1 A collaborative online AI engine for CT-based COVID-19 diagnosis

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41 Abstract

42 Artificial intelligence can potentially provide a substantial role in streamlining chest computed 43 tomography (CT) diagnosis of COVID-19 patients. However, several critical hurdles have 44 impeded the development of robust AI model, which include deficiency, isolation, and 45 heterogeneity of CT data generated from diverse institutions. These bring about lack of generalization of AI model and therefore prevent it from applications in clinical practices. To 46 47 overcome this, we proposed a federated learning-based Unified CT-COVID AI Diagnostic 48 Initiative (UCADI, http://www.ai-ct-covid.team/), a decentralized architecture where the AI 49 model is distributed to and executed at each host institution with the data sources or client ends 50 for training and inferencing without sharing individual patient data. Specifically, we firstly 51 developed an initial AI CT model based on data collected from three Tongji hospitals in Wuhan. 52 After model evaluation, we found that the initial model can identify COVID from Tongji CT test 53 data at near radiologist-level (97.5% sensitivity) but performed worse when it was tested on 54 COVID cases from Wuhan Union Hospital (72% sensitivity), indicating a lack of model 55 generalization. Next, we used the publicly available UCADI framework to build a federated 56 model which integrated COVID CT cases from the Tongji hospitals and Wuhan Union hospital 57 (WU) without transferring the WU data. The federated model not only performed similarly on 58 Tongji test data but improved the detection sensitivity (98%) on WU test cases. The UCADI 59 framework will allow participants worldwide to use and contribute to the model, to deliver a 60 real-world, globally built and validated clinic CT-COVID AI tool. This effort directly supports 61 the United Nations Sustainable Development Goals' number 3, Good Health and Well-Being, 62 and allows sharing and transferring of knowledge to fight this devastating disease around the 63 world.

64 Introduction

65 COVID-19 has become a global pandemic. RT-PCR was adopted as the main diagnostic 66 modality to detect viral nucleotide in specimens from patients with suspected COVID-19 67 infection and remained as the gold standard for active disease confirmation. However, due to the greatly variable disease course in different patients, the detection sensitivity is only 60%-71% ¹⁻³ 68 leading to considerable false negative results. These symptomatic COVID 19 patients and 69 70 asymptomatic carriers with false negative RT-PCR results pose a significant public threat to the 71 community as they may be contagious. As such, clinicians and researchers have made 72 tremendous efforts searching for alternative and/or complementary modalities to improve the 73 diagnostic accuracy for COVID-19. 74 COVID-19 patients present with certain unique radiological features on chest computed 75 tomography (CT) scans including ground glass opacity, interlobular septal thickening, consolidation etc., that have been used to differentiate COVID-19 from other bacterial or viral 76 pneumonia or healthy individuals⁴⁻⁷. CT has been utilized for diagnosis of COVID-19 in some 77 countries and regions with reportedly sensitivity of 56-98%^{2,3}. However, these radiologic 78 79 features are not specifically tied to COVID-19 pneumonia and the diagnostic accuracy heavily 80 depending on radiologists' experience. Particularly, insufficient empirical understanding of the 81 radiological morphology characteristic of this unknown pneumonia resulted in inconsistent 82 sensitivity and specificity by varying radiologists in identifying and assessing COVID-19. A 83 recent study has reported substantial differences in the specificity in differentiation of COVID-19 from other viral pneumonia by different radiologists⁸. Meanwhile, CT-based diagnostic 84 85 approaches have led to substantial challenges as many suspected cases will eventually need

86 laboratory confirmation. Therefore, there is an imperative demand for an accurate and specific 87 intelligent automatic method to help to address the clinical deficiency in current CT approaches. 88 Successful development of an automatic method depends on a tremendous amount of imaging 89 data with high quality clinical annotation for training an artificial intelligence (AI) model. We 90 confronted several challenges for developing a robust and universal AI tool for precise COVID-91 19 diagnosis: 1) data deficiency. Our high-quality CT data sets were only a small sampling of the 92 full infected cohorts and therefore it is unlikely we captured the full set radiological features. 2) 93 data isolation, Data derived across multiple centers was difficult to transfer for training due to 94 security, privacy, and data size concerns. and 3) data heterogeneity. Datasets were generated by 95 different scanner machines which introduces an additional layer of complexity to the training 96 because every vendor provides some unique capabilities. Furthermore, it is unknown whether 97 COVID-19 patients in diverse geographic locations, ethnic groups, or demographics show 98 similar or distinct CT image patterns. All of these may contribute to a lack of generalization for 99 an AI model, which a serious issue for a global AI clinical solution. 100 To solve this problem, we propose here a Unified CT-COVID AI Diagnostic Initiative (UCADI) 101 to deliver an AI-based CT diagnostic tool. We base our developmental philosophy on the 102 concept of federated learning, which enables machine learning engineers and medical data 103 scientists to work seamlessly and collectively with decentralized CT data without sharing 104 individual patient data, and therefore every participating institution can contribute to AI training 105 results of CT-COVID studies to a continuously-evolved and improved central AI model and help 106 to provide people worldwide an effective AI model for precise CT-COVID diagnosis (Fig.1).

107

108 Results

109 Building AI model using pooled data

110 We firstly gathered a dataset of 5732 CT images from 1276 individuals collected from multiple 111 centers of Tongji Hospital including Tongji Hospital Main Campus (3457 CT images from 800 112 studies), Tongji Optical Valley Hospital (882 CT images from 227 studies), and Tongji Sino-113 French New City Hospital (1393 CT images from 241 studies) (Table 1 for patient information). 114 Among these patients, 432 patients had COVID-19 pneumonia confirmed by RT-PCR; 76 115 patients had other viral pneumonia including 7 cases with respiratory syncytial virus (RSV), 13 116 with EB virus, 16 with cytomegalovirus, 3 with influenza A, 1 with parainfluenza virus and 36 117 with mixed virus pneumonia that were confirmed PCR or antibodies against corresponding 118 viruses; 350 patients had bacterial pneumonia confirmed CT scan and bacterial culture. The 119 remaining 418 individuals having clinical symptoms of respiratory system were healthy 120 individuals who had normal chest CT scans. Based on the dataset, we developed an initial deep 121 learning model by using convolutional neural networks (CNN) (detailed in Methods). 122 Next, we validated the predictive performance of the CNN through a classification task: four-123 class pneumonia partition—four featured clinical diagnoses in determining suspected cases of 124 COVID-19. This task aimed at distinguishing COVID-19 (Fig. 3. i) from three types of non-125 COVID-19 (Fig. 3. ii) including other viral pneumonia, bacterial pneumonia, and healthy cases 126 (d, e, and f in Fig. 3). We selected 20% of 1036 CT cases in training and validation set for 5-fold 127 cross-validation. The CNN demonstrated the validation result that achieved overall sensitivity of 128 77.2% and specificity of 91.9%.

We further tested the previously trained CNN by conducting a comparative study of same task 129 130 between the CNN and expert radiologists using previously separated test set (detailed in 131 Methods). Six qualified radiologists (ZL [18 years' experience], LYM [9 years' experience], 132 YZL [9 years' experience], COX [8 years' experience], HLM [4 years' experience], GC [4 133 years' experience]) from department of radiology, Tongji Hospital (Main campus), Wuhan, 134 China were asked to make diagnosis as one of above 4 classes based on CT study. In this task, 135 the CNN achieved a sensitivity of 97.5% and specificity of 89.4% in differentiating COVID-19 136 from three types of non-COVID-19 cases whereas six radiologists obtained the average 79% in 137 sensitivity (87.5%, 90%, 55%, 80%, 68%, 93%, respectively, and 90% for the maximal voting 138 value among six radiologists), and 90% in specificity (92%, 97%, 89%, 95%, 88%, 79%, 139 respectively, and 95.6% for the maximal voting value) (Fig 4). In the Tongji dataset, the CNN 140 shows performance approaching that of expert radiologists. To examine the reliability of the 141 model, we performed class activation mapping (CAM) analysis for raw CT images in both validation and test datasets⁹ and visualized the featured image regions which lead to 142 143 classification decision. As shown in Figure 3. iii, the heatmap generated by CAM mostly 144 characterized local lesions suggesting the model learned radiologic features rather than simply 145 overfitting the dataset.

To comprehensively evaluate the comparisons of two tasks, we visualized the correlation of
sensitivity and specificity via receiver operating characteristic (ROC) curve to calculate the area
under the curve (AUC) for representing the CNN's classification performance. As a result, the
AUC of the CNN attained 0.98, 0.88, 0.91, 0.98 in specifically identifying COVID-19 pneumonia,
other viral pneumonia, bacterial pneumonia, and healthy tissue from 4 classes, and 0.92, 0.92,
0.95 in assessing three ordinal severities of COVID-19. Fig. 4 illustrates the ROC curve of the

152 CNN and sensitivity-specificity points displaying radiologists' diagnosis. Importantly, the CNN

153 performed comparable sensitivity-specificity to all six radiologists in differentiating COVID-19

154 from non-COVID-19 cases (Fig. 4a). Meanwhile, the CNN also performed equivalent

sensitivity-specificity in comparison with average radiologists in the assessment of three

156 severities (e, f, g in Fig. 4). However, the CNN revealed insufficient capability in determining

157 other viral pneumonia (Fig. 4b), bacterial pneumonia (Fig. 4c), and healthy case (Fig. 4d).

158 To test the generalization of the initial model that was trained exclusively on data from Tongji

159 hospitals, we evaluated the predictive performance using CT data from 100 confirmed COVID-

160 19 cases generated at Wuhan Union hospital. The accuracy of the model was only 72%,

161 compared with a 97% sensitivity using reserved testing data from Tongji hospitals. This

162 demonstrated a lack of generalization for the initial model.

163 The global online AI diagnostic engine enabled with federated learning

164 To overcome the hurdle, we proposed a federated learning framework to facilitate UCADI, a 165 global joint effort to generate an AI based on large scale date and integration of diverse ethnic 166 patient groups. In the traditional AI approach, sensitive user data from different sources are 167 gathered and transferred to a central hub where models are trained and generated. The federated learning proposed by Google¹⁰, in contrast, is a decentralized architecture where the AI model is 168 169 distributed to and executed at each host institution with the data sources or client ends for 170 training and inferencing. The local copies of the AI model on the host institution eliminate 171 network latencies and costs incurred due to sharing large size of data with the central server. 172 Most importantly, the strategy privacy preserved by design enables medical centers collaborating 173 on the development of models, but without need of directly sharing sensitive clinical data with 174 each other.

175 We implemented the federated learning framework at http://www.ai-ct-covid.team/ where we 176 deployed the initial model to provide 1) online diagnostic interface allowing people easily query 177 the model with patient CT images and 2) AI development federated learning interface(detailed in 178 Methods). UCADI stakeholders can download the code and train a new model based on the 179 initial model. Once the new model had been trained locally for several iterations, if UCADI participants share their updated version of the model, the framework will encrypt the model 180 parameters based on Learning with Errors (LWE)-based encryption¹¹ and transfer them back to 181 182 the centralized server via a customized server protocol. Participants' datasets will keep within 183 their own secure infrastructure. The central server would then combine the contributions from all 184 of the UCADI participants. The updated model parameters would then be shared with all 185 participants, which enables continuation of local training. The framework is highly flexible, 186 allowing hospitals join or leave the UCADI initiative at any moments, because it is not tied to 187 any specific data cohorts.

188 With the framework, we deployed two experiments to validate federated learning concept on the 189 CT COVID data. Firstly, we trained three models for each of three Tongji hospital datasets, and 190 then transferred the datasets to three physically independent computer servers, respectively, and 191 trained a Tongji federated model in a simulation mode (detailed in Methods). As shown in Figure 192 4. e-h, the federated model performed close to the centralized-trained initial model and better 193 than Tongji Main Campus model for predicting COVID-19, bacterial pneumonia and healthy 194 case (the comparison not applied to models of Tongji Sino-French Hospital and Tongji Optics 195 Valley because they lack of other viral pneumonia data). It shows the effectiveness of federated 196 model. In the second experiment, we trained a federated model in real mode based on three 197 Tongji hospital datasets (432 COVID-19 cases) and 407 confirmed COVID-19 cases from

198 Wuhan Union hospital. We tested the federated model performance on predicting the same 100

199 confirmed Wuhan Union COVID-19 cases which we used to test the initial model previously.

200 The result, 98% sensitivity, was improved compared to the initial model (72% sensitivity) which

201 was centralized trained only based on data from three Tongji hospitals.

202 **Discussion**

203 COVID-19 is a global pandemic. Over 2 million people have been infected, tens of thousands hospitalized, and nearly 200,000 have died worldwide as of April 23rd, 2020. There are borders 204 205 between countries. But only real border in this war is the border between human being and virus. 206 We need a global joint effort to fight the virus. The first challenge we have confronted in this 207 war is to deliver is deliver people precise and effective diagnosis. In this study, we introduce a 208 globally collaborative AI initiative framework, UCADI, to assist radiologists, streamline, and 209 accelerate CT-based diagnosis. Firstly, we developed an initial CNN model that achieved a 210 performance comparable to expert radiologist in classifying pneumonia to identify COVID-19, 211 and additionally assessing the severity of identified COVID-19. Furthermore, we developed a 212 federated learning framework, based on which hospitals worldwide can join UCADI to jointly 213 train an AI-CT model for COVID-19 diagnosis. With CT data from multiple Wuhan hospitals, 214 we confirmed the effectiveness of this the federated learning approach. We have shared the 215 initial model and the federated learning programmatic API source code 216 (https://github.com/HUST-EIC-AI-LAB/) and encourage hospitals worldwide join UCADI to 217 form an international collaboration to fight the virus with a globally trained AI application. It is 218 worth noting that there is still need for improvement in the technical implementation in the 219 framework: 1) The number of local training iterations before global parameter updating. The

220 number of local training iterations has a direct influence on the training efficiency, effectiveness,

221 and model performance. Currently, different clients in UCADI framework train with their private 222 data for one epoch before sending the parameter gradients to the global server. We will construct 223 more detailed experiments about this hyper-parameter to explore the best trade-off between 224 model performance and communication cost. 2) Private information leakage from gradients. 225 Reconstruction of input data from the parameter gradients is possible for realistic deep 226 architectures, and an encryption-decryption module is needed in the federated learning 227 framework. We have adopted an additively homomorphic encryption scheme in our COVID 228 diagnosis framework. The parameter gradients sent to the global server are encrypted while the 229 secret key is kept confidential from the global server, which guarantees the privacy security of 230 our framework. 3) Non-IID and unbalanced data distribution. The training data available is 231 typically based on the patients in the hospital, and any particular hospital's local dataset will not 232 be representative of the entire distribution. Therefore, it requires a dynamic aggregation method 233 that aggregates different parameter gradients via dynamic weighted averaging. Hence, it can 234 decrease the influence of non-IID and unbalanced data.

235 Methods

236 CT data collecting and processing

237 This study was approved by the Ethics Committee Tongji Hospital, Tongji Medical College of

Huazhong University of Science and Technology to access this dataset for research purpose.

Here we list the three major scanners used to obtain CT scans: GE Medical

240 System/LightSpeed16, SOMATOM Definition AS+, and GE Medical Systems/Discovery 750

HD. The scanning protocols of slice thicknesses and reconstruction kernel were 1.25mm and

adaptive statistical iterative reconstruction (60%) for two GE scanners whilst 1mm and sinogram

243 affirmed iterative reconstruction for the Siemens scanner. The high-quality CT image data from

the 432 COVID-19 patients were scanned, enrolled, selected and annotated in this study since
January 7, 2020 while other image data were retrospectively collected from CT databases of the
three Tongji Hospitals. In addition, we collected an independent cohort including 507 COVID-19
pneumonia CT cases confirmed by chest CT from Union Hospital, Wuhan, China. The cohort
was used for testing the performance of initial model and the multi-hospital model using
federated learning framework.

250 We conducted image processing of the raw CT image data to reduce computing burdens. We 251 utilized a sampling method to select 5 subsets of CT slices from all sequential images of one CT 252 case using random starting positions and scalable sampling intervals on transverse view to 253 picture the infected lung regions. All 5 processed subsets were separately fed to the CNN to 254 obtain average predictive probabilities, which can effectively include impacts of different levels 255 of lung from all CT slices. To further improve computing efficiency, we resized each slice from 256 512 to 128 pixel regarding its width and height and rescaled the lung windows of CT to a range 257 from -1200 to 600 and normalized them via the Z-score means before feeding the CNN.

258 Building AI model using pooled data

259 The dataset was split out into the training and validation set with 1036 cases (80% for training, 260 20% for validation), and independent test set with 240 cases consisting of 80 COVID-19 studies 261 (28 from Main Campus Hospital, 30 Sino-French New City Hospital, 20 Optical Valley 262 Hospital), 20 with other viral pneumonia (19 from Main Campus Hospital, 1 Sino-French New 263 City Hospital), 60 with bacterial pneumonia (50 from Main Campus Hospital, 8 Sino-French 264 New City Hospital, 2 Optical Valley Hospital), and 80 healthy cases (58 Main Campus Hospital, 265 10 Sino-French New City Hospital, 12 Optical Valley Hospital). We particularly considered the 266 balanced data distribution of 4 classes in test set. We initially trained a four-class CNN (Fig. 2)

267	based on 3D-Densenet ¹² , a densely connected convolutional network, which performed
268	remarkable advantages in classifying CT images. We customized its architecture to contain 14
269	3D-convolution layers distributed in 6 dense blocks and 2 transmit blocks (Fig. 2b indicating the
270	architecture and data flow). The CNN took 16 resized 128-x128-pixel CT image sequences as
271	input of each CT case, and generated a predicted pneumonia type with maximum probability as
272	output across thousands of attached computing neurons. We defined the loss function as the
273	weighted cross entropy between predicted probability and the true labels. Fine-tuned parameters
274	of the network via back-propagation were optimized using batch size of 16, learning rate of 0.01,
275	weight decay of 0.0001, momentum of 0.9, and epsilon of 0.00001. We conducted the training
276	process utilizing a workstation equipped with 2 Tesla V100 GPUs, costing 6 hours to finish the
277	task.

278 Building AI model using federated learning

279 Data preparation:

280 In experiment I, we trained with data collected from multiple centers of Tongji Hospital

281 including Tongji Hospital Main Campus, Tongji Optical Valley Hospital, and Tongji Sino-

French New City Hospital. We assigned each hospital to a federated client and place their local

- 283 data on three different physical machines. In experiment II, besides data collected from above
- three hospitals, we added Wuhan Union Hospital as a new participant,

285 Federated model setup:

For all experiments, we used the same architecture (3D-Densenet) with data-centralized training and the same set of local training hyperparameters for all clients with SGD optimizer: batch size of 35, learning rate of 0.01, momentum of 0.9 and weight decay of 5e-4. In experiment I, we set

289 the number of federated rounds to 200 with one local epoch per federated round. A local epoch 290 means each client train with its local data once before sending information to central 291 server(cloud). We conducted the training process utilizing a workstation equipped with 3 Tesla 292 V100 GPUs, costing 16 hours to finish. In experiment II, we set the number of federated rounds 293 to 30 with one local epoch per federated round and start training with the global model coming 294 from experiment I. For all experiments, we use the same evaluation metric with data-centralized 295 training to check that our procedures are working properly. (In experiment II, we need to train 5 296 rounds before the model achieving the same performance with data-centralized training on test 297 data from Wuhan Union Hospital). 298 Model aggregation: 299 The server distributes a global model and receives synchronized weight updates (ΔW_{ν}^{t}) from all 300 clients at each federated round. Due to each client train with one epoch per federated round, so 301 we just average all the weight updates from the client with equal weight and update the global 302 model.

303 Privacy-preserving setup:

We use a variant of additively homomorphic encryption to achieve privacy-preserving, which called Learning with Errors (LWE)-based encryption. The encryption method allows us to leak no information of participants to the honest-but-curious parameter (cloud) server.

307 Data Availability All relevant data used for developing the initial model and federated models
308 during the current study are not publicly available.

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310 Model Availability

- 311 The online application of AI model is publicly available at http://www.ai-ct-covid.team/.
- 312 The initial model or offline APP is publicly available upon request at <u>tianxia@hust.edu</u> or
- 313 xbai@hust.edu.cn or through website http://www.ai-ct-covid.team/.
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- 315 Federated Learning Framework Availability. The source code can be accessed at
- 316 <u>https://github.com/HUST-EIC-AI-LAB/</u>.
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- 354 collaboration scheme.

355 Author contributions

- 356 T.X., X.B., Z.L., and C.Z, conceived the work. Y.X., L.M., F.Y., K.M., J.Y., X.Y, C.S., Z.F.,
- 357 J.G., X.Z., R.H., C.Z., X. L., D.T., C.X., W.Z., D.Y., M.W., N.H., N.J.H., I.R.K., X.P., X.W.,

- J.B. designed and developed the models and analyses; Y.X., K.M., D.L.R., J.Z., and T.X.
- 359 interpreted results; and K.M., J.W., P.M., D.L.R., J.Z., Z.L., and T.X. wrote the paper.

360 **Competing interests**

361 The authors declare no competing interests.

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363 Tables

	Male	Female	0-20 years	20-40 years	40-60 years	60-80 years	>80 years
Patient Number	617	659	40	444	421	340	31

364 Table 1 | Patient information of 1276 studies collected from Tongji Hospital regarding gender365 and age distribution.

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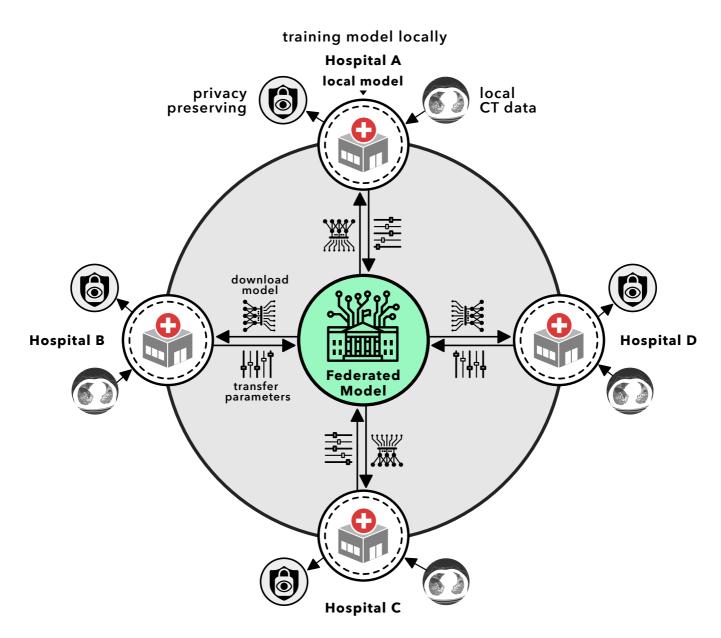


Figure 1 | **The conceptual architecture of UCADI on the basis of federated learning.** UCADI stakeholders firstly download the code and train a new model locally based on the initial model, and secondly transfer the encrypted model parameters back to the federated model. The central server combines the contributions shared from all of the UCADI participants.

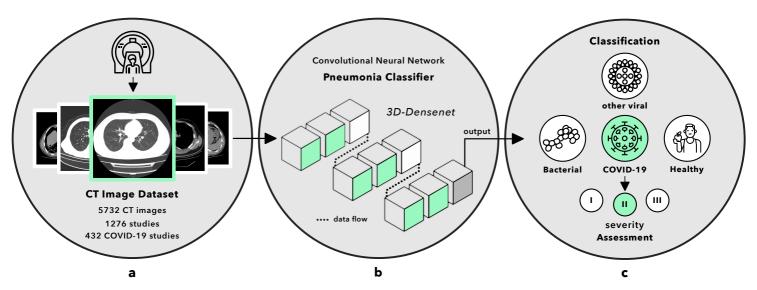


Figure 2 | **Data and strategy. a**, number of CT studies and total images. **b**, the CNN was developed based on 3D-Densenet, consisting of 6 dense blocks in green, 2 transmit blocks in white and an output layer in gray. Preprocessed 128-x-128-pixel CT images of one case were fed to the network across 14 3D-convolution layers and a number of functions embedded in 3D blocks, finally received the predicted classification result. c, the CNN classified CT case into 4 types and further assessed the severity into I or II or III if the case was predicted as COVID-19.

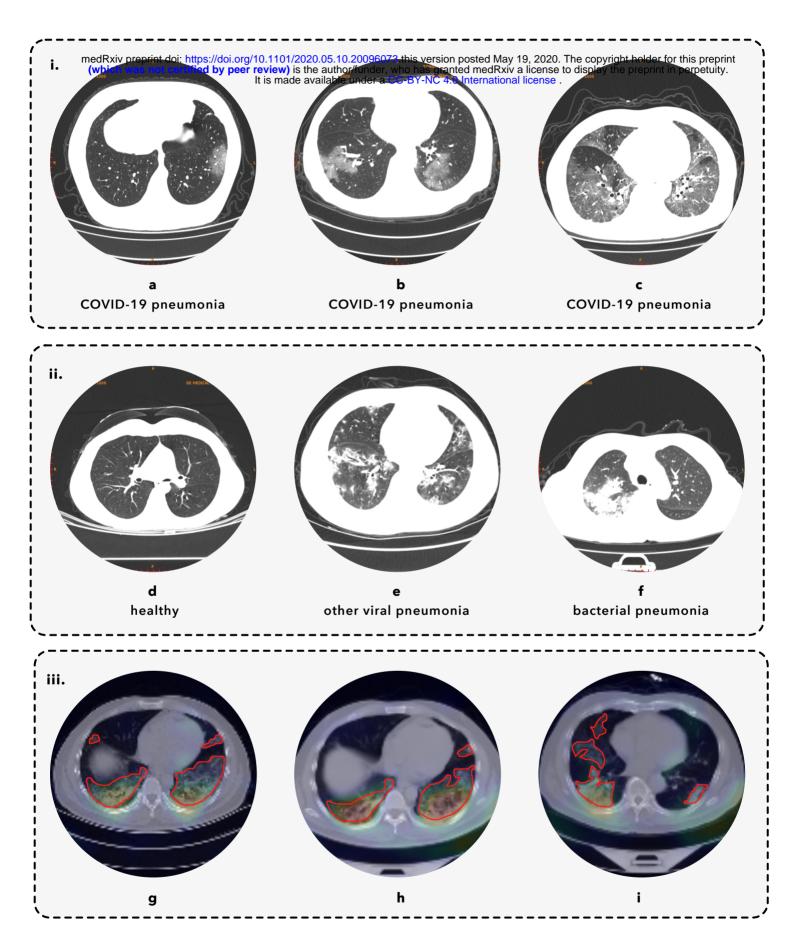
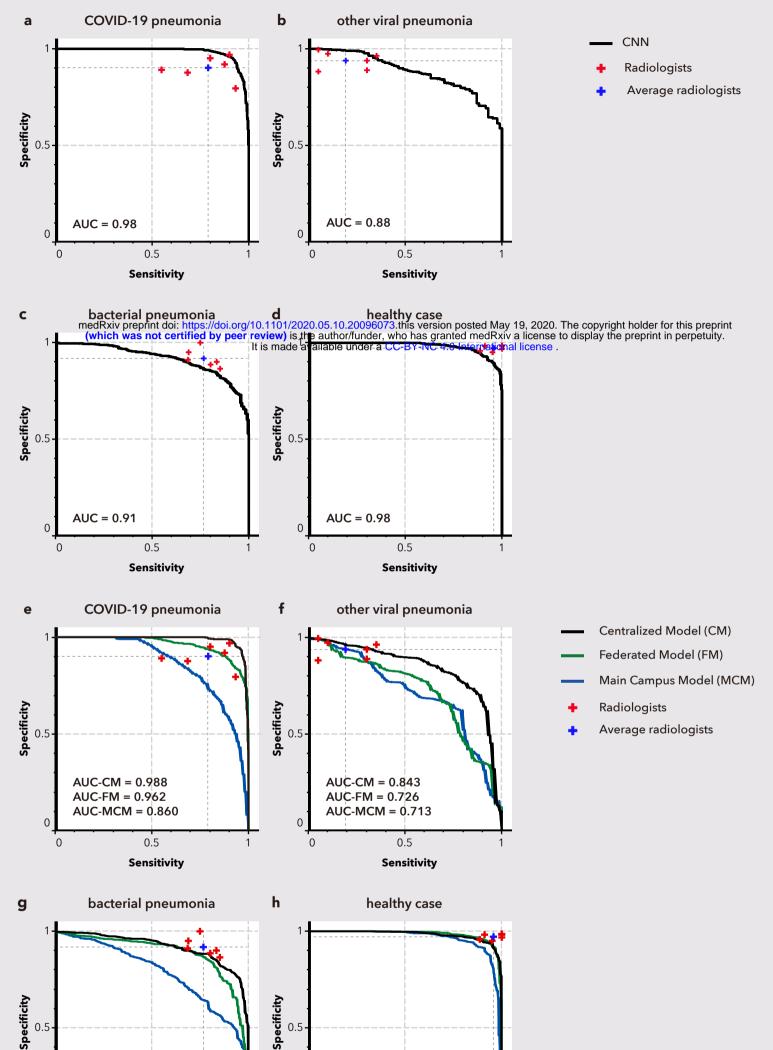


Figure 3 | **CT images. i and ii, the taxonomy of pneumonia and featured CT image for per-class. iii, the heatmap generated by GradCAM and local lesions annotated by the radiologist. i**, COVID-19 pneumonia. **a**, **b**, **c** represent the CT images of COVID-19 defined by radiological features. **ii**, non-COVID-19 cases. **d**, **e**, **f** respectively displays the CT image of healthy case, other viral pneumonia, and bacterial pneumonia. **iii**, CAM visualized the image areas which lead to classification decision. The radiologist, LYM [9 years' experience], from Department of Radiology, Tongji Hospital circumscribed the local lesions with the red curved masks. **g-h**, patients with COVID-19 pneumonia.



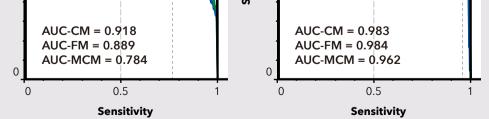


Figure 4 | **Pneumonia classification performance of CNN models and radiologists.** This figure illustrates the comparative analysis between the CNN and radiologists by correlating the ROC curve of CNN and sensitivity-specificity points of six invited radiologists for two conducted classification test tasks. **a-d**, per-class evaluation for three types of pneumonia and healthy case. The curve in black represents the performance of the CNN. Cross marks in red separately represent the performance of six radiologists and the blue mark annotates the average capability. **e-h**, comparative evaluation of centralized-trained initial model, federated model, and Tongji Main Campus model on four per-class classification tasks.