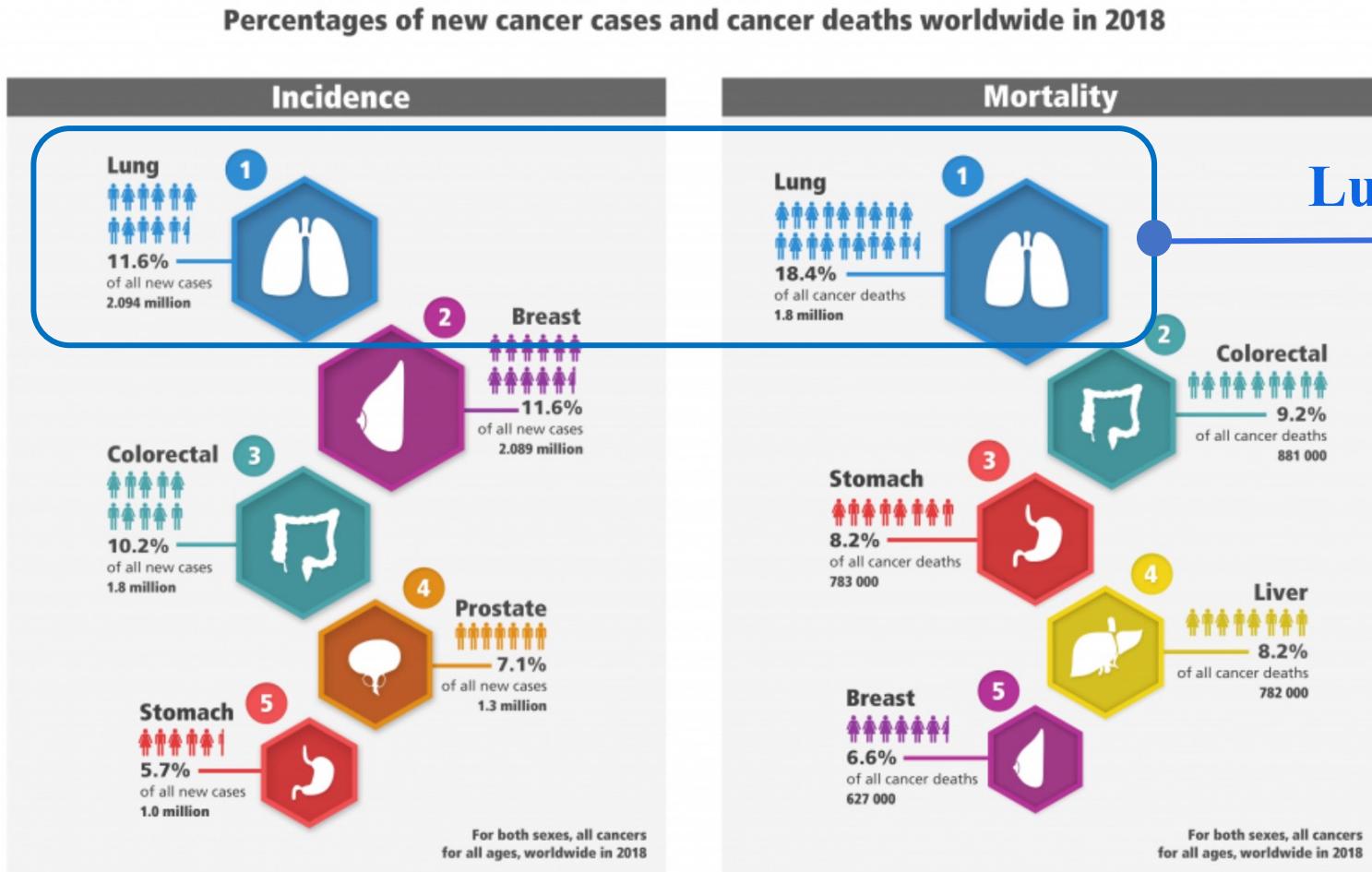

Pneumonia Intelligent Assistive Diagnostic System



Background Introduction



Data source: GLOBOCAN 2018
Available at Global Cancer Observatory (<http://gco.iarc.fr/>)
© International Agency for Research on Cancer 2018

Lung Cancer

Two main types are small-cell lung carcinoma (SCLC) and non-small-cell lung carcinoma (NSCLC).

Approved to be curable for treatment with immune checkpoint inhibitors (ICIs), but the use of ICIs may also cause checkpoint inhibitor pneumonitis.

Problem Statement: Checkpoint Inhibitor Pneumonitis

Checkpoint inhibitor pneumonitis (CIP) is an immune-related adverse event (irAE) that occurs after immune checkpoint inhibitor (ICI) therapy, particularly among patients receiving ICIs for lung cancer

ICIs in Brief: Immune check point inhibitors(ICIs) can restore the body's antitumor immune response and promote T cell-mediated clearance of tumor cells by blocking the inhibitory signaling pathways of T cells[2]

Major FDA Approvals of PD-1 / PD-L1 Inhibitors

| Drug | Commercial name | Owner | Target | First approval date |
|---------------|-----------------|----------------|--------|---------------------|
| Pembrolizumab | Keytruda | MSD | PD-1 | September 2014 |
| Nivolumab | Opdivo | BMS | PD-1 | December 2014 |
| Atezolizumab | Tecentriq | Roche | PD-L1 | May 2016 |
| Avelumab | Bevancio | EMD and Pfizer | PD-L1 | March 2017 |
| Durmalumab | Imfinzi | AstraZeneca | PD-L1 | May 2017 |

Source: Drugs.com



PD-1, PD-L1 and CTLA-4 inhibitors have become a key treatment for advanced malignant tumors.

*PD-1: Programmed Cell Death Protein 1

*PD-L1: Programmed death-ligand 1

*CTLA-4: Protein receptor on T cells to down regulate the immune responses

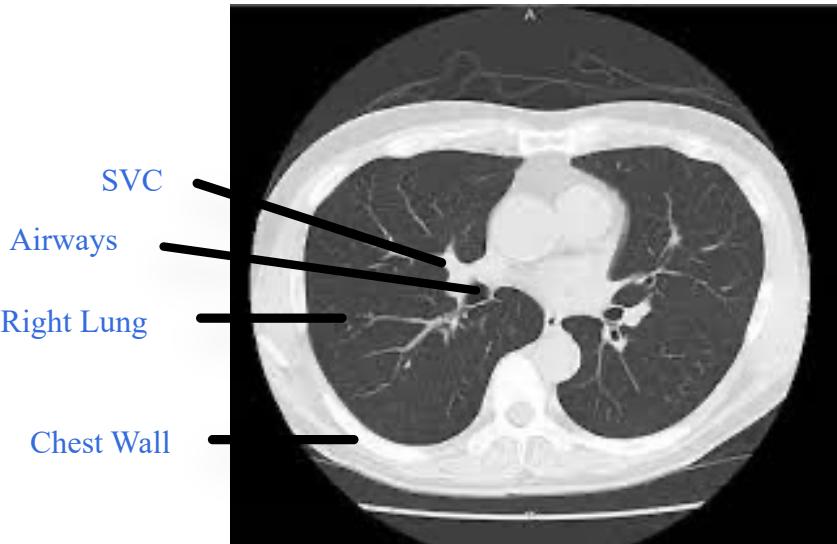
CIP occurs rate is 3% - 5% among patients received ICIs therapy [3][4]

The mortality rate of CIP is around 20% [5][6]

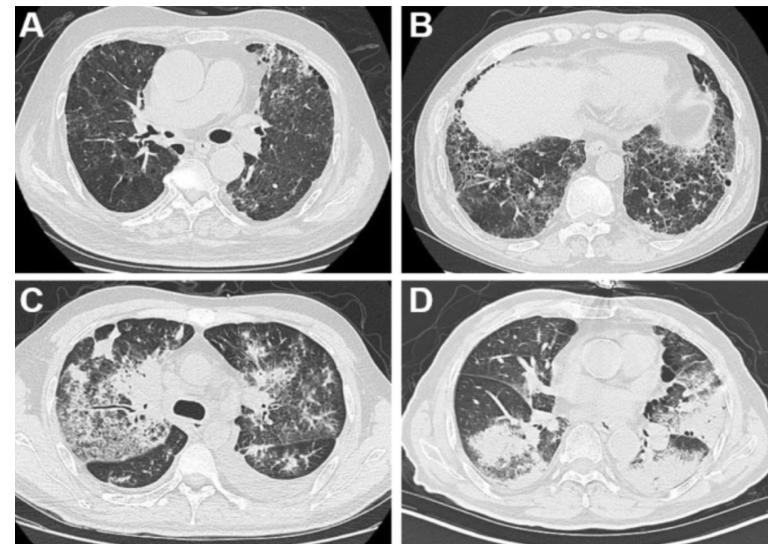
Induce Mechanisms of CIP: Current understanding of CIP is limited. Could be increased T cell activity, increased autoantibody levels, increased levels of inflammatory cytokines, and enhanced complement-mediated inflammation[7]

Problem Statement: Checkpoint Inhibitor Pneumonitis

CT Characteristics of CIP Patients



Normal Lung CT



CIP Patient's Lung CT [9]

CT scan is the imaging modality of choice for detecting CIP. Imaging symptoms of CIP include ground-glass opacity, consolidation, thickened interlobular septa, distraction branches, and nodules. CIP's clinical symptoms are nonspecific, and radiographic appearance is varied. Part of the difficulty in diagnosing CIP is the lack of specific clinical or radiographic markers.[8] [10]

- A. Ground-glass opacity in the left lung
- B. Bilateral lungs show GGO and reticulation shadows
- C. There is diffuse GGO in bilateral upper and lower lobe dorsal segments accompanied by consolidation and reticulation shadows.
- D. Right subpleural lower lung and left lung show consolidation shadows

Problem Statement: Outline

Perspective of CIP

High Mortality Rate: around 20%

Lack of Standard in Clinical Treatment

Highly various occurrence time from 9 days to 19.2 months

- 1/3 of the patients maybe asymptomatic
- A delayed diagnosis will seriously affect survival and treatment

Perspective of Technology

Application of deep learning technology in medical image analysis tasks has made outstanding achievements

- Lung nodule auxiliary diagnosis
- Liver tumor segmentation
- Chronic stroke lesion and pancreases segmentation

Problem Statement: Our Idea & Target

Idea

Assess and evaluate the prediction and diagnosis of CIP in patients with NSCLC receiving ICI treatment using advanced technical means

01

We will construct a clinical pneumonia dataset containing CIP and annotate it accurately at the pixel level using high-resolution CT images.

02

Using data mining and analysis of clinical data, we will screen for signs that pneumonia associated with immune checkpoint inhibitors will occur and combine these clinical indicators with a pneumonia identification model to forecast pneumonia occurrences.

03

We will develop doctor-oriented CIP auxiliary diagnostic software to provide pneumonia automatic labeling and quantitative analysis with high application value.

Target

The application of computer technology can reduce the labor cost and error rate of physicians when manually determining CIP and improve lung cancer cure rate by early intervention and treatment of immune adverse reactions.

Dataset: The Data Source & Data Availability Statements

Study Type: Retrospective

Data Source

- Covid-19 Dataset {
1) Hongqi Hospital Affiliated to Mudanjiang Medical University, Heilongjiang, CN - 35 patients, 24 males, 11 females
2) Zhangjiajie City People's Hospital, Hunan, CN - 72 patients, 29 males, 43 females
- CIP Dataset → 3) Harbin Medical University Cancer Hospital, Harbin – 141 patients

Data Availability Statements

Infections Diagnosis and Treatment

Infections diagnosed and treated according to Chinese National Health Commission Guidelines (Trial Version eight or earlier versions) (National Health Commission, 2020).

Ethics Committees

The study was approved by all hospital ethics committees. Informed consent was waived because the study was retrospective and posed no risk to patients. All CT data were desensitised when the experiments were conducted to remove private information such as the patient's hospital number, name and age.

Dataset: Evaluation Criteria

Age Classification Criteria

A World Health Organization age classification divided selected cases into the young (under 45 years), the middle-aged (45–59 years), and the elderly (60–89 years).



- Pathologically confirmed lung cancer
- Have received at least 1 ICI
- Full clinical and imaging data on file before and after immunotherapy



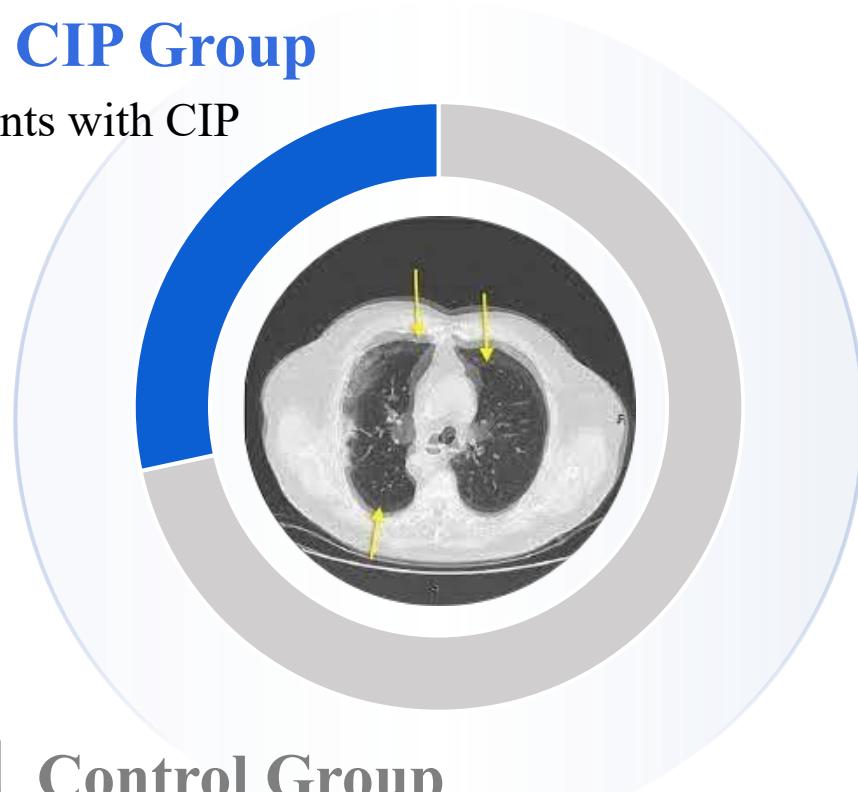
- Incomplete or missed clinical and imaging data
- Poor image quality
- Infectious diseases: bacteria, viruses, tuberculosis, fungi, Pneumocystis carinii
- Presence of autoimmune disease

Dataset: Description

The final screening yielded **141** cases of patients for inclusion in the next analysis

40 CIP Group

patients with CIP



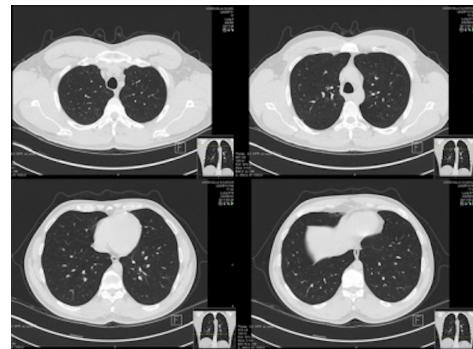
101 Control Group

patients without CIP

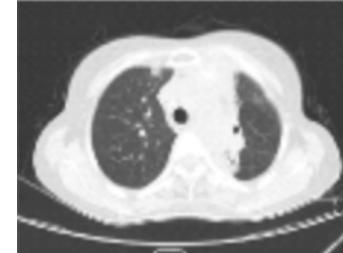
- Each positive patient has at least 2 stages of CT scan data and has CT data for their absence of CIP
- Each CT data consists of dozens to hundreds of slices with layer thicknesses ranging from 1mm to 10mm.

Dataset : Preprocessing

1. Data Preparation



CT scans (Dicom files)

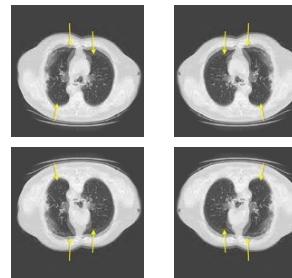


...

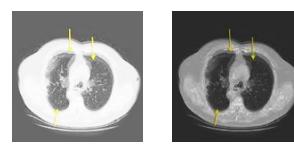


CT Images (PNG format)

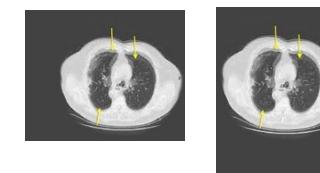
2. Data Augmentation



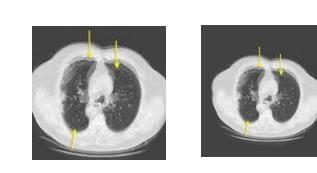
Flip & Rotation



Brightness
Adjustment



Translation



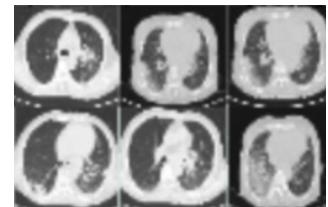
Scale & Crop



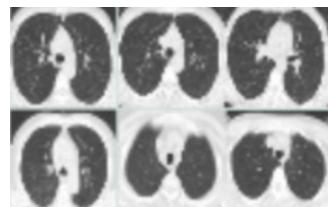
- **7-fold** increase in the number of CT slices
- Reduced probability of overfitting
- Improved **robustness** of deep learning models

Dataset : Preprocessing

3. Data Preprocessing



CIP-positive
2373 CT Images



CIP-negative
2688 CT Images



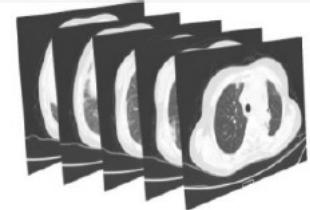
Shuffle



Training Set



Test Set



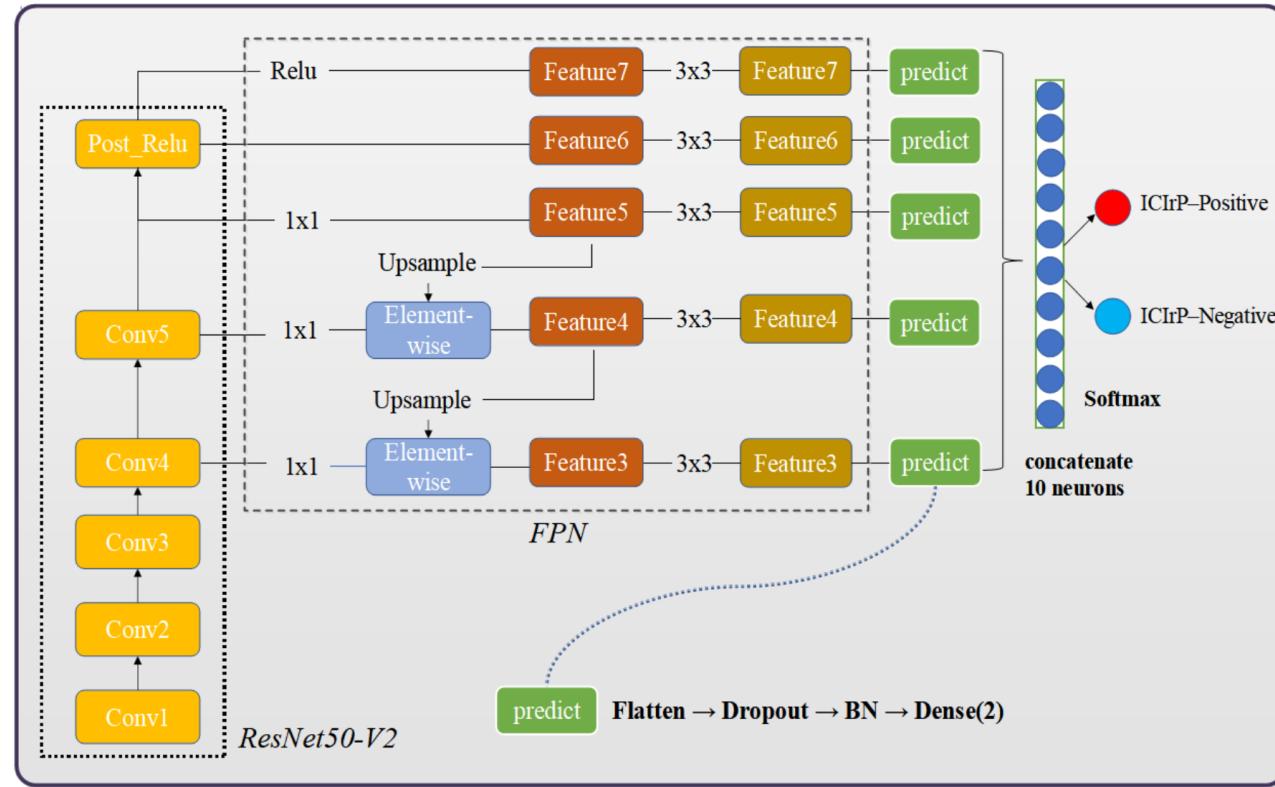
4. Pre-experiments

ResNet-50, ResNet-101, ResNet50_V2

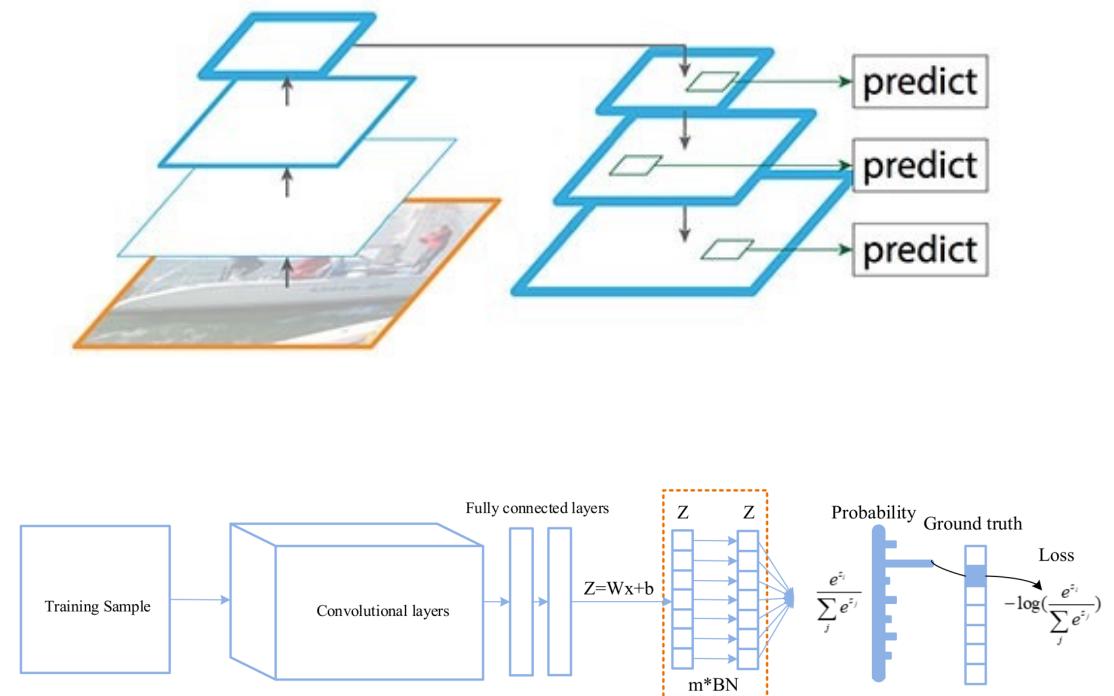
Approach 1 - Pneumonia diagnosis algorithm

Pneumonia diagnosis algorithm based on ResNet-50 V2 and Feature Pyramid Network

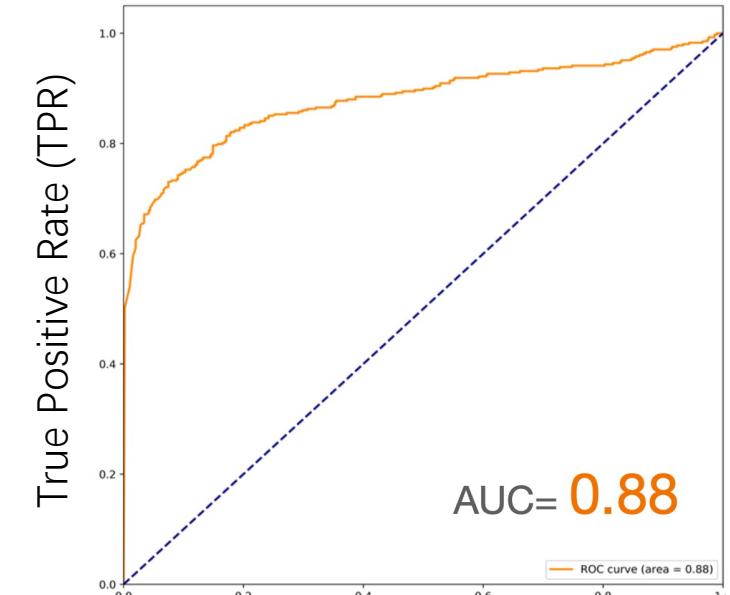
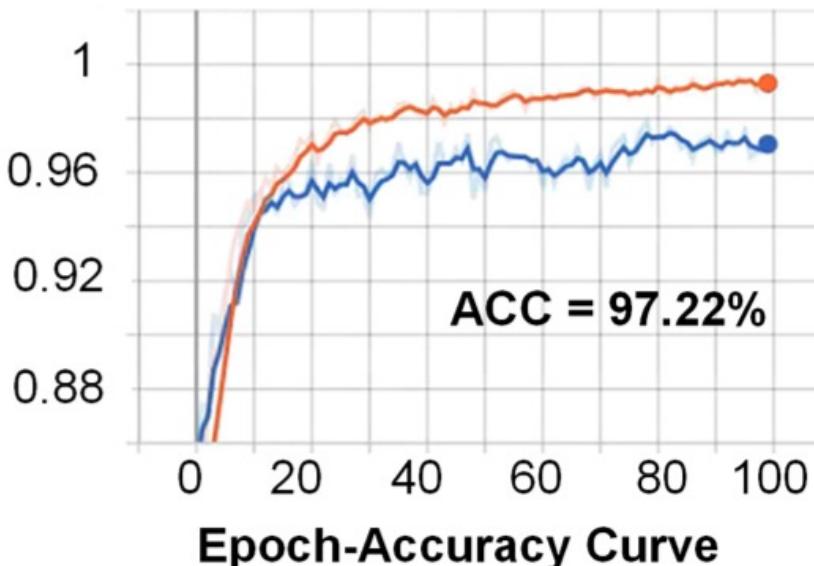
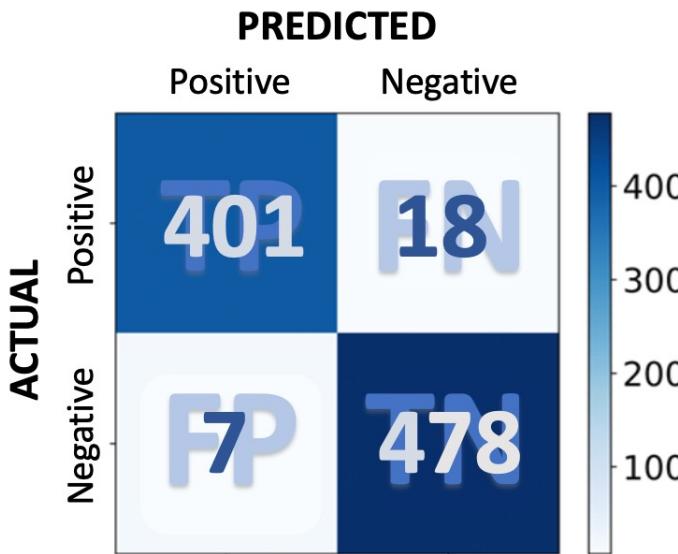
Used as a clinical aid to diagnosis, Fast, accurate and extremely practical



ResNet50_V3



Approach 1 - Pneumonia diagnosis algorithm



| | Accuracy | AUC |
|--------------|----------|------|
| Our Model | 97.22 | 0.88 |
| ResNet-50-V2 | 96.35 | 0.75 |
| Xception | 95.83 | 0.72 |

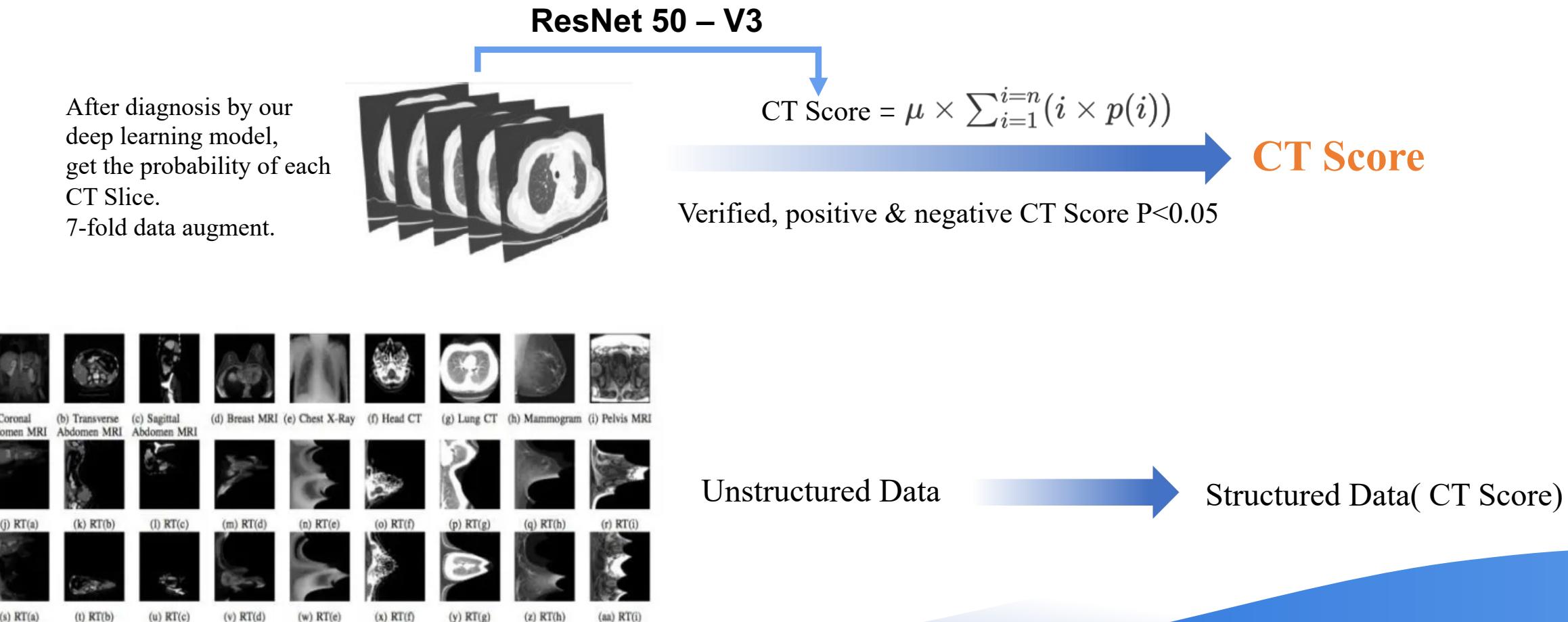
$$\text{Accuracy} = \frac{\text{TP} + \text{TN}}{\text{TP} + \text{FP} + \text{TN} + \text{FN}}$$

👉 97.22 %

Approach 2 - Non-invasive prognosis of immune pneumonia

Non-invasive prognosis of immune pneumonia based on data mining and Nomogram model

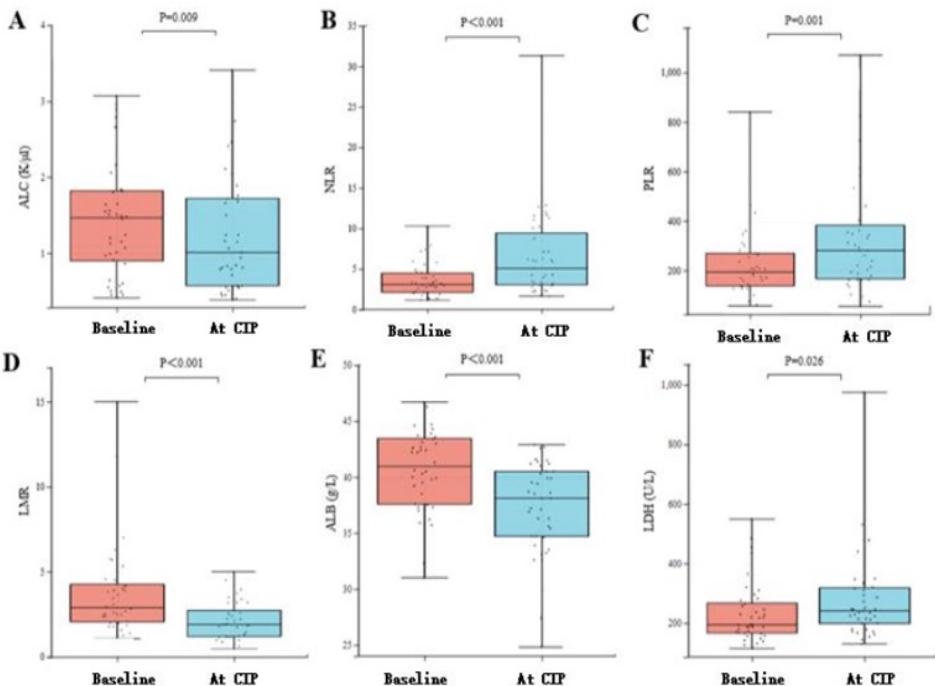
This model can be used for pre-diagnostic prediction and early detection of disease.



Approach 2 - Non-invasive prognosis of immune pneumonia

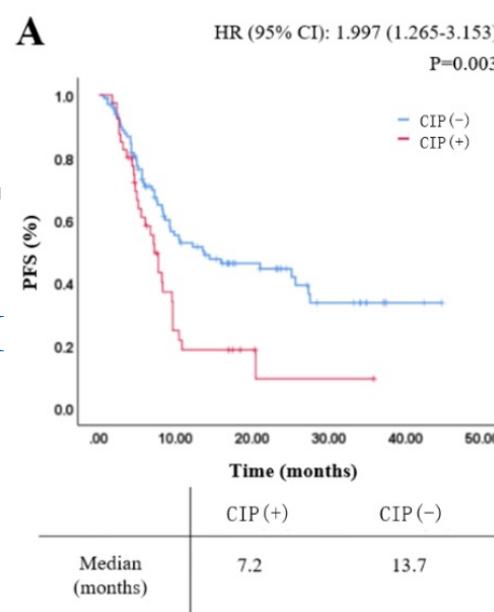
Non-invasive prognosis of immune pneumonia based on data mining and Nomogram model

This model can be used for pre-diagnostic prediction and early detection of disease.

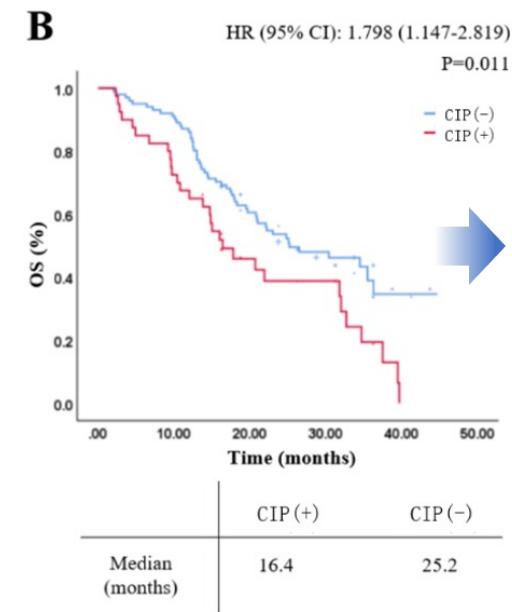


Mann Whitney U test

ALC
LDH



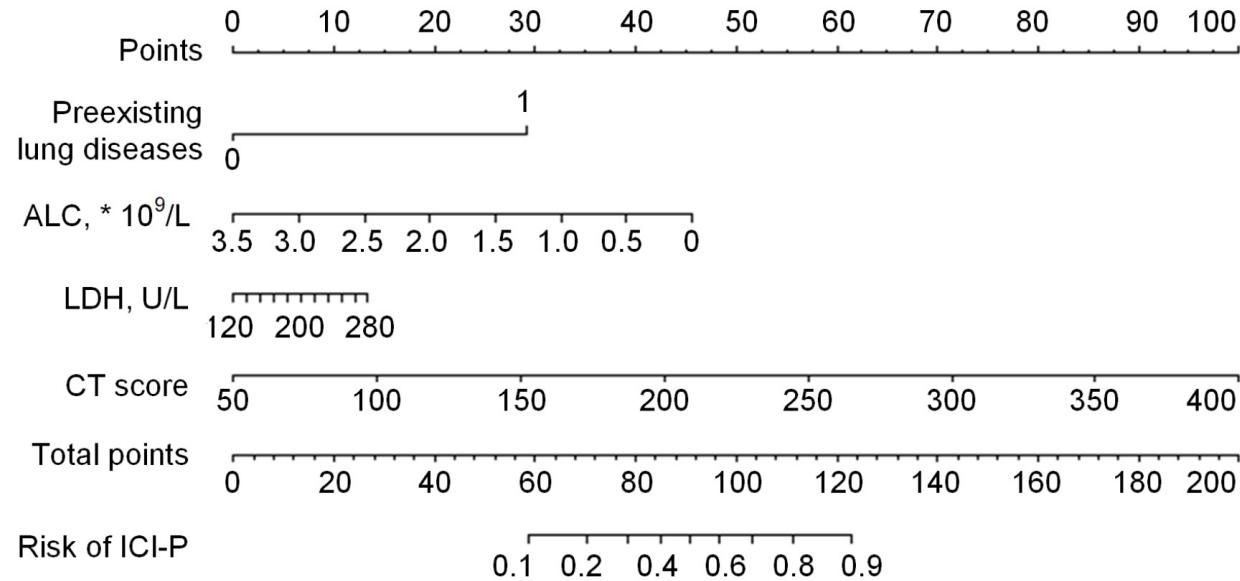
Kaplan-Meier survival curves



Preexisting
Pulmonary
Diseases

Approach 2 - Non-invasive prognosis of immune pneumonia

Nomogram Model



Nomogram Score =

Preexisting Pulmonary Diseases * 1.987-

ALC * 0.888 +

LDH * 0.005 +

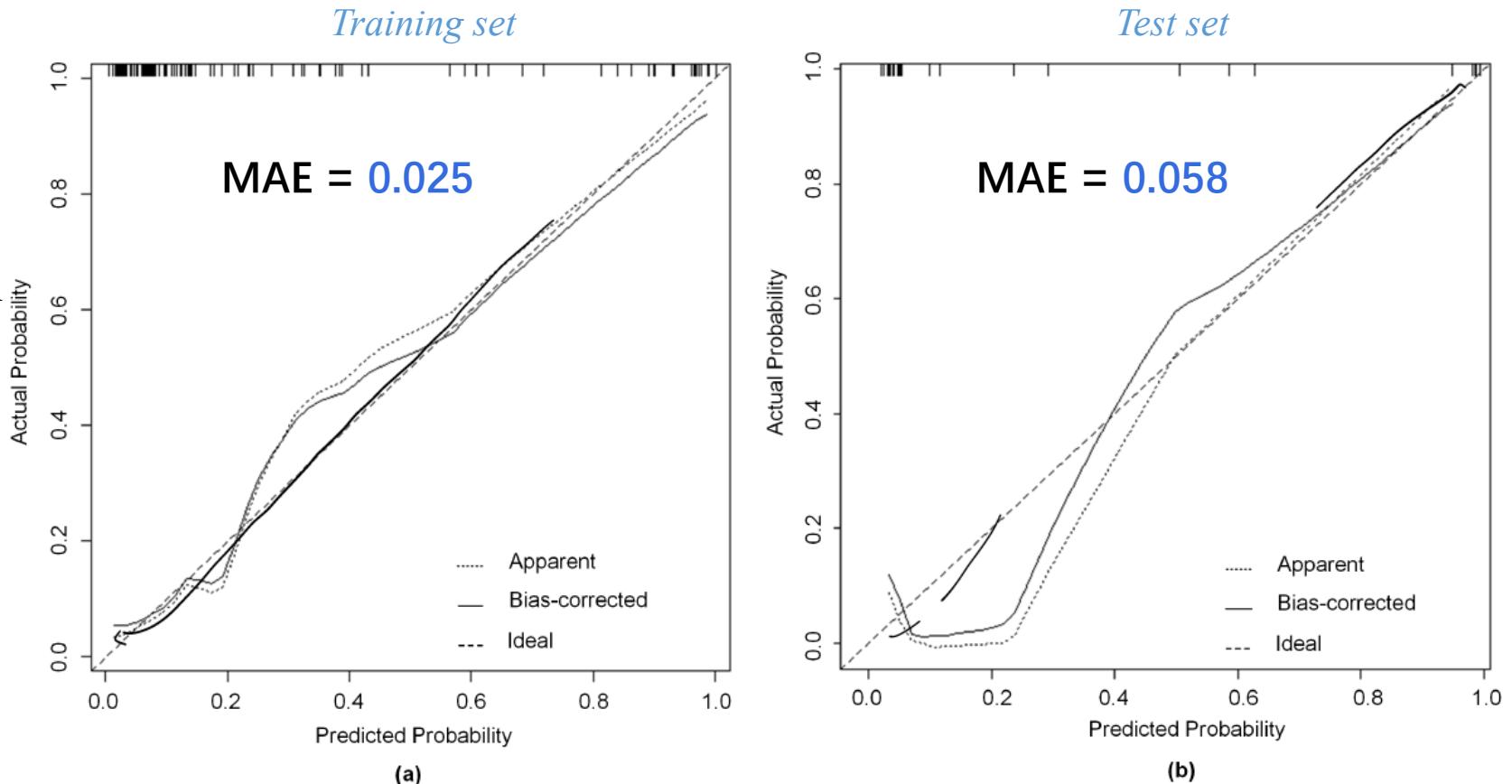
CT Score * 0.019 - 4.605

Approach 2 - Non-invasive prognosis of immune pneumonia

Calibration Curve

The **Mean Absolute Error** (MAE) of Calibration Curve for Nomogram on the training and test sets is **0.025** and **0.058**.

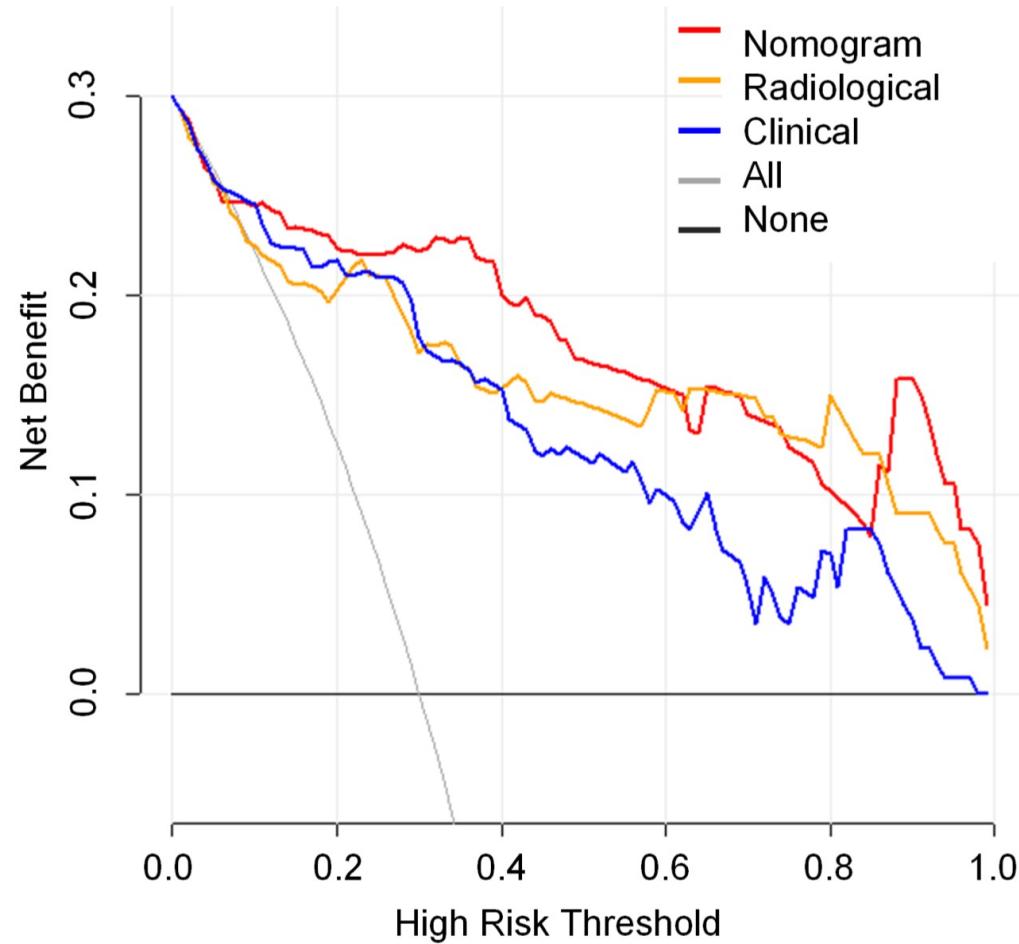
showing good agreement



Ideally, Calibration Curve is a **diagonal line** (**Predicted probability = Empirical probability**)

Approach 2 - Non-invasive prognosis of immune pneumonia

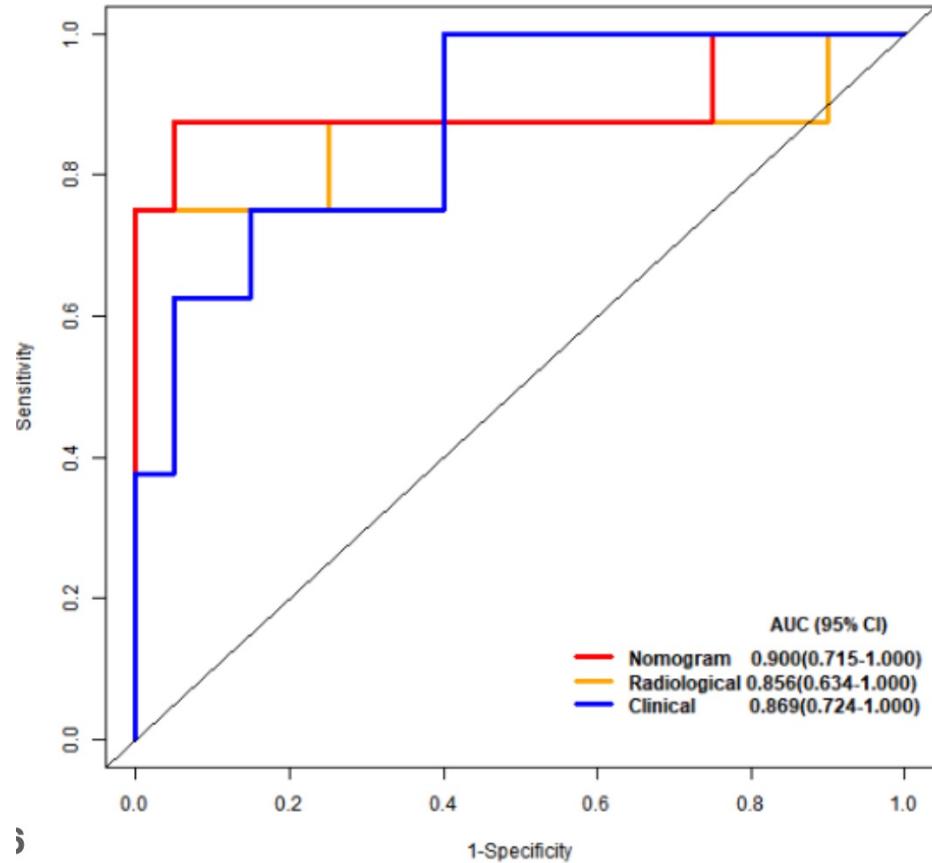
Decision Curve



Nomogram model
provide better net benefits than
Radiological & Clinical models

Approach 2 - Non-invasive prognosis of immune pneumonia

ROC Curve comparison



DL+ Data Mining model **AUC = 0.900**

Deep Learning model AUC = 0.856

Data Mining model AUC = 0.869

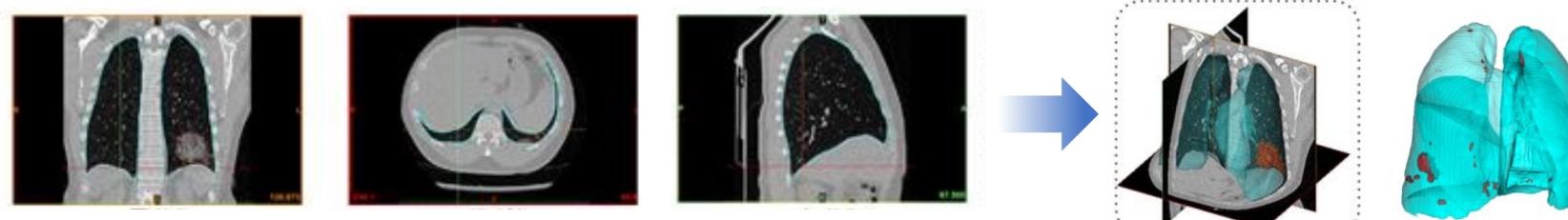


Nomogram model

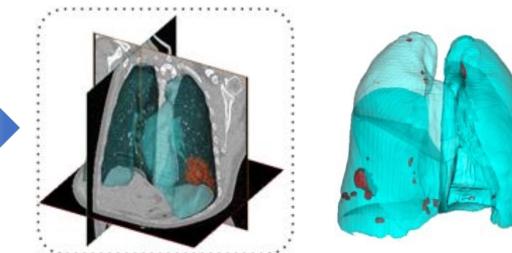
provide better net benefits than

Radiological & Clinical models

Approach 3 -Lesion segmentation & 3D reconstruction

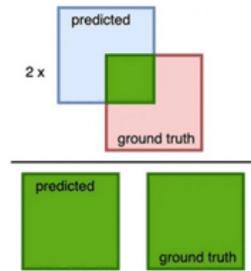


(A) Segmentation of lung parenchyma and pneumonia based on **lightweight 2.5D-U-Net**



(B) Fusion of three Masks

$$\text{DICE} = \frac{2 * |X \cap Y|}{|X| + |Y|}$$



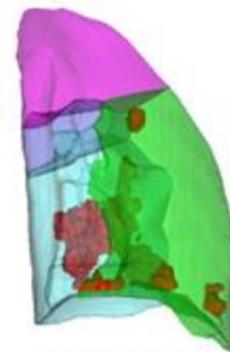
Eighteen segments



Bronchial



Five lobes of the lung



(D) Distribution of pneumonia on each lobe and lung segment by Boolean operations

(C) Stereoscopic segmentation of lobes and lung segments

Pneumonia Intelligent Assistive Diagnostic System

20+ Algorithms

2 Full
Workflows

- 1) **Non-invasive prognosis of immune pneumonia**
based on **Data Mining & Nomogram model**
- 2) **Pneumonia lesion segmentation model & 3D reconstruction**
based on **Lightweight 2.5D-UNet**

Cover Pre-diagnosis, Treatment & Post-healing

Our Project Features

Integrated

- Semantic segmentation of lesions
- 3D reconstruction of the lung
- Segmentation of parts of the lung lobes
- Quantitative analysis of disease conditions

Precise

- 97% high accuracy segmentation diagnosis of pulmonary inflammation.
- Reduce subjectivity and risk to patients

Innovation

- Selection of a lightweight 2.5D-Unet pneumonia lesion segmentation model
- Propose the concept of CT score
- Nomogram model-Non-invasive early diagnosis method
- Radiomics -based Pneumonia Classification algorithm for pneumonia

Fast

- 60 s fully complete Lung analysis, 3D modeling
- Reduce physician review time

Future Directions & Benefits

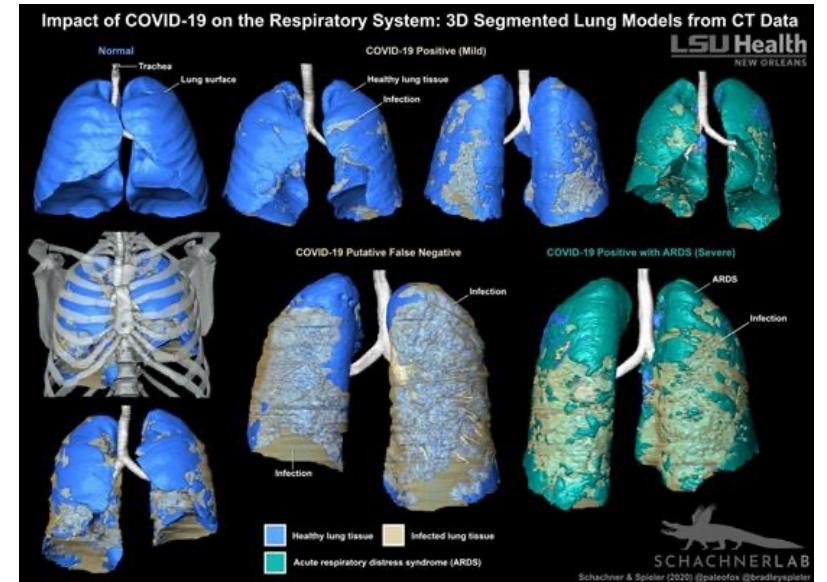
Covid-19 Pandemic & Other pneumonia

1) To Help Fight the COVID-19 Pandemic

Assisting doctors to effectively diagnose and treat the condition of patients with COVID-19.

2) Improve the rate of symmetry of information between doctors and patients

Improve the quantified intelligent pneumonia diagnosis and treatment system, improve the symmetry rate of doctor-patient information.



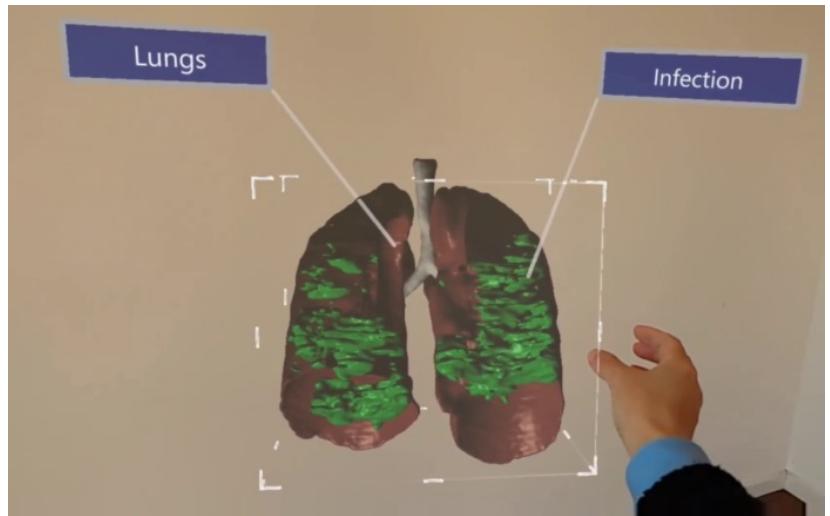
Future Directions & Benefits

AR Surgery + Telemedicine

1) Surgery Navigation

Pre-operative assessment, reduce the risk of surgery.

Visualize the infected lungs and at the same time link to the outcomes of AI analysis.



2) AR Telemedicine

AR telemedicine can realize video fusion, annotation and sketch between the guidance end and the directed end, which cannot be realized in the traditional video communication mode.



Future Directions & Benefits

Lab Teaching + Game

1) Lab Teaching

Enhance medicine Lab education and training.
Lead to better outcomes in patient care.



2) Game

Technical support for the development of medical laboratory teaching games.



Limitations & Considerations

Limited Sample Size

- Need more CT data, only 141 patients
- A larger sample size would provide a more accurate model

Need more combinations

- We need to combine **deep learning** and **dynamic changes in CIP imaging features** to develop and validate models that can predict the regression and prognosis of CIP. We can use deep learning to identify human histological and genetic features that predict the occurrence of CIP, which may help us elucidate the underlying mechanisms of CIP.

Applying the model to Singapore population

- The current model is based off patients in China
- We would have to apply for IRB approval to run the model against Singapore population to further evaluate the accuracy of the model