



Multi-center validation of an artificial intelligence system for detection of COVID-19 on chest radiographs in symptomatic patients

Michael D. Kuo^{1,2} · Keith W. H. Chiu¹ · David S. Wang³ · Anna Rita Larici^{4,5} · Dmytro Poplavskiy² · Adele Valentini⁶ · Alessandro Napoli⁷ · Andrea Borghesi⁸ · Guido Ligabue^{9,10} · Xin Hao B. Fang¹¹ · Hing Ki C. Wong¹² · Sailong Zhang¹ · John R. Hunter³ · Abeer Mousa¹³ · Amato Infante^{5,14} · Lorenzo Elia^{4,5} · Salvatore Golemi⁸ · Leung Ho P. Yu¹⁵ · Christopher K. M. Hui^{16,17} · Bradley J. Erickson¹³

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Abstract

Objectives While chest radiograph (CXR) is the first-line imaging investigation in patients with respiratory symptoms, differentiating COVID-19 from other respiratory infections on CXR remains challenging. We developed and validated an AI system for COVID-19 detection on presenting CXR.

Methods A deep learning model (RadGenX), trained on 168,850 CXRs, was validated on a large international test set of presenting CXRs of symptomatic patients from 9 study sites (US, Italy, and Hong Kong SAR) and 2 public datasets from the US and Europe. Performance was measured by area under the receiver operator characteristic curve (AUC). Bootstrapped simulations were performed to assess performance across a range of potential COVID-19 disease prevalence values (3.33 to 33.3%). Comparison against international radiologists was performed on an independent test set of 852 cases.

Results RadGenX achieved an AUC of 0.89 on 4-fold cross-validation and an AUC of 0.79 (95%CI 0.78–0.80) on an independent test cohort of 5,894 patients. Delong's test showed statistical differences in model performance across patients from different regions ($p < 0.01$), disease severity ($p < 0.001$), gender ($p < 0.001$), and age ($p = 0.03$). Prevalence simulations showed the negative predictive value increases from 86.1% at 33.3% prevalence, to greater than 98.5% at any prevalence below 4.5%. Compared with radiologists, McNemar's test showed the model has higher sensitivity ($p < 0.001$) but lower specificity ($p < 0.001$).

Conclusion An AI model that predicts COVID-19 infection on CXR in symptomatic patients was validated on a large international cohort providing valuable context on testing and performance expectations for AI systems that perform COVID-19 prediction on CXR.

Key Points

- An AI model developed using CXRs to detect COVID-19 was validated in a large multi-center cohort of 5,894 patients from 9 prospectively recruited sites and 2 public datasets.
- Differences in AI model performance were seen across region, disease severity, gender, and age.
- Prevalence simulations on the international test set demonstrate the model's NPV is greater than 98.5% at any prevalence below 4.5%.

Keywords Artificial intelligence · COVID-19 · Radiology · Thoracic · Public health

Michael D. Kuo and Keith W.H. Chiu contributed equally to this work as first authors.

David S. Wang and Anna Rita Larici contributed equally to this work as second authors.

✉ Michael D. Kuo
mikedkuo@gmail.com

Abbreviations

AI	Artificial intelligence
CXR	Chest X-ray
RT-PCR	Reverse transcription polymerase chain reaction
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2

Extended author information available on the last page of the article

Introduction

With continued uncertainties surrounding vaccine efficacy against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) transmission, waning vaccine efficacy over time, and SARS-CoV-2 variants, early diagnosis will remain central to coronavirus disease 2019 (COVID-19) prevention strategies for the foreseeable future. Timely detection of COVID-19 among symptomatic patients not only reduces transmission, but also allows appropriate treatment and prevention of clinical deterioration [1, 2]. While reverse transcription polymerase chain reaction (RT-PCR) testing remains the gold standard for COVID-19 diagnosis, prolonged test turnaround times, high test and labor costs, and testing reagent shortages have hampered access and use of RT-PCR testing [3, 4]. Indeed, decreasing analytical sensitivity in return for reduced test turnaround time and increased test accessibility can be highly effective at limiting COVID-19 transmission [5]. Accessible, accurate, and cost-effective COVID-19 screening tools are urgently needed so that symptomatic patients can be better triaged and confirmatory RT-PCR testing can be preferentially performed in those with a high pre-test probability of having and being likely to transmit COVID-19.

While computed tomography (CT) imaging has been used for both COVID-19 detection and disease characterization [6], it is clinically not indicated for the majority of patients with mild disease. Furthermore, its high financial costs and relative low throughput effectively limit its utility to first world nations. Comparatively, a chest radiograph (CXR) is often routinely obtained for the initial assessment of patients with acute respiratory symptoms who seek medical care, is cheaper, and has lower radiation dose, and it is available in clinics worldwide [7]. Thus, CXR has the potential to be used to aid COVID-19 detection in symptomatic patients without requiring additional resources. Unfortunately, detecting COVID-19 on CXR is difficult as a significant proportion of patients lack characteristic CXR findings that can be used to differentiate it from other respiratory infections [8].

Recent studies have shown that artificial intelligence (AI) models employing computer vision-based deep neural networks can detect and learn COVID-19 features on CXR that may be nonobvious to radiologists [9–13]. While promising, many AI models suffer from training dataset bias and poor generalizability [14]. Moreover with many studies focusing on detecting COVID-19 from healthy individuals, they do not address the more clinically relevant question of differentiating COVID-19 from other causes in patients with respiratory symptoms; hence, the true performance of these AI models in a clinically relevant setting remains unknown [15]. To address these challenges, we conducted a large international validation study of a COVID-19 CXR AI prediction model (RadGenX) on symptomatic patients suspected to have COVID-19 [16, 17].

Methods

This was a retrospective, observational multi-center study whose primary objective was to evaluate RadGenX's performance on predicting COVID-19 from CXR in symptomatic COVID-19 suspected patients. The overall study design is shown in Fig. 1.

International test set

Independent external testing was performed on a combined cohort consisting of CXRs of patients collected from: (1) 9 independent sites involving 11 hospitals (hereafter referred as “private” study patients) across the United States (US) ($N = 4$), Italy ($N = 5$), and Hong Kong SAR, China ($N = 2$), AND (2) two large public databases (hereafter referred as “public” study patients): one from Europe and the other from the US [18, 19]. The “international test set” consisted of the 9 private study sites plus 1 of the “public” sites (COVID-19-NY-SBU – see below). All study patients were patients ≥ 18 years old that presented with respiratory symptoms and underwent CXR and SARS-CoV-2 RT-PCR testing. The study was approved by the Institutional Review Board of each participating site and followed the guidelines outlined in the Checklist for Artificial Intelligence in Medical Imaging (CLAIM) in the reporting of the study [20].

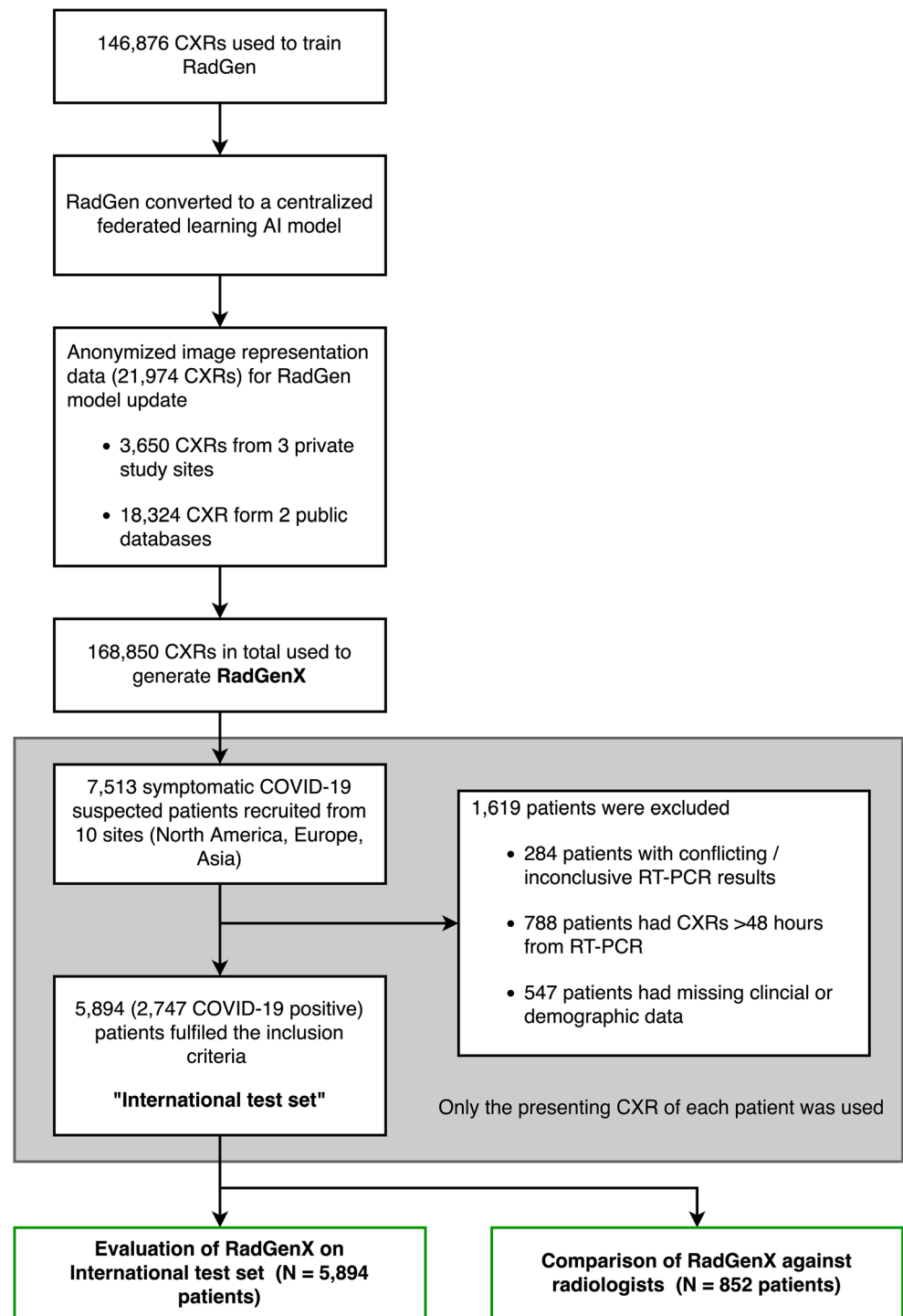
Private study patients

Per study protocol, private study patients were collected between February 1, 2020, and July 30, 2020; all study patients must have had respiratory symptoms, including but not exclusive to cough, dyspnea, or signs and symptoms of a respiratory tract infection. They must have also undergone SARS-CoV-2 RT-PCR testing with a definitive positive or negative result; patients who had equivocal or conflicting results were excluded. Historic negatives could be included by the study sites, which was defined as pre-COVID-19 era patients who similarly presented to their respective study site with respiratory symptoms prior to August 1, 2019. Only frontal CXRs were included. Demographic and clinical data (including symptom severity) of patients at presentation were also collected. Patient symptoms were stratified using the 9-point ordinal scale as recommended by the World Health Organization in COVID-19 studies into 3 categories: (mild = 1–2, moderate = 3–4, and severe = 5–7) [21]. Any patients with scores of either 0 (asymptomatic/uninfected) or 8 (dead) were excluded per study protocol.

Public study patients

In addition, a comprehensive search was performed (December 1, 2021) to identify additional public datasets for external validation with greater than 500 patients per set meeting similar criteria [22]. Of the publicly available datasets, two

Fig. 1 Overall study design



met these criteria and did not overlap with our training cohort. COVIDGR contained 852 COVID-19 positive and negative cases from Granada, Spain [18]. COVID-19-NY-SBU included 1,384 COVID-19 positive cases acquired at Stony Brook University [19]. Cases from the two public datasets similarly included in (addition to digital CXR images) basic demographics (i.e., age and gender), definitive COVID-19 status, and disease severity.

Training RadGenX AI model using a centralized federated learning system

RadGenX is based on the previously reported RadGen CXR AI prediction model [16, 17]. This original RadGen model was then updated using data from private study patients and 2 public SARS-CoV-2 CXR datasets (see supplement). Conventional computer vision-based medical AI models

typically mandate centralization of data which raises concerns for patient privacy, while classical weight-based federated models require significant compute and technical resources not readily available to the vast majority of imaging centers [23]. In order to (1) allow sites with minimal compute resources or technical knowledge to collaboratively train a shared AI model, and (2) enable these sites to still maintain sole custodianship of their patient data, we modified RadGen into a standalone Windows PC compatible software application and enabled privacy-preserving data sharing for model updating using a modified federated learning approach [24].

Of the 9 study sites, 3 sites contributed 3,650 CXRs of 2,576 patients (43.1% COVID-19 positive) between February 1, 2020, and July 30, 2020, for model updating (Table S1) (Fondazione Policlinico Universitario Agostino Gemelli IRCCS – Università Cattolica del Sacro Cuore Roma, Fondazione I.R.C.C.S. Policlinico San Matteo and University of Brescia).

The public datasets used for model updating (accessed September 15, 2020) consisted of a total of 18,072 CXRs (11,953 positive and 6,119 negative) from the BIMCIV-COVID-19 and 252 positive CXRs from the COVID-19-AR datasets [25, 26].

RadGenX model training and validation

The architectures of both RadGen and RadGenX are based on SE-ResNeXt-50-32x4d [24]. RadGenX was trained using the SGD optimizer for 120 epochs, with an initial learning rate of 0.01, decreased by 1/5 at epochs 70, 90, 110 and with norm gradient clipping of 8.0. Hard negative mining was also performed [23], by applying the partially trained model to the CheXpert dataset with the top 2,000 CXRs with the highest probability scores then considered in the loss function [27]. To offset positive-to-negative case imbalance, we generated 4 separate models with each model separately trained on each of the 4 non-overlapping data folds.

For model validation, we performed 4-fold cross-validation with each of the 4 separate models separately trained and validated on each of the 4 non-overlapping folds. A threshold based on obtaining 90.0% sensitivity was selected a priori (based on published guidelines recommended by regulatory bodies for minimum performance for serological tests for SARS-CoV-2 detection), which was applied to the aggregated held out validation sets for each of the 4 models in order to identify the corresponding cut point [28]. The final model, RadGenX, consisted of an equally weighted ensemble of the 4 models whose output was a binary prediction (based on application of the pre-specified cut-point) of SARS-CoV-2 RT-PCR positivity for a given input DICOM frontal CXR. This model was independently evaluated on the international test set.

COVID-19 prevalence analysis

While the case-control independent test set allows broad validation of RadGenX, in order to assess the performance of RadGenX under varying COVID-19 prevalences, we additionally ran a series of bootstrapped prevalence simulations leveraging data from the 9 study sites from the international test set ($n = 4,559$) across simulated disease prevalences in step-wise fashion from 3.33% (1:30) to 33.3% (1:2). The performance of RadGenX was reported as the mean prediction score at each of the simulated prevalence levels, based on a random sampling from the international test set of 100 COVID-19 positive patients against the corresponding number of randomly selected COVID-19 negative patients to meet each prevalence ratio, bootstrapped 10,000 times.

RadGenX versus reader study

In order to better understand differences in performance between RadGenX and radiologists, we performed a head-to-head comparison analysis on the COVIDGR dataset [18]. Three radiologists from the US, Italy, and HK, all board-certified, and each with over 10 years' experience (KWHC, DSW, ARL) analyzed all 852 CXRs in the COVIDGR dataset (Table S2). The readers were given the CXRs in a blinded and random order which each reader independently reviewed. Assessment of each CXR image consisted of evaluating the presence or absence of findings consistent with COVID-19 pneumonia. Reader consensus was created using the majority vote method for a given image for each of these two tasks. Their predictions were compared to those of RadGenX and the individual patient ground truth COVID-19 status.

Statistical analysis

The performances of RadGenX and the radiologists were evaluated using AUC, sensitivity, and specificity. In subgroup analysis, odds ratios were calculated and Wilcoxon test was used to compare subgroups with the overall performance of RadGenX. In the reader study, interclass correlation coefficient (ICC, two-way mixed, average score) values and 95% CI were used to assess inter-rater reliability. ICC values of 0–0.25, 0.26–0.49, 0.50–0.69, 0.70–0.89, and 0.90–1.00 indicated little or no reliability, low reliability, moderate reliability, high reliability, and very high reliability, respectively. Pearson's chi-squared tests were employed to compare RadGenX and radiologists. DeLong test was used to subgroup model performances. A p value < 0.05 was considered statistically significant. Analyses were performed with the use of R software, version 3.6.3 (R Foundation for Statistical Computing).

Results

RadGenX achieved an area under the curve (AUC) of 0.89 (95% confidence interval [CI] 0.88–0.89) across the 4 individual models on 4-fold cross-validation (Fig. 2A). The corresponding specificity at the pre-specified cut point selected to achieve 90% COVID-19 test sensitivity (see “Methods”) was 62.6% (Fig. 2B).

Evaluation of RadGenX on the international test set

Of the 8,380 symptomatic COVID-19 suspected cases curated by our 9 private studies sites, a combined 2,202 patients were used for model updating. Of the remaining 6,178 patients, 1,619 did not meet the study eligibility criteria, resulting in a total of 4,559 patients included in the international test set. This cohort consisted of 1,336, 1,456, and 1,767 patients from the US, Italy, and HK, respectively. For each country, the percentage of RT-PCR positive COVID-19 patients was 28.3%, 42.2%, and 23.8% for the US, Italy, and HK, respectively.

The NY-SBU dataset, consisting of 1,335/1,384 (100% COVID-19 positive) (mean age 57.5 [range 18 to 90], 56.5% men) that met inclusion criteria was also included in the international test set. For subgroup analysis, cases from NY-SBU was grouped with the private US cohorts. The final demographics of the international test set are summarized in Table 1 (Tables S3 & S4).

On this composite independent test set of 5,894 diverse patients from both the privately and publicly curated

datasets, RadGenX achieved an overall AUC of 0.79 (95% CI 0.78 to 0.80) for detecting RT-PCR-confirmed COVID-19 on presenting CXR on symptomatic COVID-19 suspected patients (Fig. 3A). The overall sensitivity and specificity of the model were 79.1% (95% CI 77.6 to 80.6%) and 60.5% (95% CI 58.8 to 62.2%), respectively. There was no significant difference in model performance when comparing RT-PCR negatives versus historical negatives as controls (AUC = 0.80 [95% CI 0.78 to 0.81] vs 0.81 [95% CI 0.80 to 0.83]; $p = 0.11$).

Reflective of the diverse patient composition, this cohort was similarly diverse in disease severity, region, age, and gender. We therefore explored whether these factors affected model performance. As expected, there were model performance differences as assessed by AUC across disease severity (0.72 vs 0.81 vs 0.90, for mild, moderate, and severe disease respectively, $p < 0.001$ for any combination), region (0.71 vs 0.85 vs 0.78 for US, Europe, and Hong Kong respectively, $p < 0.01$ for any combination), gender (0.82 vs 0.75 between male and female, $p < 0.001$), and age (0.78 vs 0.80 for < 65 and ≥ 65 years, $p = 0.03$) (Fig. 3B–E).

While a test’s sensitivity and specificity are fixed, variable prevalence analysis over 10,000 simulations performed on the international test set, revealed that the model’s positive predictive value (PPV) steadily increased from 8.8% at 3.33% prevalence to 50.5% at 33.3%. Conversely, the negative predictive value (NPV) increased from 86.1% at 33.3% prevalence to greater than 98.5% at any COVID-19 prevalence below 4.5%.

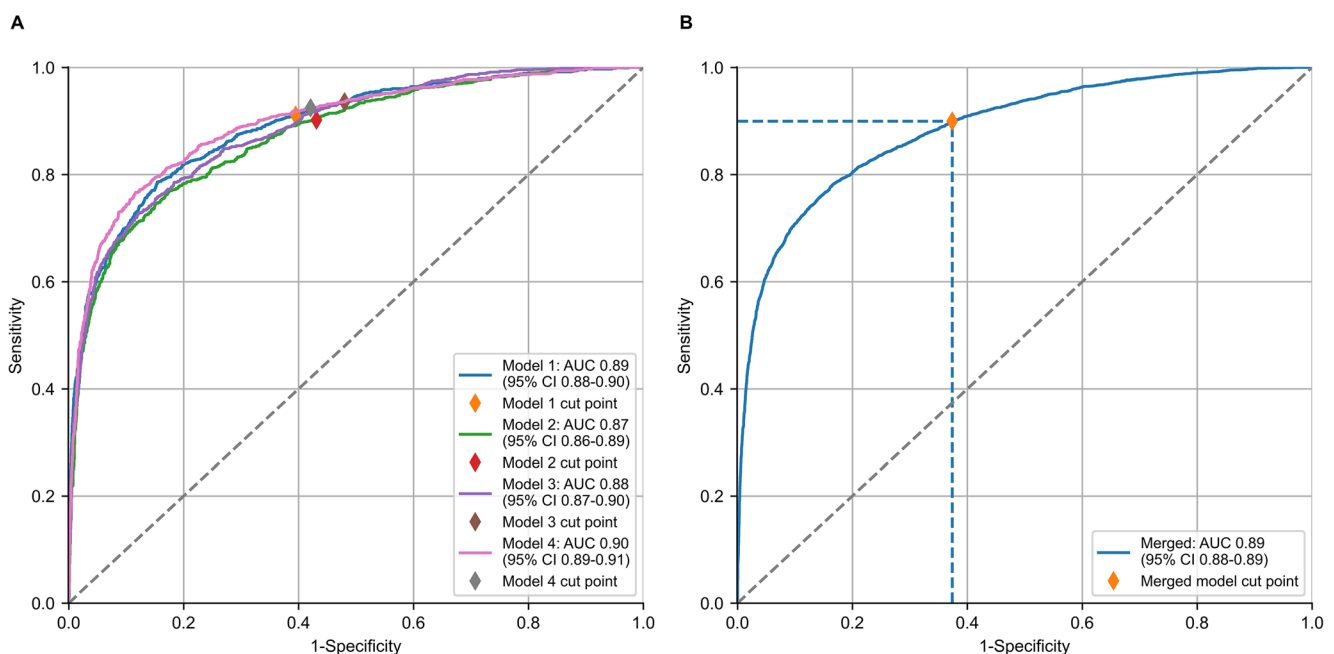


Fig. 2 AI model performance. **A** Receiver operator characteristic (ROC) curve of RadGenX AI model from 4-fold cross-validation; **B** ROC curve of RadGenX on the merged 4-fold cross-validation

Table 1 International test set patient characteristics

	Overall	COVID-19 positive**	COVID-19 negative**
Cases	5,894	2,747	3,147
Age (95%CI), years	61.34 (60.85, 61.82)	57.42 (56.75, 58.1)	64.75 (64.08, 65.43)
18–39 yr	924 (15.7%)	526 (19.1%)	398 (12.6%)
40–49 yr	672 (11.4%)	382 (13.9%)	290 (9.2%)
50–59 yr	970 (16.5%)	536 (19.5%)	434 (13.8%)
60–69 yr	1,159 (19.7%)	550 (20.0%)	609 (19.4%)
70–79 yr	976 (16.6%)	407 (14.8%)	569 (18.1%)
≥ 80 yr	1193 (20.2%)	346 (12.6%)	847 (26.9%)
Sex			
Male	3,276 (55.6%)	1,612 (58.7%)	1,664 (52.9%)
Female	2,618 (44.4%)	1,135 (41.3%)	1483 (47.1%)
Region			
US	2,671 (45.3%)	1,713 (62.4%)	958 (30.4%)
Europe	1,456 (24.7%)	614 (22.4%)	842 (26.8%)
Hong Kong	1,767 (30.0%)	420 (15.3%)	1,347 (42.8%)
Symptom severity*			
Mild	873 (14.8%)	722 (26.3%)	151 (4.8%)
Moderate	2,337 (39.7%)	1,128 (41.1%)	1,209 (38.4%)
Severe	2,684 (45.5%)	897 (32.7%)	1,787 (56.8%)

Percentages within each category are reported with respect to the total number of cases reported for that respective column (Overall, COVID-19 positive, COVID-19 negative).

*Symptom severity at the time of initial presentation was assessed using a nine-category ordinal scale recommended by the World Health Organization (WHO) [21]. Mild, moderate, and severe symptoms were defined as patients with an ordinal score of 1–2, 3–4, and 5–7, respectively.

**There are statistical differences (all $p < 0.001$) across all categories between COVID-19 positive and negative patients.

RadGenX compared to radiologists

The COVIDGR public dataset consisted of 852 patients (50% COVID-19 positive) and was used as the external test set for the radiologist-AI comparison study. The radiologists' agreement overall was high with an interclass correlation (ICC) of 0.81 (95% CI 0.78 to 0.83) for detecting COVID-19. The overall sensitivity and specificity of the radiologists for detecting COVID-19 on CXR were 51.6% (95% CI 46.9 to 56.4%) and 99.1% (95% CI 97.6 to 99.6%), respectively. RadGenX achieved an overall AUC of 0.82 (95% CI 0.79 to 0.85). Applying the pre-specified cut-point, the sensitivity and specificity of the model were 82.9% (95% CI 79.0 to 86.1%) and 56.8% (95% CI 52.1 to 61.4%) respectively (Fig. 4). Radiologists and RadGenX had false positive rates of 1% (4/426), and 43.2% (184/426), respectively, and false negative rates of 48.4% (206/426) and 17.1% (73/426), respectively.

Discussion

In summary, we validated the performance of an AI model in detecting COVID-19 on CXR in patients presenting with respiratory symptoms in a cohort of 5,894 patients from 3

different continents. The model achieved an AUC of 0.79, sensitivity of 79.1%, and specificity of 60.5%. The size and diversity of our test set allowed us to evaluate the model's "true" performance across a broad cross section of age groups, disease conditions, localities, and healthcare systems, which is particularly relevant among growing concerns of "brittle" AI, model performance overestimations, and cohort bias [29, 30]. Further, prevalence simulations demonstrated the model's performance profile across a range of potential COVID-19 prevalence levels, revealing that the model's NPV steadily increased from 86.1% at 33.3% prevalence, and exceeded 98.5% at any COVID-19 level below 4.5%. Finally, comparison of RadGenX against radiologists from Asia, the US, and EU, on an independent set of 852 positive and negative COVID-19 cases, resulted in an AUC of 0.82, sensitivity of 82.9%, and specificity of 56.8%, compared to a sensitivity and specificity of 51.6% and 99.1%, respectively, for the radiologists. The scale and scope of this study provides valuable context and perspective on realistic performance expectations for AI systems that perform COVID-19 prediction on CXR and, more broadly, on the challenges of achieving truly "generalizable" diagnostic AI models, even when the ground truth is an objective standard such as PCR testing.

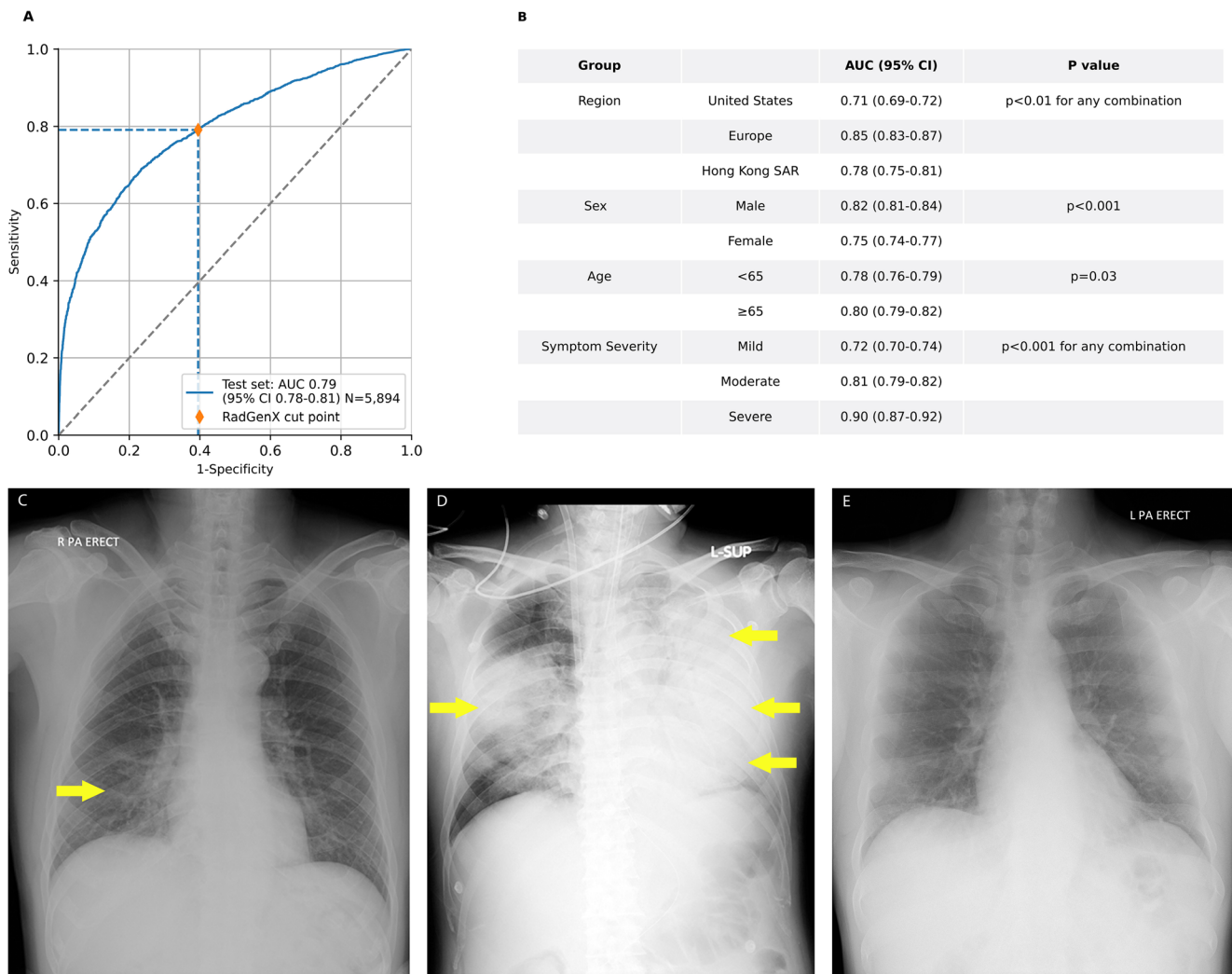


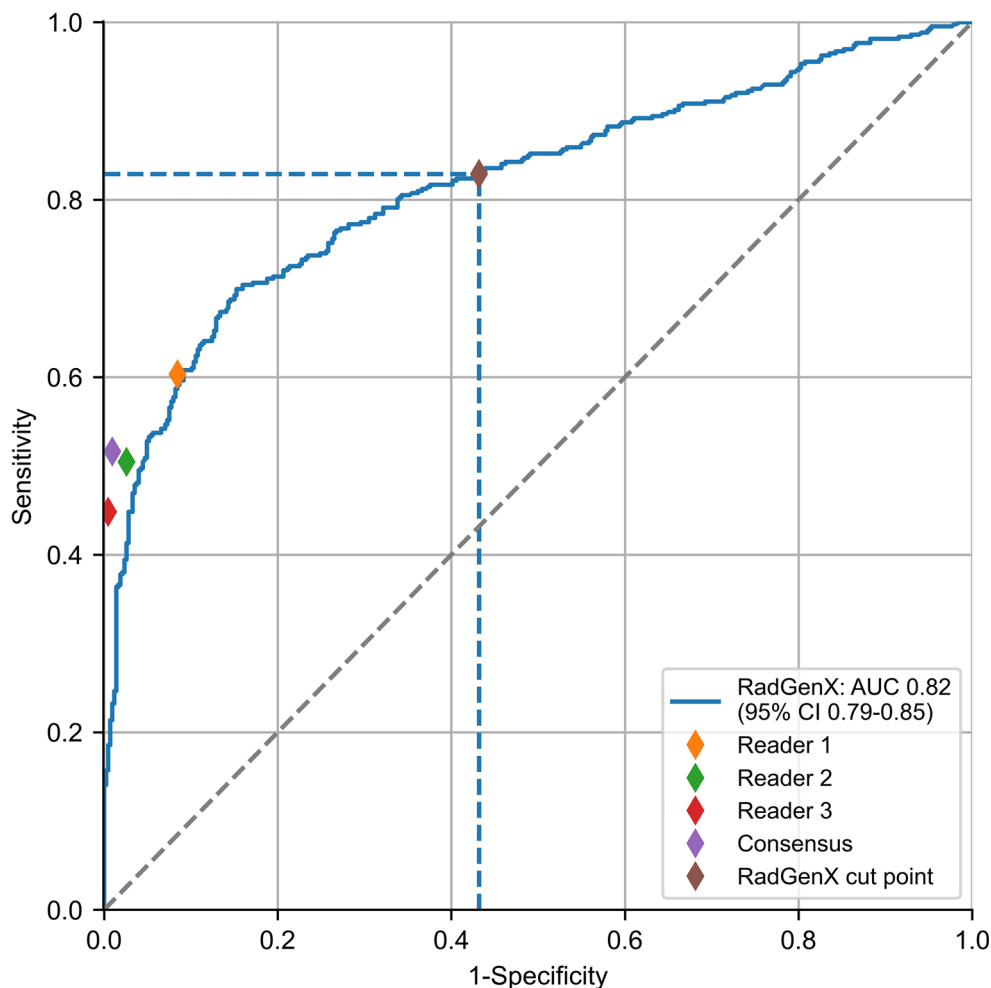
Fig. 3 RadGenX performance on the international test set. **A** ROC curve of RadGenX on the international test set ($N = 5,894$); AUC = 0.79 (95%CI 0.78–0.81). **B** RadGenX’s AUC with 95% confidence intervals (CI) across different regions, disease severity, gender and age; **C** CXR of a 60-year old male COVID-19 positive patient with mild symptoms at the time of diagnosis showing minimal air space opacities in right lower zone (yellow arrow) that RadGenX correctly predicted as COVID-19 positive.

D A 67-year old male COVID-19 negative patient with severe symptoms at presentation showing extensive consolidation in both lungs (yellow arrows) on chest X-ray that RadGenX called COVID-19 negative. **E** CXR of a 49-year-old male with mild respiratory symptoms for 2–3 days with a normal appearing chest radiograph that RadGenX correctly predicted as COVID-19 positive

Our international test set consisted of a large and geographically diverse representation of COVID-19 cases consisting of cases collected from 10 different institutions across 3 different continents. Unlike many studies that assessed AI model performance in differentiating symptomatic COVID-19 patients from normal healthy individuals, we specifically evaluated our model’s ability to differentiate among patients with respiratory symptoms on their presenting CXR [15]. We believe this is a more impactful and less well studied task as the clinically relevant conundrum arises when a symptomatic patient is first admitted to hospital as indiscriminate COVID-19 mass screening, regardless of technology, has so far shown to be expensive and of unclear benefit [31]. The more even distribution of mild, moderate, and severe hospitalized COVID-

19 cases we observed in our COVID-19 positive group compared to the negative group, is likely a reflection of the variation in country-by-country COVID-19 management strategies witnessed during the early phases of the COVID-19 pandemic. For example, a number of countries in Asia initially pursued a stringent containment policy whereby all PCR positive cases were hospitalized, regardless of disease severity, whereas many US and European systems tended to hospitalize only sick COVID positive patients, resulting in a relative enrichment of mild cases in the COVID-19 positive group (26.3%) compared to the negative group (4.8%). The resulting relatively even distribution in disease severity across mild, moderate, and severe in the positive group, powered by the large total number of patients studied, fortunately provided a

Fig. 4 RadGenX performance compared to radiologists. Receiver operator characteristic (ROC) curve of RadGenX on the independent COVIDGR dataset ($n = 852$) with the performance of the 3 board-certified radiologists from the US, Italy, and Hong Kong SAR each denoted on the plot [18]



unique opportunity to also more fully understand the impact of disease severity on model performance as we have highlighted in the results.

Given the size and diversity of our international test set, it is not surprising that differences in performance on subgroup analysis were observed [32]. Although the model performed equally well across both the privately curated and public datasets and the historical cohort and RT-PCR proven cases, unsurprisingly, significant performance differences were observed between age groups, gender, locality, and disease severity. In addition to providing insights into specific factors that increase or decrease model performance across this large study population, this also highlights one of the difficulties encountered when attempting to train a sufficiently generalizable model that often requires balancing capturing a large number of diverse cases with patient-specific data which may be difficult to balance due to patient privacy concerns. In our specific instance, it remains to be seen whether training with even larger datasets and more balanced annotated cohorts would be sufficient to overcome these subgroup differences or whether these are inherent limitations of the current model, or of the larger set of diagnostic AI models aiming to be broadly

“generalizable,” or whether it is simply a feature of this particular disease entity.

An important study limitation is whether the ongoing emergence of SAR-CoV-2 variants will affect the performance of the current RadGenX model. A number of these variants have shown increased transmissibility, morbidity, and mortality [33]. Although initial data suggest that their radiographic appearance is similar to that of the original strain, it remains unknown whether these variants will lead to a substantial divergence in radiographic phenotypes. As we have similarly demonstrated the critical importance of training set diversity on model generalizability, it will be imperative to continue to capture CXR data from SAR-CoV-2 variants as COVID-19 infections continue to surge globally. The centralized federated learning framework we employed thus enables model updating in a privacy-preserving manner allowing for incorporation of new SAR-CoV-2 variant CXR data into future iterations of our model.

In this study, we used SARS-CoV-2 RT-PCR test results as the ground truth reference for COVID-19 infection [34]. While the implication is that the performance of our AI model will never surpass nor replace RT-PCR testing, this is clearly

not the model's intent, any more so than low-dose lung CT or virtual colonoscopy is meant to replace tissue diagnosis; instead, the goal of tools such as RadGenX is to serve as an adjunct to COVID-19 RT-PCR testing [5]. Tests such as CXR are more accessible and offer faster turnaround time, and not only have the potential to improve cost effectiveness and PCR utilization, but also have been shown to have clear benefits for infection containment, which is particularly relevant in resource-constrained regions [35].

This is supported by our prevalence analysis where we interrogated the model in stepwise fashion across a range of simulated COVID-19 prevalence levels, representing on one end a “surge” prevalence of 33% as recently seen in Hong Kong and other nations [36], sequentially down to reported “endemic” prevalence rates near 3% [37]. Given the model's excellent NPV—exceeding 98.5% at any prevalence below 4.5%—a potential application could be as an adjunctive screening tool to PCR in symptomatic patients during periods when prevalence nears endemic levels, where a negative test result could be used to effectively exclude patients from PCR testing with high confidence, thus reserving PCR testing for those with higher likelihood to be PCR positive. This could potentially offer a cost-effective option for COVID-19 testing in resource-constrained regions. Prospective studies will ultimately be needed to validate its role in such a scenario.

In summary, we have validated an AI model that predicts COVID-19 status from CXR in symptomatic patients in one of the largest and most diverse, independent study populations to date. We also provide modeling analysis to show how the model performs under a wide range of simulated COVID-19 disease prevalence levels and compare it to radiologists, highlighting its potential role as an adjunctive diagnostic tool to PCR testing with good sensitivity and high NPV, which may be of utility in resource-constrained regions when COVID-19 levels are endemic. Additionally, implementation of RadGenX is simple, requiring only digital radiography and a personal computer—both of which are ubiquitous in medical clinics worldwide. More broadly, this study provides a set of parameters and realistic expectations that could be useful for studying and gauging radiological AI model performance, which is particularly relevant as an increasing number of AI models seek broad and general deployment across diagnostic imaging practices.

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Affiliations:

¹Department of Radiological, Oncological and Pathological Sciences, Sapienza University of Rome, Rome; Italy

²Radiology Department, Queen Mary Hospital; Hong Kong SAR, China

³Department of Medicine, LKS Faculty of Medicine, The University of Hong Kong; Hong Kong SAR, China

⁴Department of Clinical, Surgical, Diagnostic and Pediatric Sciences, University of Pavia; Italy

⁵Radiology Department, Mayo Clinic; Rochester, Minnesota, USA

⁶Department of Radiology, Fondazione IRCCS Policlinico San Matteo; Italy

⁷Department of Medical and Surgical Specialties, Radiological Sciences and Public Health, University of Brescia, ASST Spedali Civili of Brescia; Italy

⁸School of Public Health, LKS Faculty of Medicine, The University of Hong Kong; Hong Kong SAR, China

⁹Department of Medical and Surgical Sciences for Children & Adults, Modena and Reggio Emilia University; Italy

¹⁰Division of Radiology, Azienda Ospedaliero-Universitaria Policlinico di Modena; Italy

¹¹Division of Education, Research and Innovation, Azienda Ospedaliero-Universitaria Policlinico di Modena; Italy

¹²Radiology Department, United Christian Hospital; Hong Kong SAR, China

¹³Department of Radiological and Hematological Sciences, Section of Radiology, Università Cattolica del Sacro Cuore; Rome, Italy

¹⁴Department of Diagnostic Imaging, Oncological Radiotherapy and Hematology, Fondazione Policlinico Universitario “A. Gemelli” IRCCS; Rome, Italy

¹⁵Institute of Microbiology and Division of Clinical Microbiology, Università Cattolica del Sacro Cuore, Rome; Italy

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Declarations

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Conflict of interest The authors of this manuscript declare relationships with the following companies: MDK is a founder, shareholder and unpaid part-time employee of Ensemble Group. DP is a part-time employee of Ensemble Group. The remaining authors declare that they have no competing interests. The remaining authors of this manuscript declare no relationships with any companies, whose products or services may be related to the subject matter of the article.

Statistics and biometry HZ kindly provided statistical advice for this manuscript and has significant statistical expertise. However, no complex statistical methods were necessary for this paper.

Informed consent Written informed consent was waived by the Institutional Review Board for each participating institution.

Ethical approval Institutional Review Board approval was obtained for each participating institution.

Methodology

- Retrospective
- Observational
- Multicenter study

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Affiliations

Michael D. Kuo^{1,2} · Keith W. H. Chiu¹ · David S. Wang³ · Anna Rita Larici^{4,5} · Dmytro Poplavskiy² · Adele Valentini⁶ · Alessandro Napoli⁷ · Andrea Borghesi⁸ · Guido Ligabue^{9,10} · Xin Hao B. Fang¹¹ · Hing Ki C. Wong¹² · Sailong Zhang¹ · John R. Hunter³ · Abeer Mousa¹³ · Amato Infante^{5,14} · Lorenzo Elia^{4,5} · Salvatore Golemi⁸ · Leung Ho P. Yu¹⁵ · Christopher K. M. Hui^{16,17} · Bradley J. Erickson¹³

¹ Medical Artificial Intelligence Laboratory Program, Department of Diagnostic Radiology, LKS Faculty of Medicine, The University of Hong Kong, Hong Kong SAR, China

² Ensemble Group Holdings, Ensemblehealth.ai, Scottsdale, AZ, USA

³ Department of Radiology, Stanford Health Care, Stanford, CA, USA

⁴ Section of Radiology, Department of Radiological and Hematological Sciences, Università Cattolica del Sacro Cuore, Rome, Italy

⁵ Department of Diagnostic Imaging, Oncological Radiotherapy and Hematology, Fondazione Policlinico Universitario “A. Gemelli” IRCCS, Rome, Italy

⁶ Department of Radiology, Fondazione IRCCS Policlinico San Matteo, Pavia, Italy

⁷ Department of Radiological, Oncological and Pathological Sciences, Sapienza University of Rome, Rome, Italy

⁸ Department of Medical and Surgical Specialties, Radiological Sciences and Public Health, University of Brescia, ASST Spedali Civili of Brescia, Brescia, Italy

⁹ Department of Medical and Surgical Sciences for Children & Adults, Modena and Reggio Emilia University, Modena, Italy

¹⁰ Division of Radiology, Azienda Ospedaliero-Universitaria Policlinico di Modena, Modena, Italy

¹¹ Radiology Department, Queen Mary Hospital, Hong Kong SAR, China

¹² Radiology Department, United Christian Hospital, Hong Kong SAR, China

¹³ Radiology Department, Mayo Clinic, Rochester, MN, USA

¹⁴ Columbus Covid 2 Hospital, Rome, Italy

¹⁵ Department of Mathematics and Information Technology, The Education University of Hong Kong, Hong Kong SAR, China

¹⁶ Department of Medicine, LKS Faculty of Medicine, The University of Hong Kong, Hong Kong SAR, China

¹⁷ Department of Respiratory & Critical Care Medicine, Matilda & War Memorial Hospital, Hong Kong SAR, China