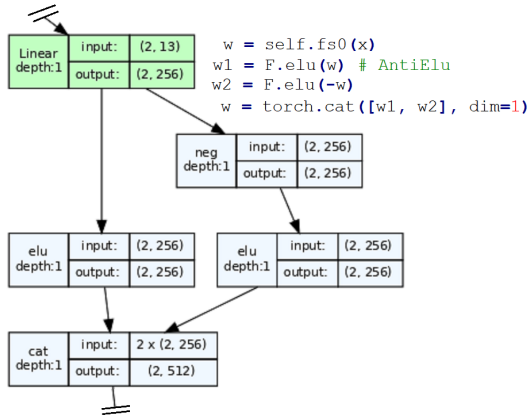$$o = \texttt{Elu}(\texttt{Linear}(o_{block\,A})) \qquad (3)$$

Figure 7: The anti-Elu block.

In comparison to a conventional confidence block, our confidence block (Fig. 8) uses anti-Relu layers to give the final estimate of the FVC in `block C` (see Fig. 9). As defined in (Eq. 4), the layer helps to enforce the inequality constraint of equation 5.
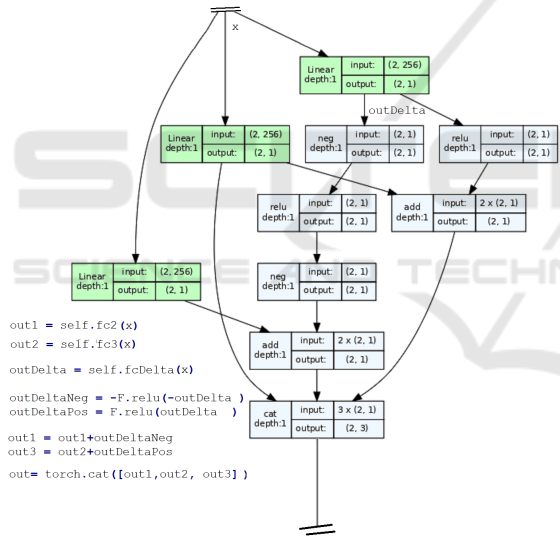

Figure 8: The anti-Relu-based confidence block.

$$x = \texttt{Linear}(\texttt{Concat}(o_{CL}, o_{CT}))$$
$$y = \texttt{Linear}(\texttt{Concat}(o_{CL}, o_{CT}))$$
$$\delta = \texttt{Linear}(\texttt{Concat}(o_{CL}, o_{CT}))$$
$$\delta^- = -\texttt{Relu}(-\delta) \tag{4}$$
$$\delta^+ = \texttt{Relu}(\delta)$$
$$\text{FVC} = \texttt{Concat}(x + \delta^-, y, y + \delta^+)$$

It should be noted that the conventional confidence of equation 1 may not ensure the desired inequality (Eq. 5) as it depends only on the model initialisation and the loss behavior during training.

$$\text{FVC}_L \leq \text{FVC}_M \leq \text{FVC}_H \tag{5}$$

4.2 Model Optimization

The mean pinball loss function is used to train the predictive model as a quantile regression model. As defined in (Eq. 6), the value of the loss is equivalent to half of the mean absolute error when the quantile parameter α is set to 0.5.

$$Pinball(y, \hat{y}) = \frac{1}{n} \sum_i^n \alpha \max(y_i - \hat{y}_i, 0)$$
$$+ (1 - \alpha) \max(\hat{y}_i - y_i, 0) \tag{6}$$

4.3 Evaluation Metric

Since the model should predict both the FVC and its confidence, we used the Laplace log likelihood (LLL) as defined in (Eq. 7). It is a well designed metric to handle the uncertainty on the predictions.

To avoid penalization from large errors, the maximum error is limited to 1000 ml. The minimum confidence values are clipped to 70 as to reflect the approximate measurement uncertainty in FVC. The final score is calculated by averaging the metric across all test set Patient-Weeks. For details and more specific considerations, refer to the modified version of the LLL used in the challenge [1].

$$\sigma_{clipped} = max(\sigma, 70)$$
$$\Delta = \min(\left| \text{FVC}_{gt} - \text{FVC}_{pred} \right|, 1000) \tag{7}$$
$$score = -\frac{\sqrt{2}\Delta}{\sigma_{clipped}} - \log \sqrt{2}\sigma_{clipped}$$

5 EXPERIMENTATION

The multimodal model portrayed in figure 9, aggregates the clinical data-based model $\texttt{model}_{CL}$ and the CT image-based model $\texttt{model}_{CT}$, in what follows we will refer to the multimodal model as $\texttt{model}_{CL,CT}$.

The CT scan-based architecture uses efficientNet-B5 as a backbone model with an input channel dimension of 1 as the scans are single channel. The classifier layer of the backbone model was replaced by a linear layer to extract the image embedding vector that is concatenated with the clinical embeddings.

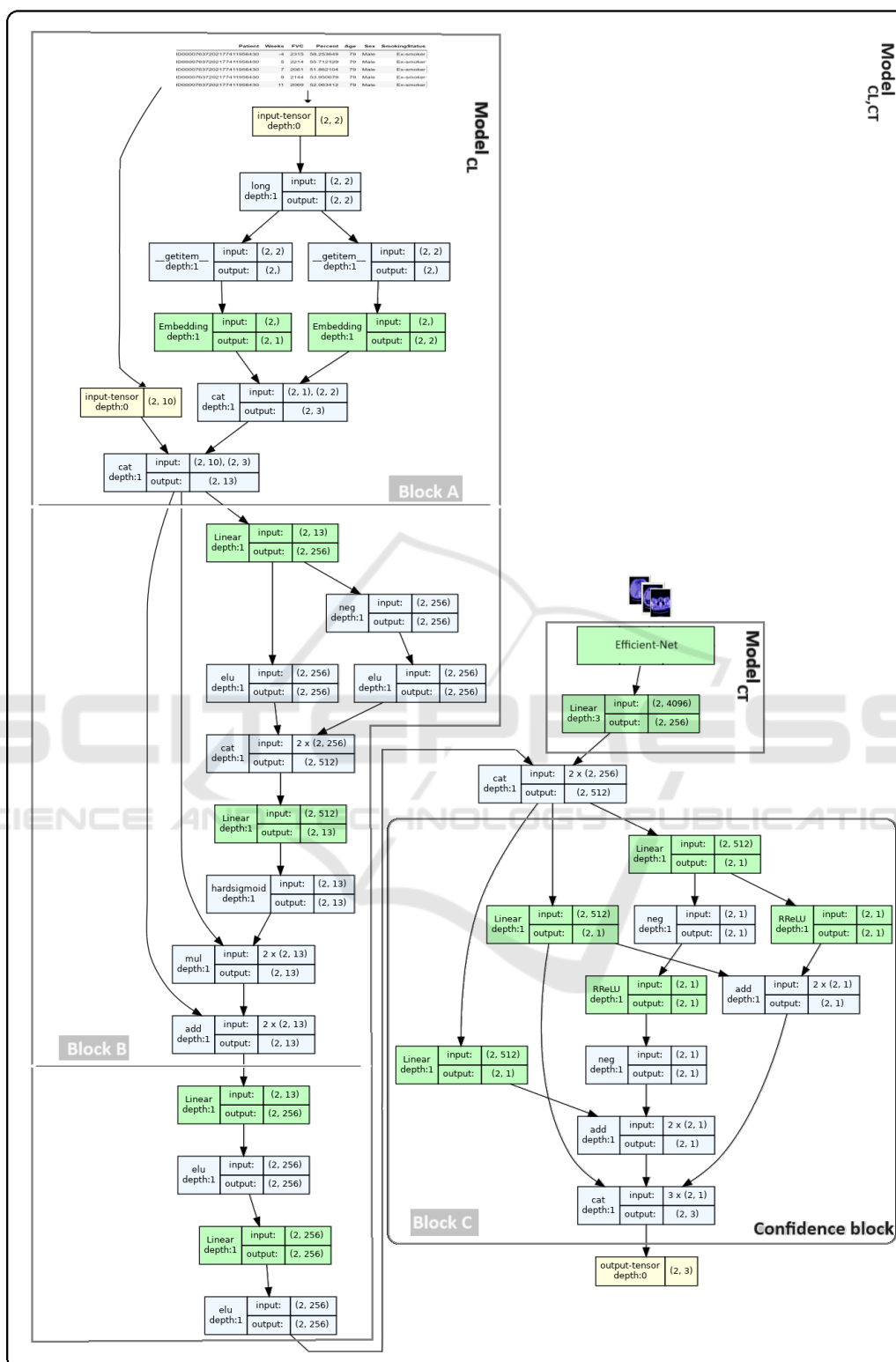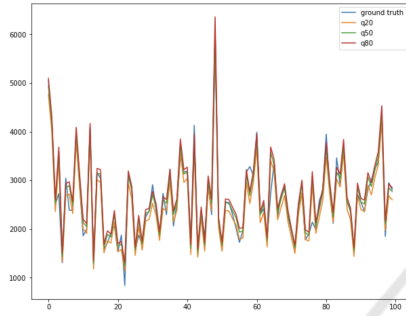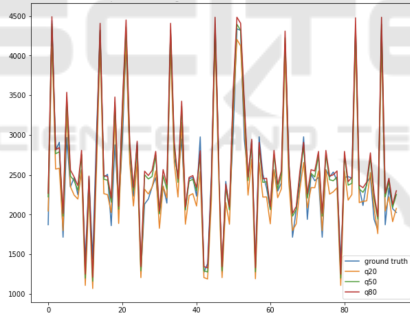[1] https://www.kaggle.com/competitions/osic-pulmonary-fibrosis-progression/overview/evaluation

Figure 9: The multimodal $\mathrm{model_{CL,CT}}$ concatenating the image model and the clinical data-based $\mathrm{model_{CL}}$. It combines three inputs, 10 continues, 2 categorical variables, and CT images.

In Figure 10, the predictions of the multiple quantile regression models $model_{CL}$ and $model_{CL,CT}$ are shown using the validation dataset. The plots corresponding to the low and high quantile, respectively, $FVC_{@.2}$ and $FVC_{@.8}$, suitably delimit the validation data. The plot referring to $FVC_{@.5}$ is well aligned with the groundtruth FVC data.

Figure 11 depicts the distribution of the FVC prediction uncertainty of $model_{CL}$ and $model_{CL,CT}$ on the validation data. The distributions show how well the distribution is preserved for both the clinical data-based $model_{CL}$ and the scan-based $model_{CL,CT}$. Globally, the distributions are almost similar.

(a) Clinical data $model_{CL}$

(b) Multimodal $model_{CL,CT}$

Figure 11: Uncertainty distribution from validation data.

tained a score of -6.8305, our enhanced $model_{Blend}$ achieved a superior LLL of -6.8227 using the proposed anti-Elu of the intermediate block and the anti-Relu confidence block.

Table 2: The Laplace log likelihood scores of the state-of-the-art models.

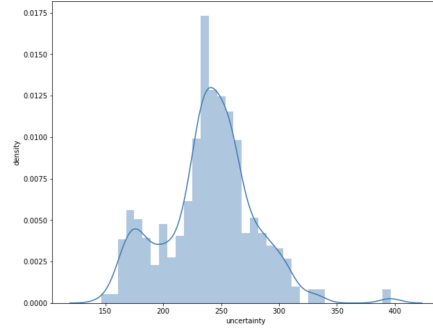| Method	LLL score ↓
Baseline (Lhagiimn, 2023)	-6.8272
OSIC 1st place (Osic, 2023)	-6.8305
- 2nd place	-6.8311
- 3rd place	-6.8336
$model_{CL}$ (ours)	-6.8234
$model_{Blend}$ (ours)	**-6.8227**

(a) Clinical data $model_{CL}$.

(b) Multimodal $model_{CL,CT}$.

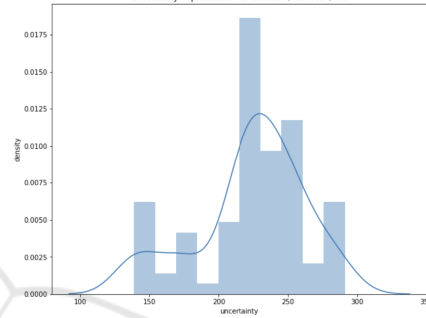Figure 10: Multiple quantile regression: FVC - predictions on the validation set.

The final FVC values and the corresponding uncertainty was formulated as a blending of $model_{CL}$ and $model_{CL,CT}$ predictions (Eq. 8). The weighting parameters $w_{CL,CT} = 0.1$ and $w_{CL} = 0.9$ that represent the contribution of the respective model were experimentally determined.

$$FVC_{Blend} = w_{CL,CT} FVC_{CL,CT} + w_{CL} FVC_{CL} \quad (8)$$

Table 2 summarizes the performance of the blended model on the private test set. The baseline model achieved a LLL score of -6.8272. Compared to the LLL of the state of the art approach which ob-

6 CONCLUSION

In this article, we investigated the problem of predicting the progression of pulmonary fibrosis (FVC) from clinical data and CT-scan images. The problem was approached as a multiple quantile regression problem. The visual scan data modality was compared to clinical metadata modality, and then used together in a multimodal model. The introduced anti-

Elu block intermediate block with the anti-Relu confidence block enhanced the multimodal timely prediction of the pulmonary fibrosis progression with uncertainty estimation. The achieved performance against the state-of-the-art models proved the effectiveness of the proposed multimodal quantile regression-based approach. This demonstrates once again that integrating the visual modality along with clinical metadata is beneficial for the robustness of the predictive model.

ACKNOWLEDGEMENTS

REFERENCES

Agarwala, S. et al. (2020). Deep learning for screening of interstitial lung disease patterns in high-resolution CT images. *Clinical Radiology*, 75(6):481.e1–481.e8.

Christe, A. et al. (2019). Computer-aided diagnosis of pulmonary fibrosis using deep learning and CT images. *Investigative Radiology*, 54(10):627–632.

Comelli, A. et al. (2020). Lung segmentation on high-resolution computerized tomography images using deep learning: A preliminary step for radiomics studies. *Journal of Imaging*, 6(11).

du Bois, R. M. et al. (2011). Forced vital capacity in patients with idiopathic pulmonary fibrosis. *American Journal of Respiratory and Critical Care Medicine*, 184(12):1382–1389.

Hutchinson, J. et al. (2015). Global incidence and mortality of idiopathic pulmonary fibrosis: a systematic review. *European Respiratory Journal*, 46(3):795–806.

Kido, S. et al. (2022). Segmentation of Lung Nodules on CT Images Using a Nested Three-Dimensional Fully Connected Convolutional Network. *Frontiers in Artificial Intelligence*, 5.

Lhagiimn (2023). www.kaggle.com/code/lhagiimn/solution-for-the-first-place-but-we-didn-t-select (accessed: 15.10.2023).

Mandal, S., Balas, V. E., Shaw, R. N., and Ghosh, A. (2020). Prediction analysis of idiopathic pulmonary fibrosis progression from osic dataset. In *2020 IEEE International Conference on Computing, Power and Communication Technologies (GUCON)*, pages 861–865.

Nalysnyk, L., Cid-Ruzafa, J., Rotella, P., and Esser, D. (2012). Incidence and prevalence of idiopathic pulmonary fibrosis: review of the literature. *European Respiratory Review*, 21(126):355–361.

Noth, I. et al. (2021). Home spirometry in patients with idiopathic pulmonary fibrosis: data from the INMARK trial. *Eur. Respir. J.*, 58(1):1–10.

Osic (2023). OSICcompetition leaderboard. www.kaggle.com/competitions/osic-pulmonary-fibrosis-progression/leaderboard (accessed: 15.10.2023).

Raghu, G., Chen, S.-Y., Yeh, W.-S., Maroni, B., Li, Q., Lee, Y.-C., and Collard, H. R. (2014). Idiopathic pulmonary fibrosis in us medicare beneficiaries aged 65 years and older: incidence, prevalence, and survival, 2001–11. *The Lancet Respiratory Medicine*, 2(7):566–572.

Raghu, G. et al. (2006). Incidence and prevalence of idiopathic pulmonary fibrosis. *American Journal of Respiratory and Critical Care Medicine*, 174(7):810–816.

Scatarige, J. C. et al. (2003). Utility of high-resolution ct for management of diffuse lung disease: Results of a survey of u.s. pulmonary physicians. *Academic Radiology*, 10(2):167–175.

Soffer, S. et al. (2022). Artificial intelligence for interstitial lung disease analysis on chest computed tomography: A systematic review. *Academic Radiology*, 29:S226–S235. Special Issue: Pulmonary.

Walsh, S. L. F. et al. (2018). Deep learning for classifying fibrotic lung disease on high-resolution computed tomography: a case-cohort study. *The Lancet Respiratory Medicine*, 6(11):837–845.

Watters, L. C. et al. (1986). A clinical, radiographic, and physiologic scoring system for the longitudinal assessment of patients with idiopathic pulmonary fibrosis. *American Review of Respiratory Disease*, 133(1):97–103.

Wells, A. U. and Kokosi, M. A. (2016). Subclinical interstitial lung abnormalities: Toward the early detection of idiopathic pulmonary fibrosis? *American Journal of Respiratory and Critical Care Medicine*, 194(12):1445–1446.

Wong, A. et al. (2021). Fibrosis-net: A tailored deep convolutional neural network design for prediction of pulmonary fibrosis progression from chest CT images. *Frontiers in Artificial Intelligence*, 4.

Yadav, A. et al. (2022). FVC-NET: An automated diagnosis of pulmonary fibrosis progression prediction using honeycombing and deep learning. *Computational Intelligence and Neuroscience*, 2022:1–12.

Zucker, E. J. et al. (2020). Deep learning to automate brasfield chest radiographic scoring for cystic fibrosis. *Journal of Cystic Fibrosis*, 19(1):131–138.