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Title: Assessing the Severity of COVID-19 Lung Injury in Rheumatic Diseases versus the General Population Using Deep Learning-Derived Chest Radiograph Scores

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Abstract

Objective: COVID-19 patients with rheumatic disease have a higher risk of mechanical ventilation than the general population. We assessed lung involvement using a validated deep learning algorithm that extracts a quantitative measure of radiographic lung disease severity.

Methods: We performed a comparative cohort study of rheumatic disease patients with COVID-19 and ≥ 1 chest radiograph within ±2 weeks of COVID-19 diagnosis and matched comparators. We used unadjusted and adjusted (for age, Charlson Comorbidity Index, and interstitial lung disease) quantile regression to compare the maximum Pulmonary X-Ray Severity (PXS) score at the 10^{th}-90^{th} percentiles between groups. We evaluated the association of severe PXS score (>9) with mechanical ventilation and death using Cox regression.

Results: We identified 70 patients with rheumatic disease and 463 general population comparators. Maximum PXS scores were similar in the rheumatic disease patients and comparators at the 10^{th}-60^{th} percentiles but significantly higher among rheumatic disease patients at the 70^{th}-90^{th} percentiles (90^{th} percentile score of 10.2 vs. 9.2, adjusted p=0.03). Rheumatic disease patients were more likely to have a PXS score >9 (20% vs. 11%, p=0.02), indicating severe pulmonary disease. Rheumatic disease patients with PXS scores >9 vs. ≤9 had higher risk of mechanical ventilation (HR 24.1 [95% CI: 6.7, 86.9]) and death (HR 8.2 [95% CI: 0.7, 90.4]).

Conclusions: Rheumatic disease patients with COVID-19 had more severe radiographic lung involvement than comparators. Higher PXS scores were associated with mechanical ventilation and will be important for future studies leveraging big data to assess COVID-19 outcomes in rheumatic disease patients.

Significance and Innovation

- Rheumatic disease patients with COVID-19 may be at higher risk of poor outcomes, including mechanical ventilation and death, but differences in the severity of imaging findings of COVID-19-associated lung disease that may contribute to these associations remain poorly understood.
- Using the PXS score, a validated measure of lung disease severity in COVID-19, we found that rheumatic disease patients were more likely to have more severe lung disease compared to general population comparators with COVID-19.
- Among rheumatic disease patients, those with higher PXS scores (representing severe radiographic lung disease) were more likely to require mechanical ventilation or die than those with lower PXS scores.
- PXS scores may be leveraged in future studies using big data to assess outcomes of COVID-19 in patients with rheumatic disease.

Keywords: COVID-19, coronavirus, machine learning, chest radiograph, rheumatic disease

Introduction

Patients with rheumatic diseases and COVID-19 may have higher risk of mechanical ventilation and other poor outcomes versus general population comparators who also have COVID-19; factors driving these associations may include differences in comorbidity burden and immunosuppressive medication use.[1-6] These associations suggest that rheumatic disease patients have more severe COVID-19 lung disease, but the pulmonary manifestations of COVID-19 remain poorly understood in this population.

Among patients with symptomatic COVID-19 in the general population, radiographic severity correlates with severe COVID-19 outcomes.[7] However, there can be significant variability in the interpretation and grading of disease severity on radiographs. A convolutional Siamese neural network-based algorithm was previously validated to estimate COVID-19 radiographic severity on portable chest radiographs, yielding Pulmonary X-ray Severity (PXS) scores.[8] PXS scores correlate with manual assessment of lung severity (combined evaluation of density and extent of lung opacities) by multiple radiologists, and PXS scores from hospital admission radiographs were predictive of subsequent mechanical ventilation or death within three days.[8]

Higher radiographic severity of COVID-19, as indicated by higher PXS scores, may indicate more severe subsequent pulmonary complications of COVID-19 in rheumatic disease patients, explaining some of the observed associations between these conditions and higher risk of mechanical ventilation and/or death than the general population. Additionally, since rheumatic disease patients are more likely than the general population to have baseline chronic lung disease, it is unclear whether PXS scores may reliably predict risk of severe COVID-19

outcomes in this population. If so, deep learning-derived x-ray scores may be leveraged for use in larger studies evaluating the relationships between rheumatic disease, immunosuppression, imaging results, and COVID-19 outcomes. In this study, we examined whether patients with rheumatic disease and COVID-19 have worse PXS scores than general population comparators with COVID-19 and aimed to validate the use of the PXS score in rheumatic disease patients.

Materials and Methods

Study population and rheumatic disease identification

From a previously described cohort of patients at Mass General Brigham with confirmed rheumatic disease and COVID-19[1,2], we identified patients ≥18 years of age seen at Massachusetts General Hospital or Brigham and Women's Hospital (tertiary care hospitals in Boston, Massachusetts) between January 31, 2020 and January 31, 2021 who had chest radiographs performed within ± 2 weeks of their initial positive COVID-19 test result. This study was approved by the MGB Institutional Review Board (2020P000833). Patients were not involved in the design, conduct, or reporting of this study.

Comparator Identification

Each rheumatic disease patient was matched to up to 10 comparators without rheumatic disease; comparators also had confirmed COVID-19 (by polymerase chain reaction [PCR], or less commonly antigen testing) and a chest radiograph performed within ± 2 weeks of COVID-19 diagnosis. Rheumatic disease patients were matched based on age (± 5 years), sex, hospital site at which the chest radiograph was performed (to account for technical differences), and the date of positive COVID-19 test result (± 14 days, to control for calendar time since testing criteria, hospital capacity, and treatment strategies changed over time). The date of the earliest positive COVID-19 test was used as the index date.

Pulmonary X-ray Severity (PXS) Score

All patients included in the study had at least one chest radiograph within ± 2 weeks of COVID-19 diagnosis. Chest radiographs were assessed using a previously validated convolutional Siamese neural network algorithm to assess COVID-19 lung disease severity, which had been further tuned and tested for both anterior-posterior and posterior-anterior frontal chest views.[8,9] In this model, the inputs are pixel-level image data from frontal chest radiographs, and the output is a quantitative score of COVID-19 lung severity--the PXS score (https://github.com/QTIM-Lab/PXS-score). The PXS score quantifies the extent as well as the density of any pulmonary opacities and is not specific for COVID-19-related pulmonary findings. PXS scores range from approximately 0 to 24, with higher PXS scores indicative of more severe radiographic lung disease (**Figure 1**).

We defined a PXS score of ≤ 9 as indicating non-severe disease and a score > 9 as indicating severe disease based on previously determined thresholds.[10] Prior data have shown 5-fold higher odds of subsequent intubation or death within 3 days of hospital admission in the general population with PXS score > 9 compared to all patients n with COVID-19.[10] For those patients with multiple radiographs, we used the maximum PXS score within ± 14 days of COVID-19 diagnosis for each patient for the primary analysis; we also performed secondary analyses using initial PXS scores. For those who were mechanically ventilated, we used the maximum PXS score prior to the time of mechanical ventilation in the analysis assessing the risk of mechanical ventilation with high versus low maximum PXS score.

Covariates and Clinical Outcome Assessments

For the patients with rheumatic disease, clinical variables of interest were extracted from the electronic health record (EHR) by manual record review. These included the rheumatic

disease diagnosis and duration, immunomodulatory medications at the time of COVID-19 diagnosis (including specific dose of glucocorticoids when applicable), and disease activity level (based on global assessment by the treating provider as documented in the EHR).

For rheumatic disease patients and comparators, additional variables were extracted from the COVID-19 Data Mart, an EHR-based data enclave established by MGB that includes all patients diagnosed with COVID-19. Variables extracted from the COVID-19 Data Mart included location (outpatient, emergency department, or inpatient) of the maximally scored chest radiograph, site of COVID-19 test, demographics (age, sex, and self-identified race/ethnicity), smoking status, and medical comorbidities.[11] Baseline characteristics including comorbidities and body mass index (BMI) were assessed in the 1 year prior to the index date, and the Charlson Comorbidity Index (CCI) was calculated from diagnosis codes in the EHR using any data available prior to the index date.[12]

COVID-19 clinical outcomes, specifically mechanical ventilation and death, were also extracted from the COVID-19 Data Mart.

Statistical analysis

Categorical variables were presented as number (%) and continuous variables were presented as mean ± standard deviation (SD) or median ± interquartile range (IQR), as appropriate. Continuous variables were compared using a two-sample *t*-test for continuous normally distributed variables or Wilcoxon test for continuous non-normally distributed variables. Categorical variables were compared using Chi-square tests.

For each group (rheumatic disease patients and comparators), we determined the PXS score at the 10^{th}, 20^{th}, 30^{th}, 40^{th}, 50^{th}, 60^{th}, 70^{th}, 80^{th}, and 90^{th} percentiles. We then compared the PXS scores between matched rheumatic disease patients and comparators using unadjusted and

adjusted quantile regression at each percentile. We initially used unadjusted analyses since rheumatic disease patients and comparators were matched on a number of relevant potential confounders (e.g., age, sex, time of COVID-19 infection), and other covariates (e.g., comorbidity scores) are likely mediators of the association between the exposure (rheumatic disease versus no rheumatic disease) and the outcome (PXS score). We also performed adjusted quantile regression, adjusting for age, Charlson Comorbidity Index (dichotomized by <2 or ≥ 2), and interstitial lung disease in the 12 months prior to COVID-19 diagnosis. We used Poisson regression to compare the number of chest radiographs per subject. For both the time from COVID-19 diagnosis to initial or maximum PXS score and median initial PXS score, we used a Wilcoxon test for unadjusted analyses and quantile regression for adjusted analyses. We used a Chi-square test to compare the site where the maximally scored chest radiograph was performed in unadjusted analyses and multinomial regression in adjusted analyses. In unadjusted and multivariable adjusted quantile regression, we added an "id" variable to indicate matched sets in the MODEL statement to account for the correlation among subjects within the matched set.

In the analysis comparing the outcomes of mechanical ventilation and death between those with maximum PXS score > 9 (indicating severe lung disease) to those with a maximum PXS score ≤ 9 within ± 14 days of COVID-19 diagnosis, the index date was considered to be the time of either the initial or maximum PXS score. Person-months of follow-up were determined for each subject from the index date to the first of any of the following events: occurrence of the outcome of interest, death, or date of the last encounter in MGB at the time of data analysis. We calculated incidence rates as events/1,000 person-months. Cox proportional hazard regression models were used to estimate HRs and 95% CIs for the outcomes of mechanical ventilation and death, comparing patients with rheumatic diseases with maximum PXS score > 9 to those with a

maximum PXS score ≤9. We also performed a secondary analysis among rheumatic disease patients evaluating those with an initial PXS score > 9 to those with an initial PXS score ≤9 as well as a secondary analysis among general population comparators evaluating those with either an initial or maximum PXS score > 9 to those with an initial or maximum PXS score ≤9, respectively. The level of significance was set as a two-tailed $p<0.05$, and statistical analyses were completed using SAS statistical software (version 9.4; SAS Institute, Inc.).

Results

Cohort Characteristics

Out of 624 patients with rheumatic disease and confirmed COVID-19 who were seen at either Massachusetts General Hospital or Brigham and Women's Hospital, 70 patients had at least one chest radiograph available for review. Thus, 70 patients with rheumatic disease and 463 matched comparators, all with confirmed COVID-19, were included in our analyses. Patients with rheumatic disease and their comparators had similar demographics; the mean age was 62 years in each group, with 69% females in the rheumatic disease group and 68% females in the comparators (**Table 1**). The distribution of race/ethnicity and smoking status was similar between groups. The Charlson Comorbidity Index was higher in the rheumatic disease patients than comparators (median of 4 vs. 1, $p<0.001$). Four (6%) patients with rheumatic diseases had interstitial lung disease (ILD) compared with 5 (1%) in the comparator group ($p=0.005$). Among the patients with rheumatic disease, the most common diagnosis was rheumatoid arthritis (26, [37%]), followed by other inflammatory arthritis (12, [17%]) and systemic lupus erythematosus (10, [14%]) (**Table 2**). Many patients (27, [39%]) were taking oral glucocorticoids (median prednisone-equivalent daily dose of 5mg), and a majority were on other immunomodulatory medications (**Table 2**). Most COVID-19 tests were performed in the outpatient setting (43 [61%]

vs. 232 [50%] in rheumatic disease patients and comparators, respectively) rather than the emergency department or inpatient setting (27 [39%] vs. 231 [50%] in rheumatic disease patients and comparators, respectively) (p=0.08 for difference between groups across categories).

Comparisons of PXS scores between rheumatic disease patients and comparators

In 70 rheumatic disease patients, there were a total of 206 chest radiographs analyzed within two weeks of COVID-19 diagnosis date compared with 463 comparators who had 936 chest radiographs in the same time frame (**Table 3**). The majority of initial radiographs in each group were performed in the emergency department (40 [57%] vs. 295 [64%] in rheumatic disease patients and comparators, respectively) compared to 21 (30%) vs. 126 (27%) in the outpatient setting and 9 (13%) vs. 42 (9%) in the inpatient setting (p=0.16 for difference between groups across all categories) (**Supplementary Table 1**). The median (IQR) number of chest x-rays per person was 1 (1, 3) in the rheumatic disease patients and 1 (1, 2) in the comparators. The median (IQR) time from COVID-19 diagnosis to initial chest radiograph was 0 days (0, 2) in rheumatic patients and 0 days (0, 0) in comparators, and the time from COVID-19 diagnosis to the chest radiograph with the maximum PXS score was 1 day (0, 6) in rheumatic patients and 0 days (0, 4) in comparators (**Supplementary Figure 1**). PXS scores ranged from 0.8 to 16.5 in rheumatic disease patients and 0.7 to 15.9 in comparators. Using unadjusted quantile regression, the maximum PXS scores for each patient were not significantly different between rheumatic disease patients and comparators at the 10^{th}-60^{th} percentiles in each respective group (e.g., 50^{th} percentile scores of 3.1 vs. 3.2, respectively, difference of -0.1 [95% CI: -1.8 to 1.7], p=0.95) (**Table 3**). However, PXS scores were significantly higher in rheumatic disease patients at the 70^{th} percentile (6.8 vs. 5.6, difference of 1.2 [95% CI: 0.4 to 2.0], p=0.01), 80^{th} percentile (8.9 vs. 7.3, difference of 1.5 [95% CI: 1.0 to 2.2], p<0.001), and 90^{th} percentiles (10.2 vs. 9.2, difference

of 1.0 [95% CI: 0.12 to 1.96], p=0.01). After adjusting for age, Charlson Comorbidity Index (dichotomized by <2 or ≥2), and interstitial lung disease, maximum PXS scores were still significantly higher at the 80th and 90th percentiles in rheumatic disease patients (e.g., 90th percentile scores of 10.2 vs. 9.2, p=0.03) (**Table 3**). A higher proportion of patients with rheumatic disease had maximum PXS scores indicating severe lung disease (>9) than comparators (14 [20%] vs. 49 [11%], p=0.03). These findings persisted when we excluded patients with ILD from the rheumatic disease patient and comparator groups. **Figure 2** illustrates the frequency of different PXS scores in both the rheumatic disease patients and comparators. PXS scores from the initial chest radiograph were similar across the 10th-90th percentiles between rheumatic disease patients and comparators (e.g., 50th percentile score of 2.2 vs. 2.5, respectively, unadjusted p-value 0.56 and adjusted p-value of 0.81) (**Supplementary Table 2, Supplementary Figure 2**).

PXS scores and severe COVID-19 outcomes

Among patients with rheumatic disease (n=70), those with a maximum PXS score >9 (n=14) compared to those with PXS scores ≤9 (n=56) had higher rates of mechanical ventilation (578.9 vs. 2.7 events/1,000 months; HR 24.1 [95% CI: 6.7, 86.9], p<0.001) (**Table 4**). Those with PXS scores >9 had numerically higher rates of death compared to those with PXS scores ≤9, although this was not statistically significant (7.5 vs. 0.9 events/1,000 months; HR 8.2 [95% CI: 0.7, 90.4], p=0.09). These differences in outcomes between those with higher and lower PXS scores also persisted when we excluded patients with ILD from the rheumatic disease patient and comparator groups.

Similar results were seen when using initial instead of maximum PXS score. Among patients with rheumatic diseases, those with an initial PXS score >9 compared to those with PXS

scores ≤9 had higher rates of mechanical ventilation significant (36,000 vs. 9.7 events/1,000 months; HR 26.4 [95% CI: 7.5, 92.8], p<0.001) and death (18.4 vs. 1.5 events/1,000 months; HR 11.7 [95% CI: 0.95, 142.8], p=0.045) (**Supplementary Table 3**).

These associations with both mechanical ventilation and death were similarly seen in general population comparators. General population comparators with a maximum PXS score >9 had higher rates of mechanical ventilation (134.7 vs. 5.9 events/1,000 months; HR 11.4 [95% CI: 6.9, 18.9], p<0.001) and death (23.5 vs. 4.7 events/1,000 months; HR 3.8 [95% CI: 1.9, 7.6], p<0.001) (**Supplementary Table 4**). General population comparators with initial PXS score >9 also had higher rates of mechanical ventilation (116.6 vs. 7.8 events/1,000 months; HR 6.6 [95% CI: 3.9, 11.3], p<0.001) and death (31.1 vs. 5.1 events/1,000 months; HR 4.8 [95% CI: 2.1, 11.2], p<0.001) (**Supplementary Table 4**).

Discussion

Using a previously validated deep learning-derived scoring algorithm, we found that patients with rheumatic disease and COVID-19 had more severe radiographic lung disease than matched comparators with COVID-19. Our results provide validation of the use of both the initial and maximum PXS score among rheumatic disease patients and corroborate previous studies suggesting increased risk for mechanical ventilation. As rheumatic disease patients may be more susceptible to severe lung involvement from COVID-19 than the general population,[1,2] additional studies are needed to determine how PXS scores may be helpful in clinical research studies studying risk factors for poor COVID-19 outcomes in rheumatic disease and other patients. Our results emphasize the importance of COVID-19 risk mitigation strategies, such as vaccination with an additional dose and post-exposure prophylaxis with monoclonal antibodies,

in patients with rheumatic diseases due to their increased susceptibility to severe pulmonary involvement from COVID-19.

PXS scores have been previously validated as a prognostic tool in general population patients with COVID-19. In both training and validation data sets, PXS scores correlated well with radiologist-determined radiographic lung disease severity (Pearson correlation coefficient of 0.86), and the initial PXS score was predictive of subsequent intubation or death (receiver operating characteristic area under the curve = 0.80).[8] The PXS algorithm has been further tuned using inpatient and outpatient COVID-19 data sets in the U.S. and Brazil.[9] After an intervention in which radiologists were exposed to machine learning-derived PXS scores of different chest radiographs, the interrater agreement among subsequent diagnostic radiologists improved (Fleiss kappa coefficient 0.40 to 0.66), indicating that PXS scores could be integrated into the radiology workflow to standardize interpretation of COVID-19 chest radiographs without requiring additional training of radiologists.[10] PXS scores have also been used to examine the association of radiographic lung severity of COVID-19 with other factors such as acute neurological disease and right ventricular strain. Lang *et al* examined PXS scores in patients with acute neuroimaging findings (e.g., intracranial hemorrhage, infarction, or leukoencephalopathy) and found that they had significantly higher mean PXS scores than comparators (9.2 vs. 5.0, $p<0.001$).[13] Gibson *et al* found that right ventricular strain is common in intubated patients with COVID-19 but is not associated with radiographic lung disease.[14]

We found that initial PXS scores were similar between rheumatic disease patients and general population comparators but that maximum PXS scores were higher in rheumatic disease patients; this underscores the similar nature of both groups at baseline as well as the natural history of acute COVID-19 which often does not reach peak severity until a week or more into

the clinical course.[15] Several factors may explain why rheumatic disease patients are at higher risk for worsened lung disease over the course of acute COVID-19. First, patients with rheumatic diseases are commonly treated with immunosuppressive medications that might increase the severity of infection. Second, rheumatic diseases are often associated with chronic systemic inflammation which might predispose these patients to more severe hyperinflammatory responses to COVID-19. Indeed, our prior work demonstrated that, compared with general population patients, those with rheumatic diseases and COVID-19 had a more severe inflammatory state.[16] Third, some rheumatic diseases are associated with inflammatory lung disease (e.g., interstitial lung disease) and the trigger underlying this manifestation is unknown. Infectious etiologies, like COVID-19, may be responsible for precipitating inflammatory lung disease in predisposed rheumatic disease patients. These hypotheses deserve additional study. Notably, the differences in maximum PXS scores between groups persisted after adjusting for comorbidities, suggesting that either the underlying rheumatic disease or possibly immunosuppressive medications may contribute to these differences. Additionally, as a PXS score difference of >1 between two x-rays can be distinguished by a radiologist, these differences are likely to be clinically meaningful on a population level.

Our study has some strengths and limitations. We performed a systematic interpretation of chest radiographs at two academic hospitals, and patients were matched by site to account for differences in chest radiograph technique and other site differences such as triage and preference of ordering radiographs. Details regarding rheumatic disease diagnosis were available for all patients by manual chart review. Most patients received their care within the MGB system, thus reducing missing data, and data were obtained systematically from a centralized data warehouse. Our study also has certain limitations. Chest radiographs were not available for all patients in our

initial rheumatic disease cohort; thus, our sample may be biased toward those with more severe disease or in whom the clinician was concerned about more severe disease. However, we would not expect access to chest radiographs to be misclassified between rheumatic disease patients and comparators. It is possible that clinicians may have been more likely to order radiographs for rheumatic disease patients (while the median number of chest radiographs is 1 in each group, the interquartile range is 1-3 in rheumatic disease patients compared to 1-2 in comparators), which would have biased results towards the null and would not explain a higher proportion of severe scores in the rheumatic disease patients. We did not have pre-COVID-19 radiographs available on all patients so could not evaluate changes from baseline. While we had ILD diagnosis available, it is possible that some rheumatic disease patients had subclinical lung damage from ILD prior to COVID-19 that contributed to the findings though our results remained unchanged in sensitivity analyses excluding patients with known baseline ILD. Additionally, our study was conducted at two tertiary care hospitals in the same geographic region, which may limit generalizability. The small sample size reduced our ability to assess the impact of potential confounders or mediators on the relationship between rheumatic disease and PXS scores and to determine the significance of differences in deaths between those with severe and non-severe scores. Finally, our sample size limited our ability to perform subgroup analyses of patients with different rheumatic diseases or on different immunosuppressive medications. Nevertheless, our findings indicate that patients with rheumatic diseases have more severe pulmonary radiologic manifestations of COVID-19 and that higher PXS scores identify those most likely to experience subsequent respiratory decompensation.

Conclusions

In conclusion, we used a machine learning algorithm that assessed the severity of chest x-ray findings and found that patients with rheumatic disease were more likely to have more severe COVID-19 related lung disease. Our study confirms that rheumatic disease patients are more susceptible to lung involvement from COVID-19 and corroborates previous findings suggesting increased risk for mechanical ventilation and mortality. The higher risk of severe pulmonary involvement from COVID-19 provides additional support for COVID-19 vaccination and risk mitigation among rheumatic disease patients.

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Tables

Table 1. Clinical characteristics of COVID-19 patients with rheumatic disease and comparators without rheumatic disease who had chest x-rays performed.

Characteristic	Rheumatic Disease Patients (n=70)	Comparators without Rheumatic Disease (n=463)	p-value
Age, years (mean ± SD)*	62 ± 16	62 ± 15	0.77
Female, n (%)*	48 (69)	315 (68)	0.93
Race, n (%)			0.20
White	33 (47)	227 (49)	
Black or African American	13 (19)	56 (12)	
Asian	5 (7)	18 (4)	
Other	19 (27)	162 (35)	
Hispanic or Latinx ethnicity, n (%)	4 (6)	40 (9)	0.41
Body mass index, kg/m^2 (mean ± SD)	29.9 ± 6.7	29.7 ± 6.4	0.72
Smoking status, n (%)			0.11
Never	41 (59)	289 (62)	
Former	27 (39)	129 (28)	
Current	2 (3)	36 (8)	
Unknown	0 (0)	9 (2)	
Charlson Comorbidity Index (median [IQR])	4 (2, 7)	1 (0, 3)	<0.0001
Comorbidities, n (%)			
Hypertension	38 (54)	146 (32)	<0.01
Diabetes	22 (31)	71 (15)	<0.01
Coronary artery disease	15 (21)	47 (10)	<0.01
Heart failure	8 (11)	36 (8)	0.30
Asthma	13 (19)	32 (7)	<0.01
Chronic obstructive pulmonary disease	6 (9)	20 (4)	0.12
Obstructive sleep apnea	7 (10)	31 (7)	0.32
Chronic kidney disease	21 (30)	46 (10)	<0.0001
Interstitial lung disease	4 (6)	5 (1)	0.01
Site where COVID-19 test was performed			0.08
Outpatient, n (%)	43 (61)	232 (50)	
Emergency department or inpatient, n (%)	27 (39)	231 (50)	
Site where initial CXR was performed			0.47
Outpatient, n (%)	21 (30)	126 (27)	
Emergency department, n (%)	40 (57)	295 (64)	
Inpatient, n (%)	9 (13)	42 (9)	
Time from COVID-19 diagnosis to initial CXR, days (median [IQR])	0 (0, 2)	0 (0, 0)	0.01

COVID-19, Coronavirus Disease 2019; SD, standard deviation; IQR, interquartile range.

*Matching factors

Table 2. Detailed characteristics of patients with rheumatic disease and COVID-19 who had chest x-rays performed within 2 weeks of COVID-19 diagnosis.

Characteristic	Rheumatic Disease Patients (n=70)
Rheumatic disease diagnosis, n (%)	
Rheumatoid arthritis	26 (37)
Other inflammatory arthritis*	12 (17)
Systemic lupus erythematosus	10 (14)
Vasculitis†	7 (10)
Inflammatory myopathy	5 (7)
Polymyalgia rheumatica	4 (6)
Other rheumatic conditions‡	8 (11)
Autoimmune disease duration, years (median [IQR])	9 (3, 16)
Autoimmune disease status, n (%)	
Remission	21 (30)
Low activity	28 (40)
Moderate/high activity	15 (21)
Unknown	6 (9)
Immunomodulatory medication at the time of COVID-19 diagnosis	
Biologic DMARDs	
CD20 inhibitor	10 (14)
TNF inhibitor	3 (4)
IL-6 receptor inhibitor	4 (6)
IL-12/IL-23 inhibitor	1 (1)
CTLA-4 immunoglobulin	2 (3)
Targeted synthetic DMARDs	
JAK inhibitor	2 (3)
Conventional synthetic DMARDs	
Hydroxychloroquine	18 (26)
Methotrexate	11 (16)
Mycophenolate mofetil	4 (6)
Azathioprine	3 (4)
Other§	4 (6)
Oral glucocorticoid	27 (39)
Prednisone-equivalent daily dose, mg (median [IQR])	5 (5, 10)

COVID-19, Coronavirus Disease 2019; IQR, interquartile range; DMARD, disease-modifying anti-rheumatic drug; TNF, tumor necrosis factor; IL, interleukin; CTLA-4, cytotoxic T-lymphocyte-associated protein 4; JAK, Janus kinase.

*Includes other inflammatory arthritis (n=8), psoriatic arthritis (n=2), non-systemic juvenile idiopathic arthritis (n=1), and ankylosing spondylitis (n=1).

†Includes other vasculitides (n=3), giant cell arteritis (n=2), granulomatosis with polyangiitis (n=1), and Behçet's disease (n=1).

‡Includes antiphospholipid syndrome (n=2), mixed connective tissue disease (n=2), IgG4-related disease (n=1), Sjögren's syndrome (n=1), systemic sclerosis (n=1), undifferentiated connective tissue disease (n=1).

§Includes leflunomide (n=1), cyclophosphamide (n=1), sulfasalazine (n=1), tacrolimus (n=1).

Table 3. PXS scores from chest x-rays in rheumatic disease patients and matched comparators, using PXS scores from within 2 weeks before or after COVID-19 diagnosis.

Characteristic	Rheumatic Disease Patients (n=70)	Comparators without Rheumatic Disease (n=463)	Unadjusted p-value	Adjusted p-value*
Total number of CXRs, N	206	936		
Number of CXRs per subject, median (IQR)	1 (1, 3)	1 (1, 2)	<0.001	<0.001
PXS score ≤9, n (%)†	56 (80)	414 (89)	0.03	0.01
PXS score >9, n (%)†	14 (20)	49 (11)		
Maximum PXS score†				
10th percentile PXS score	0.9	0.9	0.60	0.31
20th percentile PXS score	1.0	1.1	0.38	0.76
30th percentile PXS score	1.5	1.5	0.90	0.61
40th percentile PXS score	2.1	2.2	0.75	0.56
50th percentile PXS score	3.1	3.2	0.95	0.93
60th percentile PXS score	4.4	4.1	0.76	0.41
70th percentile PXS score	6.8	5.6	0.01	0.18
80th percentile PXS score	8.9	7.3	<0.001	<0.001
90th percentile PXS score	10.2	9.2	0.01	0.03

PXS, pulmonary x-ray severity score; COVID-19, Coronavirus Disease 2019; CXR, chest x-ray

*Adjusted for age, CCI (dichotomized as <2 or ≥2), and interstitial lung disease

†Based on the highest PXS score per patient within ±2 weeks of COVID-19 diagnosis.

Table 4. Risk of mechanical ventilation or death in patients with rheumatic diseases and COVID-19 with high versus low maximum PXS scores

Outcomes	PXS score >9*	PXS score ≤9*	p-value
Mechanical ventilation			
Patients in PXS category, N	14	56	
Mechanical ventilation, n†	11	3	
Person-time (months)	19	1102	
Rate (events/1,000months) (95% CI)	578.9 (236.8, 921.1)	2.7 (0.0, 5.8)	
Hazard ratio (95% CI)	24.13 (6.7, 86.9)	Ref	<0.001
Death			
Patients in PXS category, N	13	57	
Death, n	2	1	
Person-time (months)	266.6	1144.33	
Rate (events/1,000 months) (95% CI)	7.5 (0.0, 17.9)	0.9 (0.0, 2.6)	
Hazard ratio (95% CI)	8.2 (0.7, 90.4)	Ref	0.087

PXS, pulmonary x-ray severity score; COVID-19, Coronavirus Disease 2019

*Based on the highest PXS score within ±2 weeks of COVID-19 diagnosis.

†For mechanical ventilation outcome, the highest PXS score on radiographs prior to intubation was used.

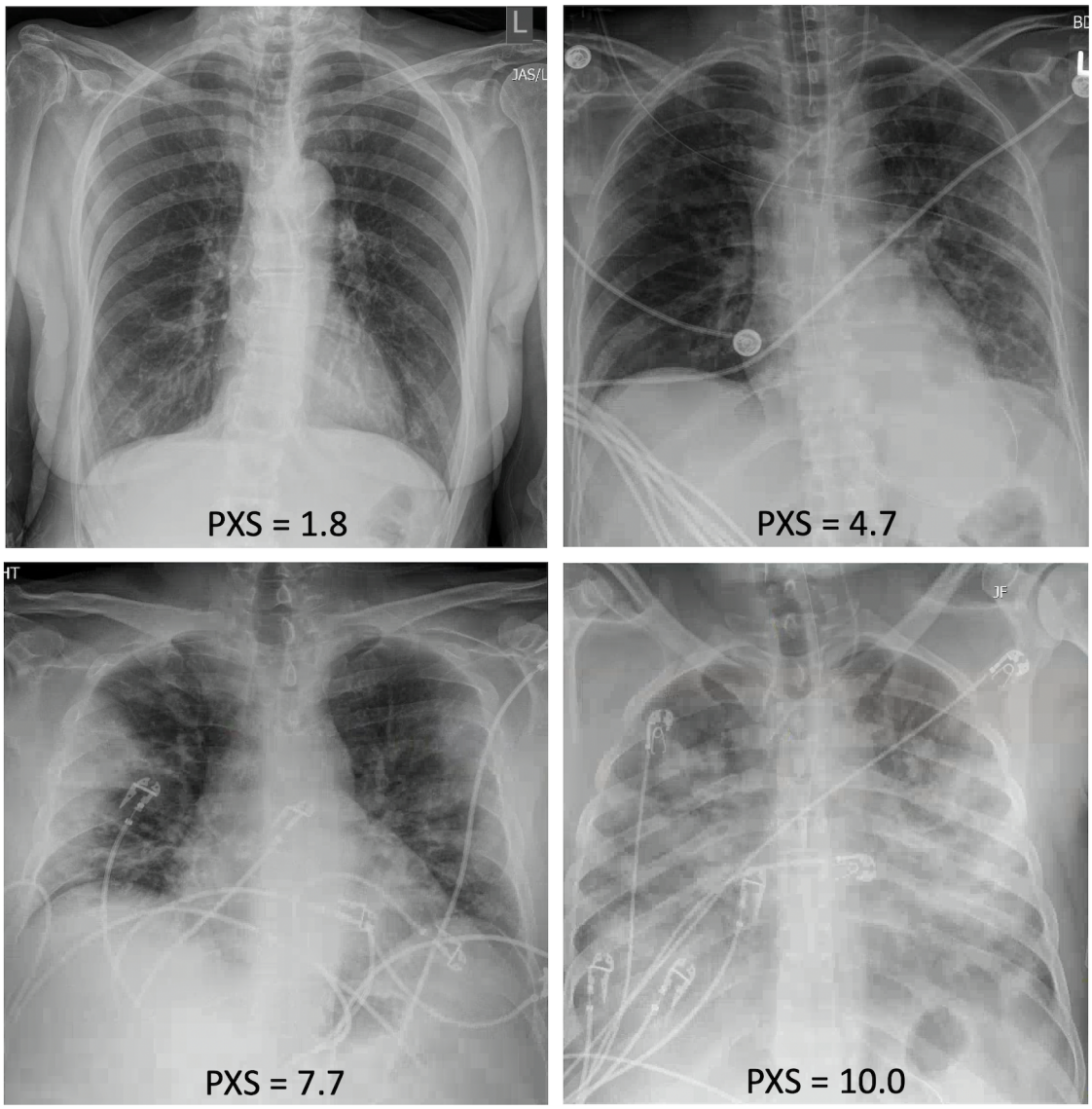
Figure Titles & Legends

Figure 1. Examples of chest radiographs from patients with COVID-19 and their associated Pulmonary X-Ray Severity (PXS) scores

PXS, pulmonary x-ray severity score

Figure 2. Frequency of Maximum Pulmonary X-Ray Severity (PXS) scores in rheumatic disease patients and comparators

PXS, pulmonary x-ray severity score, based on the highest score within 14 days of COVID-19 diagnosis
Purple represents overlap in the percentages of rheumatic disease patients and comparators. Red represents excess percentage of rheumatic disease patients over comparators. Blue represents excess percentage of comparators over rheumatic disease patients. B. Lines represent cumulative probability curves (red: rheumatic disease patients; blue: comparators).



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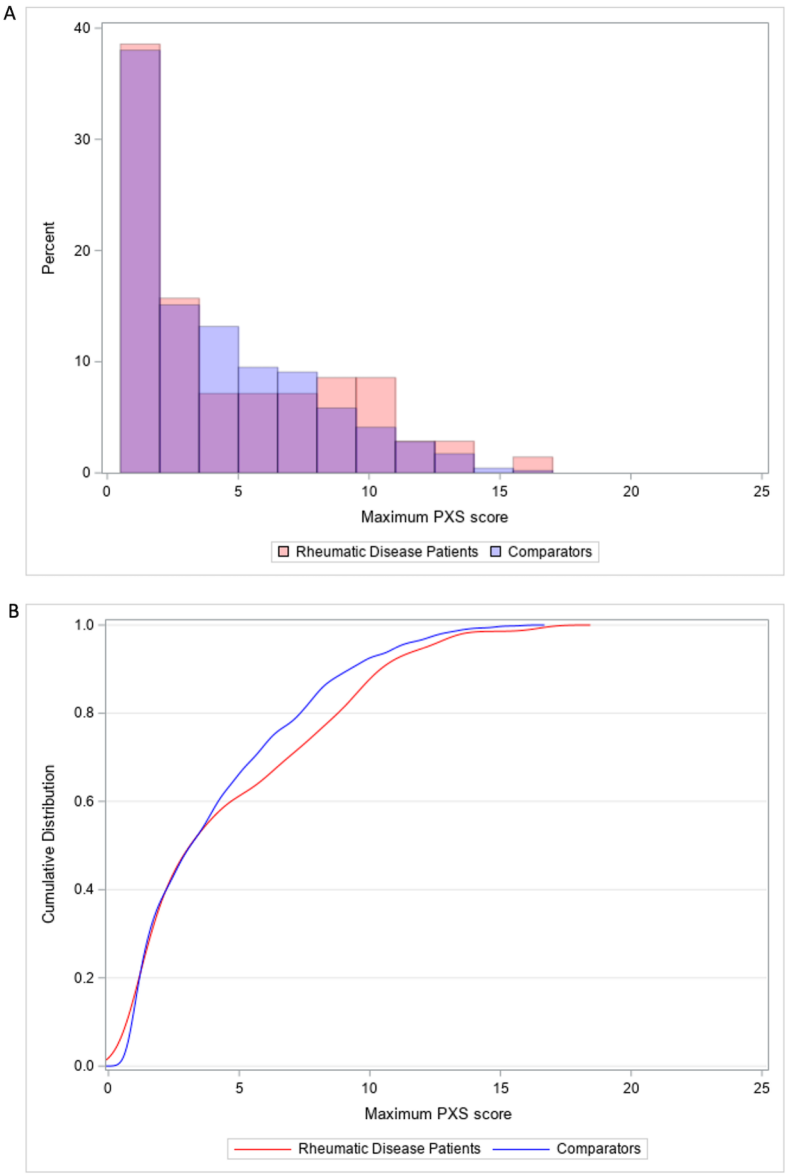

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