

Chest radiography to assess and prognosticate COVID-19

Terrence Chi Hong Hui

Department of Diagnostic Radiology, Tan Tock Seng Hospital

Hau Wei Khoo

Department of Diagnostic Radiology, Tan Tock Seng Hospital

Barnaby Edward Young

National Centre for Infectious Diseases and Department of Infectious Diseases, Tan Tock Seng Hospital and Lee Kong Chian School of Medicine, Singapore

Sean Wei Xiang Ong

National Centre for Infectious Diseases and Department of Infectious Diseases, Tan Tock Seng Hospital, Singapore

Salahudeen Mohamed Haja Mohideen

Department of Diagnostic Radiology, Singapore General Hospital

Shirin Kalimuddin

Department of Infectious Diseases, Singapore General Hospital and Duke-NUS Medical School, Singapore

Jenny Guek-Hong Low

Department of Infectious Diseases, Singapore General Hospital and Duke-NUS Medical School, Singapore

Charlene Jin Yee Liew

Department of Diagnostic Radiology, Changi General Hospital

Seow Yen Tan

Department of Infectious Diseases, Changi General Hospital, Singapore

Shawn Shi Xian Kok

Department of Radiology, Sengkang General Hospital, Singapore

Jiashen Loh

Department of Infectious Diseases, Sengkang General Hospital, Singapore

Lai Peng Chan

Department of Diagnostic Radiology, Singapore General Hospital and Yong Loo Lin School of Medicine, National University of Singapore, Singapore

Angeline Choo Choo Poh

Department of Diagnostic Radiology, Changi General Hospital, Singapore

Steven Bak Siew Wong

Department of Radiology, Sengkang General Hospital, Singapore

Chien Joo Lim

Clinical Research & Innovations Office, Tan Tock Seng Hospital, Singapore

Raymond Tzer Pin Lin

National Centre for Infectious Diseases, Singapore

Yee-Sin Leo

National Centre for Infectious Diseases and Department of Infectious Diseases and Lee Kong Chian School of Medicine and Yong Loo Lin School of Medicine and Saw Swee Hock School of Public Health, National University of Singapore, Singapore

Gregory Jon Leng Kaw

Department of Diagnostic Radiology, Tan Tock Seng Hospital, Singapore

David Chien Lye

National Centre for Infectious Diseases and Department of Infectious Diseases, Tan Tock Seng Hospital and Lee Kong Chian School of Medicine and Yong Loo Lin School of Medicine, National University of Singapore, Singapore

Cher Heng Tan (✉ cher_heng_tan@ttsh.com.sg)

Department of Diagnostic Radiology, Tan Tock Seng Hospital and Lee Kong Chian School of Medicine, Singapore

Research Article

Keywords: COVID-19, chest radiography, radiographic scoring system

Posted Date: April 8th, 2020

DOI: <https://doi.org/10.21203/rs.3.rs-21854/v1>

License:  This work is licensed under a Creative Commons Attribution 4.0 International License. [Read Full License](#)

Abstract

Background To determine the utility of chest radiography (CXR) for assessing and prognosticating COVID-19 disease with an objective radiographic scoring system.

Methods A multicenter, prospective study was conducted, forty patients were included. Seventy-eight CXR's were performed on the first derivation cohort of twenty patients with COVID-19 (median age 47.5 years, 10 females and four with comorbidities) admitted between 22 January 2020 and 1 February 2020. Each CXR was scored by three radiologists in consensus and graded on a 72-point COVID-19 Radiographic Score (CRS). This was correlated with supplemental oxygen requirement, C-reactive protein (CRP), lactate dehydrogenase (LDH) and lymphocyte count. To validate our findings, the parameters of another validation cohort of twenty patients with 65 CXRs were analysed.

Results In the derivation cohort, seven patients needed supplemental oxygen and one was intubated for mechanical ventilation with no death. The maximum CRS was significantly different between patients on and not on supplemental oxygen ($p < .001$). There was strong correlation between maximum CRS and lowest oxygen saturation ($r = -.849$), maximum CRP ($r = .832$) and maximum LDH ($r = .873$). These findings were consistent in the validation cohort. An increment of 2 points in CRS had an accuracy of 0.938 with 100.0% sensitivity (95% CI 100.0-100.0) and 83.3% (95% CI 65.1-100.0) specificity in predicting supplemental oxygen requirement.

Conclusion Using an objective scoring system (CRS), the degree of abnormalities on CXR correlates closely with known markers of disease severity. CRS may further be applied to predict patients who require oxygen supplementation during the course of their disease.

Introduction

Coronavirus disease 2019 (COVID-19) was first reported in the Chinese city of Wuhan in mid- December 2019. (1) The causative severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) represents the third zoonotic novel coronavirus to cause potentially fatal human lower respiratory tract infection.(1) Compared with SARS-CoV and Middle East respiratory syndrome (MERS)-CoV, SARS-CoV-2 appears less pathogenic but more transmissible.(2, 3) As of 19 March 2020, more than 230,000 COVID-19 cases and 9800 deaths have been reported globally.(4)

Reports from China emphasised the use of computed tomography (CT) of the chest in the diagnostic criteria of SARS-CoV-2 as CT was reported to be more sensitive than nucleic acid detection from small case series in China.(5-9) In early reports from Wuhan, CT appeared to be used exclusively which showed bilateral pulmonary infiltrates in 98-100% of patients.(10, 11) Guidance from United States Center for Disease Control and Prevention as well as World Health Organization is silent on the choice of radiology and emphasises the use of real-time reverse transcription polymerase chain reaction (RT-PCR).(12, 13)

In Singapore and many parts of the world, chest X-ray (CXR) is an essential imaging modality in the diagnosis and management of COVID-19. It is widely available, low cost and can be performed at bedside. Movement of patients with COVID-19 out of negative pressured isolation rooms is minimized unless clinically indicated to avoid nosocomial transmission. During SARS, radiographic scores for CXR correlated well with hypoxia.(14)

Similarly, the Radiographic Assessment of Lung Edema (RALE) score was useful in gauging the severity of acute respiratory distress syndrome (ARDS).(15)

The objectives of this study are to investigate the utility of CXR objectively (using a radiographic scoring system – COVID–19 Radiographic Score [CRS]), examine the correlation between extent of CXR abnormalities and other known markers of severity, and determine how well CRS predicts the need for supplemental oxygen in patients with COVID–19 .

Methods

Clinical management and data collection

A multicenter prospective study of all patients with COVID–19 confirmed by RT-PCR (supplementary material) and hospitalized in Singapore between 22 January 2020 and 1 February 2020 was performed. In Singapore, Ministry of Health alerted all doctors to refer patients fulfilling prevailing case definitions of COVID–19 (supplementary table 1) to National Centre for Infectious Diseases (NCID) for evaluation; patients may present on their own to any hospital emergency. Patients were isolated in single rooms with negative pressure and anteroom, and movement out of isolation rooms was minimized to prevent nosocomial transmission.

At baseline, patients underwent CXR and blood investigations including complete blood count, renal and liver function tests, C-reactive protein (CRP) and lactate dehydrogenase (LDH). Complete blood count, CRP, LDH and CXR were repeated at interval to monitor disease progression. Lopinavir-ritonavir was offered as an antiviral after discussion on limited in vitro and animal data, and clinical experience in SARS before verbal informed consent was obtained from patients.(16) Daily nasopharyngeal samples for RT-PCR for SARS-CoV–2 was taken to document cessation of viral shedding; two negative PCR's 24 hours apart were required before de-isolation and hospital discharge. Empiric broad-spectrum antibiotics and oseltamivir were prescribed for suspected community-acquired pneumonia, which were ceased if no bacterial cause or influenza was detected. Corticosteroid was avoided given inconsistent data and potential harm in SARS- CoV.(16) Approval to collect clinical data was obtained from Ministry of Health, Singapore for patients who did not participate in PROTECT study (National Healthcare Group Domain Specific Review Board, Study Reference 2012/00917) and “A prospective study to detect novel pathogens & characterize emerging infections” (SingHealth Centralized Institutional Review Board

Reference 2018/3045), otherwise informed consent was obtained. A standardized case report form modified from ISARIC was used to extract age, gender, smoking history, comorbidities, symptoms and signs, vital signs, hematology and biochemistry data.(17)

Radiological assessment

All CXR's were acquired on digital radiography, exported from Picture Archiving and Communication System, in Digital Imaging and Communications in Medicine format, and anonymized. All CXR's were reviewed on a 2048x2048-pixel monitor (Barco, Sunnyvale, CA, USA) by 3 fellowship-trained radiologists with 12, 15 and 17 years of experience respectively and the CXR's were graded in consensus. The readers were blinded to the subjects' clinical outcome and the CXR's were randomized. The radiographs were first determined to be 'normal'

or 'abnormal'. A 'normal' radiograph was defined as devoid of opacity in the lung fields and absence of ancillary findings such as pleural effusion and pneumothorax. Radiographs with opacities were deemed 'abnormal' and assessed for predominant pattern and distribution of opacities. Predominant pattern of opacities may be consolidation (homogeneous opacification, obscuring the blood vessels), ground-glass (hazy opacity without obscuring the blood vessels), nodular (focal round opacities) or reticular opacities (linear opacities). An opacity was considered central if most of it was within 2/3 of the hilum and peripheral if it was in the outer 1/3 of the hemithorax.

An objective COVID-19 Radiographic Score (CRS) was calculated for each CXR modified from the RALE score. (15) Each lung field was divided into three zones (upper, middle, lower); each zone spanned one-third of the lung field craniocaudally. Each lung zone was scored for extent of opacities (Grade 0, no opacity; Grade 1, <25% opacity; Grade 2, 25-49% opacity; Grade 3, 50-74% opacity; Grade 4, >75% opacity). The density of the opacity was scored (Grade 0, clear; Grade 1, hazy [vessel markings clearly visible]; Grade 2, moderate [vessel markings are partially obscured]; Grade 3, dense [vessels are obscured, air-bronchograms may be present]). *Figure 1* illustrates how the score was tabulated. For each zone, the extent of involvement was multiplied by the density yielding a score upon 12. The sum of the scores of each zone was tabulated to give a total score upon 72.

Statistical analysis

The primary study endpoint was the need for supplemental oxygen, usually administered if oxygen saturation by pulse oximetry was <92%. Mann-Whitney U test was used to assess the difference between continuous variables and Fisher's exact test for categorical variables for patients with and without supplemental oxygen. Spearman correlation was used to test the correlation between maximum CRS with maximum CRP, maximum LDH, lowest lymphocyte count and lowest oxygen saturation. Lower lymphocyte count and higher LDH were significantly associated with intensive care unit admission while higher CRP with desaturation in our case series.(10, 11, 18)

To investigate if an increase in CRS can predict the need for supplemental oxygen, we calculated the difference between the CRS of the initial CXR and CRS of a subsequent CXR within 48 hours prior to desaturation and oxygen supplementation. For patients without supplemental oxygen, the difference between the CRS of the initial CXR and the maximum CRS was used. In this analysis, patients who needed oxygen therapy on admission or had only one CXR were excluded. Receiver operator curve (ROC) analysis, including area under ROC, sensitivity, specificity, positive and negative predictive values, was performed for each variable: change in CRS (Δ CRS), CRS, CRP, LDH and lymphocyte count. A cut-off value that provided optimal sensitivity and specificity in predicting the need for supplemental oxygen was subsequently derived for each of these variables.

To validate CRS, we recruited another cohort of COVID-19 patients at NCID fulfilling the same criteria of having at least one CXR and seven days of inpatient follow-up. Chest radiographs were scored with CRS and a similar analysis was performed. The results from the validation cohort was compared with the derivation cohort (study population).

Statistical analysis was performed using IBM SPSS version 19.0 (IBM Corp, Armonk, NY). All statistical tests were two-sided and P value <0.05 was considered statistically significant.

Results

Characteristics of the forty included patients on hospital admission including initial CXR, and comparison of baseline data between patients with and without supplemental oxygen are summarized in *Table 1*. Briefly, for the main derivation cohort of twenty patients, the mean age was 47.5 years (range, 31–74 years), females comprised half the patients, only four had comorbidities and median time from symptom onset to admission was 1 day (range, 0–9 days). Two patients required oxygen at presentation and another five desaturated subsequently during the course of hospitalization. One required intubation for mechanical ventilation with no death. The most common symptoms were fever (75%), cough (80%) and sore throat (55%); diarrhea was reported in 15%. Leukopenia was noted in seven (35%), lymphopenia in nine (45%) and thrombocytopenia in six (30%). Older age and an elevated CRP were significantly associated with desaturation and need for supplemental oxygen. Compared with the derivation cohort, the twenty patients in the validation cohort presented later, more reported dyspnea and required oxygen on admission. Reported fever, higher measured temperature, lower lymphocyte, and higher CRP and LDH were significantly associated with need for supplemental oxygen in the validation cohort.

A total of 78 CXR's were performed on the first twenty patients (61 anteroposterior, eight posteroanterior, nine supine) (median CXR per patient 3, range 1–11). The median time from symptom onset to first CXR was 1.5 days (range, 0–9 days). On admission, ten initial CXR's were 'abnormal'. Of the ten abnormal CXR's, eight showed consolidation as the predominant pattern of opacity and two showed predominantly ground-glass opacities. Pattern of distribution were mixed peripheral and central (n = 5), central (n = 4) and peripheral (n = 1). Of the ten patients with initial normal CXR, three developed CXR changes and two desaturated during hospitalization requiring supplemental oxygen. Seven patients had 'normal' CXR's throughout hospitalization and none required supplemental oxygen. Hence, two of ten (20%) patients with initial normal CXR versus five of ten (50%) patients with initial abnormal CXR desaturated subsequently after admission (P = 0.350).

The median initial CRS for all patients in the derivation cohort was 1 (range, 0–19) with no statistically significant difference between patients with or without supplemental oxygen. However, an initial CRS ≥ 5 appeared to differentiate patients with or without supplemental oxygen (4 of 7 and 1 of 13, P = 0.031). Of the thirteen patients with at least one abnormal CXR, the median time from symptom onset to maximum CRS was 6 days (range, 0–11 days) and the median time from first CXR to maximum CRS was 2 days (range, 0–8 days). The median increase in CRS was 8.5 (range, 3–13) versus 0 (range, 0–9) between patients with and without supplemental oxygen (P = 0.008).

Comparison of initial and maximum CRS, maximum CRP, maximum LDH and lowest lymphocyte count between patients who needed supplemental oxygen versus those who did not in both derivation and validation cohorts is shown in *Table 2*. Maximum CRS (p = <.001), maximum CRP (p = <.001), maximum LDH (p = .001) and lowest lymphocyte count (p = 0.037) were significantly different between the two groups. Comparable performance characteristics were observed in the validation cohort which showed initial CRS (p = 0.01), maximum CRS (p = <0.01), maximum CRP (p = <0.01), maximum LDH (p = <0.01) and lowest lymphocyte count (p = <0.01) to be significantly different between the two groups. The results of the Spearman's Rank correlation tests are shown in *Figure 2*. There was strong correlation between maximum CRS and CRP (coefficient 0.832, p \leq 0.001), maximum LDH (coefficient = 0.873, p \leq 0.001) and lowest oxygen saturation (coefficient = -0.849, p = <0.001). Moderate correlation was found between maximum CRS and lowest lymphocyte count (coefficient = -.662, p = 0.001).

Figure 3 illustrates the ROC analysis of change in CRS, CRS, CRP, LDH and lymphocyte count prior to desaturation and need for supplemental oxygen in the derivation cohort. For the oxygenation group, the median time between CXR prior to desaturation and start of oxygen was 0.5 days (range 0–2 days). An increase in CRS (area under ROC [AUROC]: 0.938) and an elevated CRP (AUROC: 0.972) had high accuracy in predicting desaturation. Cut-off values were determined to optimize sensitivity and specificity (Table 3). An increase of 2 points in CRS (sensitivity 100.0%, specificity 83.3%, positive predictive value 66.7%, negative predictive value 100.0%) and serum CRP of ≥ 26.95 mg/L (sensitivity 100.0%, specificity 88.9%, positive predictive value 80.0%, negative predictive value 100.0%) performed best in predicting desaturation and need for supplemental oxygen. Because five of six patients on oxygen required it on admission, this analysis could not be performed for the validation cohort because of small number of patients with the primary endpoint.

Discussion

Half of the CXR at presentation in our initial derivation cohort of twenty patients were “normal”. This could be because patients did not yet develop pneumonia at initial presentation, CXR is insensitive in detecting pulmonary parenchymal involvement or some patients do not progress to pneumonia in COVID–19. Interestingly, three of these ten patients developed new CXR changes and two patients desaturated while all seven patients whose CXR remained “normal” did not desaturate. This observation prompted us to investigate a more sensitive method of evaluating CXR changes in COVID–19. We found an initial CRS value ≥ 5 differentiated patients who required supplemental oxygen from those who did not. Although CT chest has been widely used in reported studies of COVID–19 (5,10,11), and may precede a positive RT-PCR in patients at risk for COVID–19 (9), the imaging features of COVID–19 are not specific and overlap with other viral pneumonia, such as seasonal and avian influenza, and SARS.(14, 15) Additionally, Chung et al found that three of twenty-one initial CT chest of COVID–19 patients showed no ground glass or consolidative opacity.(16) Our study showed that CXR was clinically useful in its ability to reflect disease severity and prognosticate oxygen supplementation without the need for transfer to the imaging department for CT scan.

Huang et al found higher levels of inflammatory cytokines in patients requiring ICU admission versus the non-ICU group.(10) While the pathogenesis of pneumonia in COVID–19 is not well understood, this suggested that a ‘cytokine storm’ triggered by the virus resulted in lung inflammation and parenchymal damage similar to SARS.(12) Higher LDH and lower lymphocyte count were observed in patients requiring ICU versus no ICU.(10, 11) Our data showed higher CRP in patients needing oxygen versus those who did not. We found that maximum CRS correlated well with maximum LDH ($r = .873$) and CRP ($r = .832$), and inversely correlated with lymphocyte count ($r = -.662$) and oxygen saturation ($r = -.849$). In a study on patients with SARS, Ooi et al found that their maximal radiographic score correlated inversely with oxygen saturation.(14)

In our study, maximum CRS was significantly different between patients with or without supplemental oxygen, suggesting CRS may be a useful marker of disease severity. We found that an increase of ≥ 2 points in CRS and a CRS score of ≥ 5.5 had good sensitivity and negative predictive value (sensitivity 100% and 80%, and negative predictive value 100% and 91% respectively) in identifying patients needing supplemental oxygen.

Notably, applying the CRS score cut-off of ≥ 5.5 on a second validation cohort of twenty patients was important. Our findings in this cohort attested to the high sensitivity (100%) of using the CRS, in predicting the need for supplemental oxygen. Interestingly, serum CRP ≥ 26.95 mg/L and a low lymphocyte count < 0.74 remained highly

sensitive too. In practice, the CXR is simple and immediately available for viewing while blood investigations take time, making it useful to screen for high-risk individuals who require intensive monitoring and oxygen therapy.

There are several limitations to our pilot study: (a) Small sample size. Despite that, the results of our validation cohort paralleled closely that of the initial derivation cohort. (b) There were differences in CXR frequency across the four hospitals. To ensure meaningful analysis of the predictive value of CXR, we specifically excluded CXR performed on the same day as oxygen supplementation. In doing so, we were not able to assess five out of six of the patients (all of whom had CRS ≥ 5.5 [median 15, 9–24]) in the validation cohort. (c) Patients were followed up for a minimum of 7 days, not to discharge or death in this early part of the epidemic; hitherto there was no death among the Singapore cohort. To minimize subjectivity, a common problem with CXR interpretation, we adopted CRS as an objective scoring method. Ongoing work is taking place to combine CRS with laboratory markers (CRP and LDH) in a larger sample of COVID–19 patients. Work on convoluted neural networks (artificial intelligence) for detecting COVID–19 pneumonia with CXR has started. Artificial intelligence has the potential to reliably provide an objective assessment in the setting of COVID–19 and allow immediate segregation of patients with CXR abnormality from others seeking care, while awaiting verification by a radiologist.

In conclusion, the degree of CXR abnormalities graded using CRS correlates closely with known markers of disease severity in COVID–19. CRS may be further applied to predict patients who require oxygen supplementation during the course of their disease.

References

1. Zhu N, Zhang D, Wang W, Li X, Yang B, Song J, et al. A Novel Coronavirus from Patients with Pneumonia in China, 2019. *N Engl J Med*.
2. Chen J. Pathogenicity and Transmissibility of 2019-nCoV-A Quick Overview and Comparison with Other Emerging Viruses. *Microbes Infect*.
3. Liu Y, Gayle AA, Wilder-Smith A, Rocklöv J. The reproductive number of COVID-19 is higher compared to SARS coronavirus. *J Travel Med*.
4. Coronavirus disease 2019 (COVID-19) Situation Report – 60: World Health Organization; 2020 [Available from: https://who.int/docs/default-source/coronaviruse/situation-reports/20200320-sitrep-60-covid-19.pdf?sfvrsn=8894045a_2]
5. Zhang J, Zhou L, Yang Y, Peng W, Wang W, Chen X. Therapeutic and triage strategies for 2019 novel coronavirus disease in fever clinics. *Lancet Respir Med*.
6. Duan YN, Qin J. Pre- and Posttreatment Chest CT Findings: 2019 Novel Coronavirus (2019-nCoV) Pneumonia. *Radiology*. 2020:200323.
7. Xie X, Zhong Z, Zhao W, Zheng C, Wang F, Liu J. Chest CT for Typical 2019-nCoV Pneumonia: Relationship to Negative RT-PCR Testing. *Radiology*. 2020:200343.
8. Fang Y, Zhang H, Xu Y, Xie J, Pang P, Ji W. CT Manifestations of Two Cases of 2019 Novel Coronavirus (2019-nCoV) Pneumonia. *Radiology*. 2020:200280.
9. Lei J, Li J, Li X, Qi X. CT Imaging of the 2019 Novel Coronavirus (2019-nCoV) *Radiology*. 2020:200236.
10. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet*.

11. Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, et al. Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus-Infected Pneumonia in Wuhan, China. *JAMA*.
12. Interim Clinical Guidance for Management of Patients with Confirmed 2019 Novel Coronavirus (2019-nCoV) Infection: Centers for Disease Control and Prevention; 2020 [Available from: <https://cdc.gov/coronavirus/2019-ncov/hcp/clinical-guidance-management-patients.html>].
13. Coronavirus disease (COVID-19) technical guidance: World Health Organization; 2020 [Available from: <https://who.int/emergencies/diseases/novel-coronavirus-2019/technical-guidance>].
14. Ooi CG, Khong PL, Lam B, Ho JC, Yiu WC, Wong WM, et al. Severe acute respiratory syndrome: relationship between radiologic and clinical parameters. *Radiology*. 2003;229(2):492-9.
15. Warren MA, Zhao Z, Koyama T, Bastarache JA, Shaver CM, Semler MW, et al. Severity scoring of lung oedema on the chest radiograph is associated with clinical outcomes in ARDS. *Thorax*. 2018;73(9):840-6.
16. Stockman LJ, Bellamy R, Garner P. SARS: systematic review of treatment effects. *PLoS* 2006;3(9):e343.
17. COVID-19 Clinical Research Resources: ISARIC; 2020 [Available from: isaric.tghn.org/covid-19-clinical-research-resources/].
18. Young BE, Ong SWX, Kalimuddin S, Low JG, Tan SY, Loh J, et al. Epidemiologic Features and Clinical Course of Patients Infected With SARS-CoV-2 in Singapore. *JAMA*.

Declarations

Funding

This work was supported by the Singapore National Medical Research Council [NMRC Ref TR19NMR119SD; Project Ref. No.: CCGSFPOR20001].

Competing Interests

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: no support from any organization for the submitted work; no financial relationships with any organizations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

Acknowledgements

We thank all clinical and nursing staff who provided care for the patients at National Centre for Infectious Diseases, Singapore General Hospital, Changi General Hospital and Sengkang General Hospital; and staff in Singapore Infectious Disease Clinical Research Network and Infectious Disease Research and Training Office, National Centre for Infectious Diseases for coordinating patient recruitment.

Author Contributions

TCHH, HWK, DCL, CHT conceptualized the paper with inputs from GJLK, SMHM, CJYL. TCH H, HWK, BEY, SWXO, SMHM, SK, JGL, CJYL, SYT, SSXK, JL, LPC, ACCP, SBSW, CJL, RTPL, YSL, GJLK, DCL, CHT (all authors) were

involved in the design of the project. BEY, SK, SYT, SSXK, TCHH, HWK collected the clinical data (acquisition). SMHM, CJYL and CHT reviewed the CXRs in consensus. CJL and TCHH analyzed the data with inputs from DCL, CHT, BEY, YSL. TCHH, CHT, DCL, CJL wrote the initial draft. TCH H, HWK, BEY, SWXO, SMHM, SK, JGL, CJYL, SYT, SSXK, JL, LPC, ACCP, SBSW, CJL, RTPL, YSL, GJLK, DCL, CHT (all authors) provided critical feedback and edits to subsequent revisions. All authors approved the final draft of the manuscript. DCL is the study's guarantor. The corresponding author (CHT) attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

Ethics approval and informed consent

Approval to collect clinical data was obtained from Ministry of Health, Singapore for patients who did not participate in PROTECT study (National Healthcare Group Domain Specific Review Board, Study Reference 2012/00917) and "A prospective study to detect novel pathogens & characterize emerging infections" (SingHealth Centralized Institutional Review Board Reference 2018/3045), otherwise informed consent was obtained. All methods were carried out in accordance with relevant guidelines and regulations.

Notation of prior abstract publication/presentation

None

Tables

Table 1: Characteristics of patients with COVID-19 on hospital admission

Variable	Derivation (n=20)			Validation (n=20)		
	Total	Needed Supplemental Oxygen		Total	Needed Supplemental Oxygen	
		Yes=7	No=13		Yes=6	No=14
Age (years), median (95%CI)	47.5 (38.0, 56.0)	57.0 (47.0, 74.0)*	38.0 (32.0, 56.0)*	49.5 (40.0, 54.0)	53 (41.0, 71.0)	43.5 (35.0, 55.0)
Gender, n						
Male	10	3	7	13	6	7
Female	10	4	6	7	0	7
Smoker, n	8	3	5	1	0	1
Co-morbidities, n	4	3	1	3	2	4
Days from symptom onset to admission, median (95%CI)	1.0 (1.0, 3.0)	1.0 (0.0, 9.0)	1.0 (1.0, 3.0)	4 (2.0, 8.0)	8 (1, 9)	4 (1, 10)
Presenting symptoms, n						
Fever	15	7	8	12	6*	6*
Cough	16	6	10	14	4	10
Sputum production	6	2	4	5	2	3
Shortness of breath	2	1	1	7	3	4
Running nose	1	0	1	4	2	2
Sore throat	11	3	8	5	1	4
Diarrhea	3	0	3	3	2	1
Vital signs						
Temperature (°C), median (95%CI)	37.9 (37.1, 38.4)	37.7 (36.1, 39.3)	38.3 (36.8, 38.6)	37.7 (36.9, 38.4)	38.7 (37.7, 39.1)*	37.2 (36.3, 38.2)*
Mean arterial pressure (mmHg), median (95%CI)	93.3 (81., 102.3)	91.3 (78.3, 105.7)	93.5 (79.0, 102.3)	94.8 (91.0, 103.0)	98.3 (83.0, 139.0)	94.5 (88.3, 103.7)
Heart rate (beats per minute), median (95%CI)	93.0 (84.0, 100.0)	88.0 (78.0, 102.0)	99.0 (84.0, 101.0)	97 (83.0, 106.0)	108 (85.0, 133.0)	90.5 (67.0, 106.0)
Respiratory rate (breaths per minute), median (95%CI)	18.0 (17.0, 20.0)	20.0 (16.0, 21.0)	18.0 (17.0, 18.0)	18 (18.0, 19.0)	19 (17, 24)	18 (17, 19)
Oxygen saturation (%), median (95%CI)	98.0 (97.0, 98.0)	97.0 (95.0, 100.0)	98.0 (97.0, 100.0)	98 (96.0, 99.0)	95.5 (93-100)	98.5 (96-100)
Oxygen supplementation, n	2	2	0	5	5*	0*
Laboratory data						
Total white count x10 ⁹ /L, median (95%CI)	4.6 (3.8, 5.5)	3.8 (2.6, 10.4)	4.6 (4.0, 5.7)	4.5 (4.0, 5.2)	4.4 (3.5, 9.6)	4.5 (3.9, 5.4)
Hemoglobin (g/dL), median (95%CI)	13.5 (12.8, 14.0)	13.3 (11.7, 14.0)	13.9 (11.8, 15.6)	14.3 (13.2, 14.9)	13.6 (11.6, 14.5)	14.6 (12.9, 15.3)
Platelet count x10 ⁹ /L, median (95%CI)	159.0 (132.0, 184.0)	160.0 (116.0, 217.0)	159.0 (129.0, 184.0)	207 (164.0, 261.0)	189.5 (147.0, 301.0)	207.0 (148.0, 275.0)
Neutrophil count x10 ⁹ /L, median (95%CI)	2.7 (2.1, 3.7)	2.1 (1.2, 9.8)	2.8 (2.2, 4.1)	2.6 (2.1, 3.1)	3.2 (2.8, 8.7)*	2.2 (1.4, 3.1)
Lymphocyte count x10 ⁹ /L, median (95%CI)	1.1 (0.8, 1.4)	1.1 (0.4, 1.7)	1.2 (0.8, 1.4)	1.2 (0.8, 1.8)	0.6 (0.5, 0.9)*	1.5 (0.9, 2.1) *
Creatinine (µmol/L), median (95%CI)	66.5 (50.0, 75.0)	66.0 (50.0, 78.0)	67.0 (44.0, 84.0)	59.5 (55.0, 64.0)	56.5 (41.0, 61.0)	62.0 (50.0, 78.0)
C-reactive protein (mg/L), median (95%CI)	18.3 (8.5, 67.4)	67.4 (47.5, 199.6)*	11.6 (1.5, 17.5)*	13.2 (2.5, 68.7)	125.6 (56.0, 231.7)*	7.3 (7.3, 1.3, 18.0) *
Lactate dehydrogenase (unit/L), median (95%CI)	487.5 (387.0, 629.0)	550.0 (512.0, 796.0)	432.0 (359.0, 629.0)	386 (352.0, 481.0)	515.0 (371.0, 655.0)*	373.5 (301.0, 447.0) *
Chest X-ray						
Abnormality detected on admission, n	10	5	5	14	5	9
Initial CRS, median (95%CI)	1.0 (0.0, 4.0)	7.0 (0.0, 19.0)	0.0 (0.0, 4.0)	2 (0.0, 9.0)	15 (0, 24)*	1 (0, 5) *
Initial CRS ≥5	5	4*	1*	8	5*	3*

* Denotes statistically significant differences between patients with and without supplemental oxygen for both derivation and validation cohorts. P-value of <.05 is considered statistically significant.

Table 2: COVID-19 Radiographic Scores and known severity markers for patients with COVID-19

Variable	Derivation (n=20)		Validation (n=20)	
	Needed Supplemental Oxygen		Needed Supplemental Oxygen	
	Yes=7	No=13	Yes=6	No=14
COVID-19 Radiographic Score (CRS)				
Initial CRS, median (95%CI)	7.0 (0.0, 19.0)	0.0 (0.0, 4.0)	15 (0, 24) *	1 (0, 5) *
Maximum CRS, median (95%CI)	23 (13.0, 44.0) *	0 (0.0, 10.0) *	24.5 (21.0, 48.0) *	2 (0.0, 6.0) *
Laboratory data				
Maximum CRP (mg/L), median (95%CI)	157.7 (73.2, 279.1) *	11.6 (2.2, 18.0) *	152.9 (60.5, 341.9) *	7.4 (01.3, 28.8) *
Maximum LDH (unit/L), median (95%CI)	796.0 (631.0, 932.0) *	432.0 (387.0, 520.0) *	877.5 (622.0, 1460.0) *	403.5 (339.0, 651.0) *
Lowest lymphocyte count x10 ⁹ /L, median (95%CI)	0.5 (0.4, 1.3) *	1.0 (0.8, 1.4) *	0.44 (0.38, 0.58) *	1.26 (0.91, 2.06) *

* Denotes statistically significant differences between patients with and without supplemental oxygen in both derivation and validation cohorts. P-value of <.05 is considered statistically significant.

Abbreviations: CRS, COVID-19 Radiographic Score; IQR, interquartile range; CRP, C-reactive protein; LDH, Lactate dehydrogenase

Table 3. Cut-off values for change in CRS, CRS, CRP, LDH and lymphocyte count for predicting the need for supplemental oxygen, and associated sensitivity, specificity, positive and negative predictive values (derivation cohort).

	Supplemental oxygen		Sensitivity (95%CI)	Specificity (95%CI)	PPV (95%CI)	NPV (95%CI)
	Yes=7	No=13				
Change in CRS			100.0 (100.0, 100.0)	83.3 (65.1, 100.0)	66.7 (43.6, 89.8)	100.0 (100.0, 100.0)
≥2	4	2				
<2	0	10				
CRS			80.0 (61.5, 98.5)	76.9 (57.5, 96.4)	57.1 (34.3, 80.0)	90.9 (77.6, 100.0)
≥5.5	4	3				
<5.5	1	10				
Serum CRP (mg/L)			100.0 (100.0, 100.0)	88.9 (71.8, 100.0)	80.0 (58.3, 100.0)	100.0 (100.0, 100.0)
≥26.95	4	1				
<26.95	0	8				
Serum LDH (U/L)			75.0 (51.5, 98.5)	77.8 (55.2, 100.0)	60.0 (33.4, 86.6)	87.5 (69.5, 100.0)
≥487.5	3	2				
<487.5	1	7				
Lymphocyte count x10 ⁹ /L			92.3 (80.0, 100.0)	80.0 (61.2, 98.5)	92.3 (80.0, 100.0)	80.0 (61.5, 98.5)
<0.74	4	1				
≥0.74	1	12				

Abbreviations: PPV, Positive predictive value; NPV, Negative predictive value; CRS, COVID-19 Radiographic Score; CI, Confidence Interval; CRP, C-reactive protein; LDH, Lactate dehydrogenase

Figures

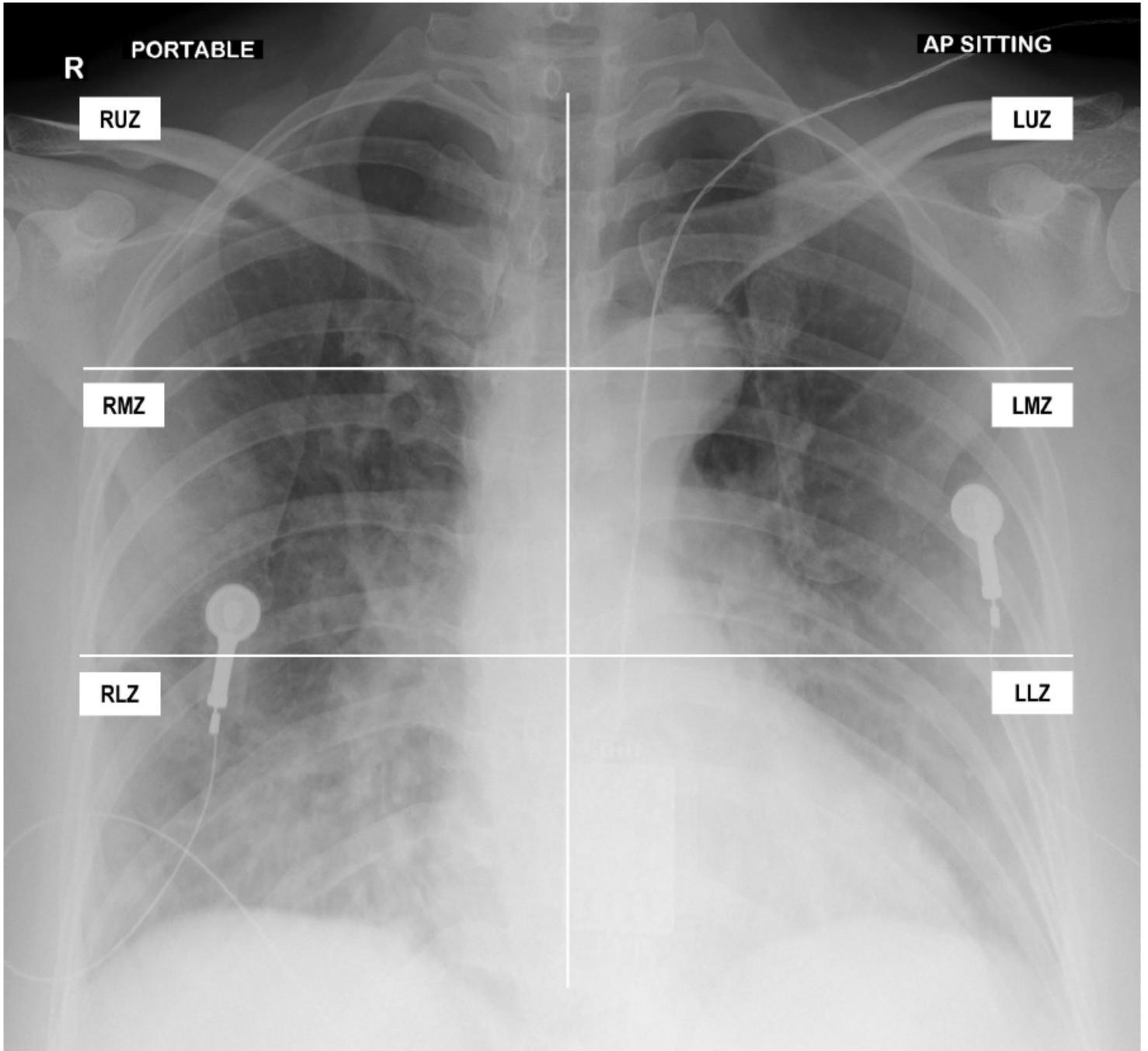


Figure 1

How COVID-19 Radiographic Score (CRS) was calculated in a 47-year-old female with COVID-19 infection. Right upper zone (RUZ) was graded 0 (no opacity), right middle zone (RMZ) was graded 2 (25-49% opacity) with grade 1 density, right lower zone was graded 4 (>75% opacity) with grade 2 (moderate) density, left upper zone (LUZ) was graded no opacity, left middle zone (LMZ) was graded 2 (25-49% opacity) with grade 2 (moderate) density, left lower zone was graded 3 (50-74% opacity) with grade 2 (moderate) density. A CRS of 20 (0+2+8+0+4+6) was obtained. The patient's SpO₂ was 92% on room-air.

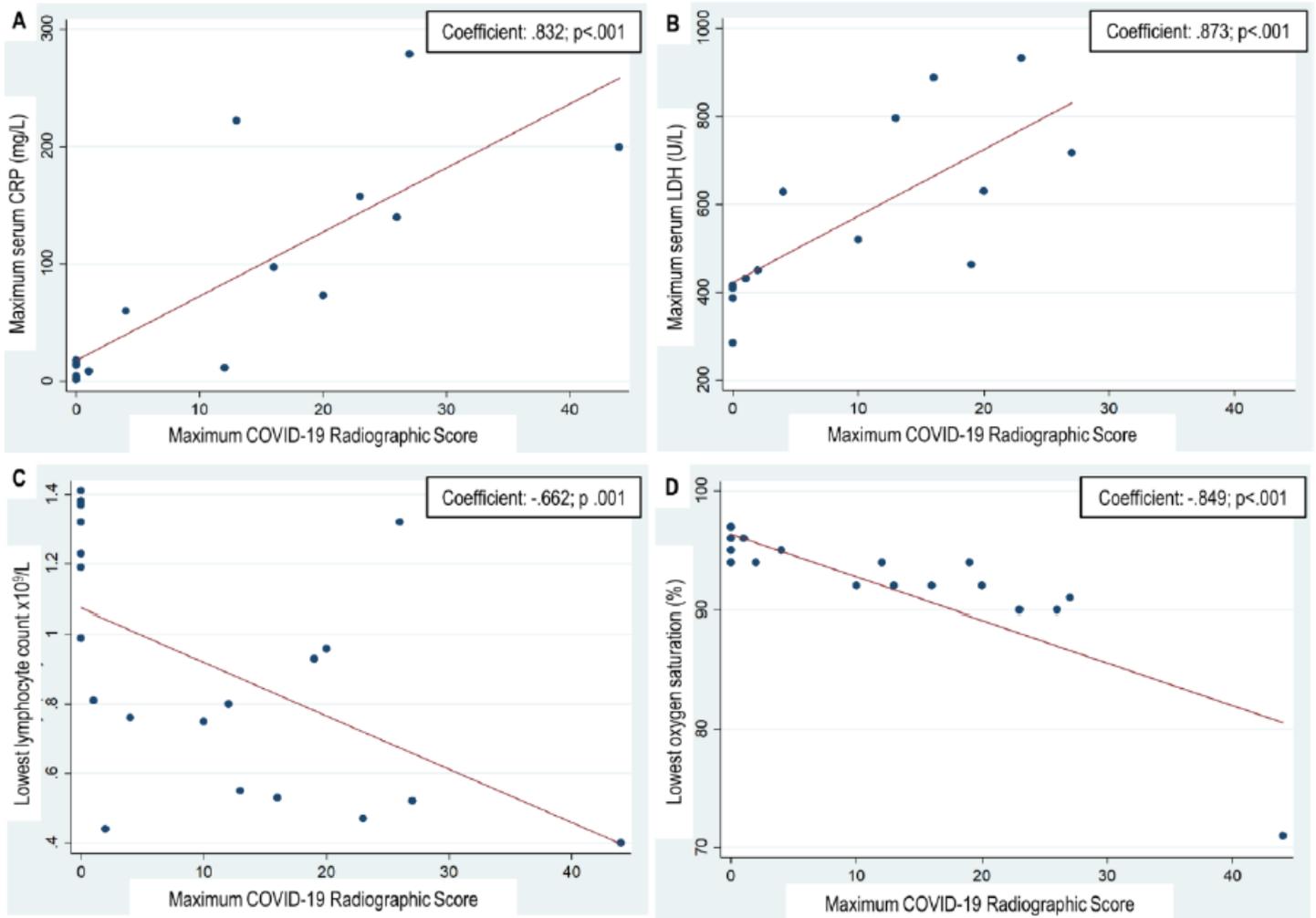


Figure 2

Scatterplot diagrams illustrate relationships between maximum COVID-19 Radiographic Score and (A) Maximum CRP, (B) Maximum LDH, (C) Lowest lymphocyte count and (D) Lowest oxygen saturation. Abbreviations: CRP, C-reactive protein; LDH, Lactate dehydrogenase

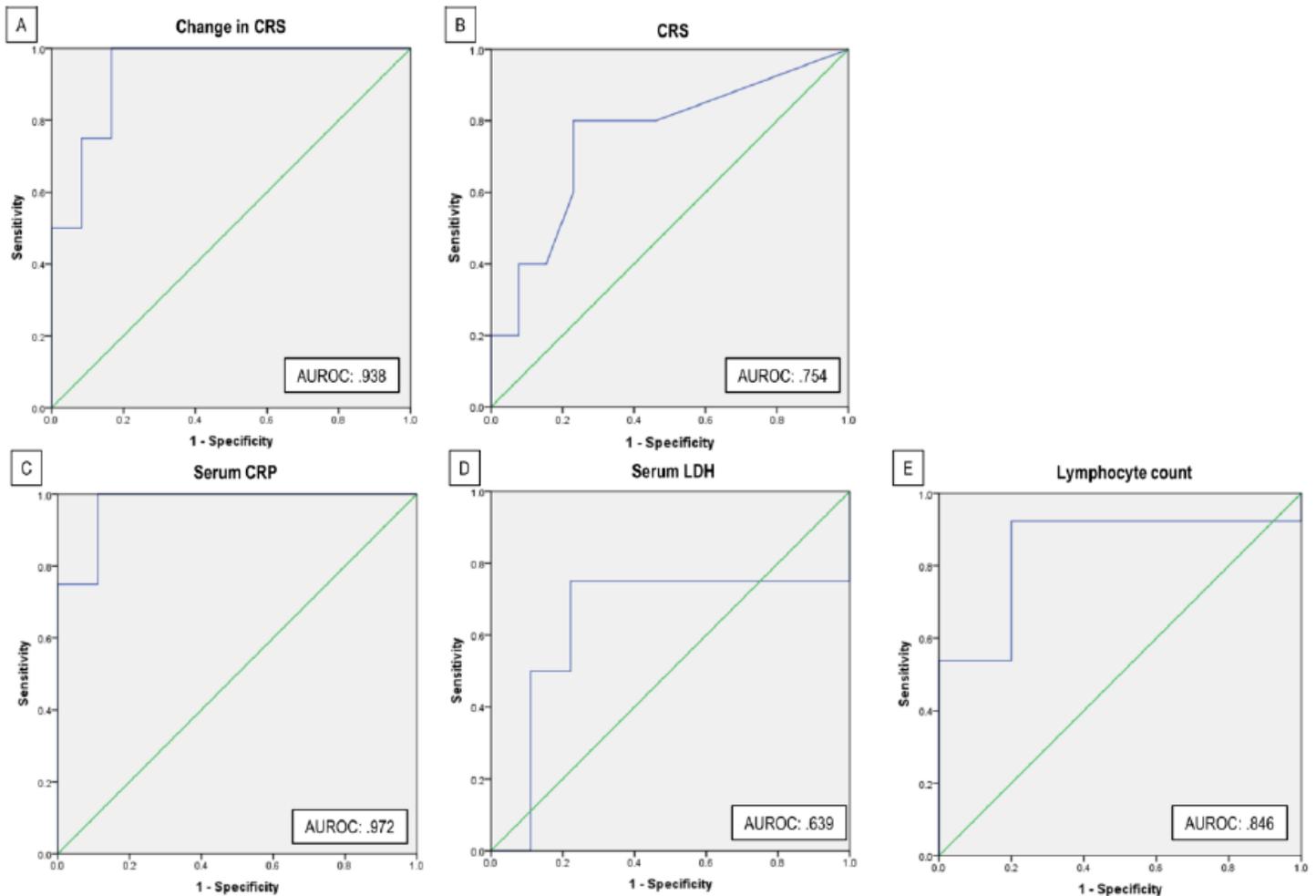


Figure 3

Accuracy of predicting the need for supplemental oxygen by receiver operating curve analysis for (A) Change in CRS, (B) CRS, (C) C-reactive protein, (D) Lactate dehydrogenase and (E) Lymphocyte count. Abbreviations: COVID-19 Radiographic Score; AUROC, Area under receiver operating curve; CRP, C-reactive protein; LDH, Lactate dehydrogenase

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [Supplementaryinformation.pdf](#)