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# Development of a Prediction Model for COVID-19 Acute Respiratory Distress Syndrome in Patients With Rheumatic Diseases: Results From the Global Rheumatology Alliance Registry

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**Objective.** Some patients with rheumatic diseases might be at higher risk for coronavirus disease 2019 (COVID-19) acute respiratory distress syndrome (ARDS). We aimed to develop a prediction model for COVID-19 ARDS in this population and to create a simple risk score calculator for use in clinical settings.

**Methods.** Data were derived from the COVID-19 Global Rheumatology Alliance Registry from March 24, 2020, to May 12, 2021. Seven machine learning classifiers were trained on ARDS outcomes using 83 variables obtained at COVID-19 diagnosis. Predictive performance was assessed in a US test set and was validated in patients from four countries with independent registries using area under the curve (AUC), accuracy, sensitivity, and specificity. A simple risk score calculator was developed using a regression model incorporating the most influential predictors from the best performing classifier.

**Results.** The study included 8633 patients from 74 countries, of whom 523 (6%) had ARDS. Gradient boosting had the highest mean AUC (0.78; 95% confidence interval [CI]: 0.67-0.88) and was considered the top performing classifier. Ten predictors were identified as key risk factors and were included in a regression model. The regression model that predicted ARDS with 71% (95% CI: 61%-83%) sensitivity in the test set, and with sensitivities ranging from 61% to 80% in countries with independent registries, was used to develop the risk score calculator.

**Conclusion.** We were able to predict ARDS with good sensitivity using information readily available at COVID-19 diagnosis. The proposed risk score calculator has the potential to guide risk stratification for treatments, such as monoclonal antibodies, that have potential to reduce COVID-19 disease progression.

## INTRODUCTION

Acute respiratory distress syndrome (ARDS), affecting about 5% of patients with coronavirus disease 2019 (COVID-19) (1) and one third of hospitalized patients (2), is a life-threatening complication of the severe acute respiratory syndrome coronavirus 2 infection. ARDS in the setting of COVID-19 has a mortality rate of 26% to 62% in people admitted to a critical care setting and 66% to

The views expressed herein are those of the authors and participating members of the COVID-19 Global Rheumatology Alliance and do not necessarily represent the views of the American College of Rheumatology (ACR), the European Alliance of Associations for Rheumatology (EULAR), the UK National Health Service (NHS), the National Institute for Health Research (NIHR), or the UK Department of Health.

94% in patients who received mechanical ventilation (3). ARDS frequently causes long-lasting effects beyond hospitalization, from cognitive impairment to physical weakness (4). Given the high mortality and long-term consequences of ARDS, and the direct burden on the health care system, identification of patients at risk for this complication and use of potentially mitigating treatment strategies are important.

There is controversy regarding the existence of an increased risk of severe COVID-19 outcomes in people with rheumatic diseases (5–8). For example, reports from a Swedish nationwide study showed that the risks of COVID-19-related hospitalization and death (but not intensive care unit [ICU] admission) were increased in rheumatoid arthritis (RA), whereas for other inflammatory joint diseases, only the risk of COVID-19-related hospitalization were increased, compared with population referents. However, these risks were comparable to the increased risk of all-cause hospitalization in patients with rheumatic diseases and the increased all-cause mortality risk in patients with RA, and the increased mortality risk in 2020 in patients with RA was not different from that in 2015-2019 (5). In the United States, a multi-institutional electronic health record (EHR) study found higher risks of hospitalization, ICU admission, acute renal failure, and venous thromboembolism (but not death) in patients with rheumatic diseases compared with matched controls (9). Another study conducted at a multi-institutional health system among patients admitted to the hospital with COVID-19 showed higher odds of admission to intensive care and of mechanical ventilation in patients with rheumatic diseases compared with matched controls (10).

The risk factors most strongly associated with ARDS, the key life-threatening organ involvement in COVID-19, are not yet identified. Predicting ARDS using information available at the time of COVID-19 diagnosis has the potential to guide clinical risk stratification and the management of COVID-19 in this population. Because ARDS is a relatively rare event in people who develop COVID-19, there are special considerations in developing statistical models predicting this outcome. Prediction using traditional regression methods can lead to overfitting, limiting the number of predictors that can reliably be used in the prediction model (11). In addition, regression models typically limit the link between outcome and predictor variables to be linear and additive; as a result, regression models may fail to adequately represent complex interactions and high-dimensional relationships that may be present in patients with rheumatic diseases (12). Machine learning algorithms provide an alternative approach with the potential to improve predictive performance, in particular sensitivity, in the setting of relatively rare events, such as ARDS.

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This study aimed to develop a prediction model for ARDS in individuals with COVID-19 and pre-existing rheumatic diseases using information obtained at the time of COVID-19 diagnosis and a series of machine-learning algorithms for predictor selection. An additional aim was to develop a simple and interpretable risk-score calculator for potential use in clinical settings.

## MATERIALS AND METHODS

The dataset for this study, the COVID-19 Global Rheumatology Alliance (GRA) provider registry, contains only limited data; no personal identifiers, with the exception of COVID-19 diagnosis dates, are included. Because of the limited data and the noninterventional nature of the study, the GRA registry was determined to be nonhuman subjects research by the UK Health Research Authority, the University of Manchester, and the University of California, San Francisco. An institutional review board or ethics committee approval or informed consent was therefore not required.

**Study design.** This study used data from the COVID-19 GRA registry (13) from March 24, 2020, to May 12, 2021. Briefly, data from adults with rheumatic diseases diagnosed with COVID-19 are entered by rheumatology clinicians via one of two parallel international data entry portals: one (14) limited to European countries and a second (15) for the rest of the world. Five countries in Europe—France (8,16,17), Germany (18–20), Italy (21), Portugal (22,23), and Sweden (24)—and two countries in South America—Brazil (25,26) and Argentina (27)—host national registries supported by their respective national societies. National data from these countries are regularly transferred and merged into the GRA registry. Although GRA data largely depend on convenience sampling, rheumatology practices from two large health systems within the United States (Mass General Brigham in Massachusetts and Mayo Clinic in Minnesota and Florida) have processes in place to systematically report all symptomatic and asymptomatic COVID-19 diagnoses, irrespective of COVID-19 severity.

Patient demographics, rheumatic disease characteristics, comorbidities, COVID-19 outcomes, and complications are entered by reporting clinicians. Methods of COVID-19 diagnosis are indicated, including one or more of the following: polymerase chain reaction, antigen testing, antibody testing, metagenomic testing, computed topography scan, laboratory assay, or a presumptive diagnosis based on symptoms or close contact alone. Quality is assessed by data validation teams who remove all known or potential duplicates and address erroneous or ineligible reports. We followed the Transparent Reporting of a Multivariable Prediction Model for Individual Prognosis or Diagnosis statement for prediction model development and validation (28).

**Inclusion and exclusion criteria.** We included patients with a reconciled status only, defined as the highest COVID-19 illness severity level being confirmed. Patients with a COVID-19 diagnosis date that preceded January 1, 2020, were excluded (n = 7). Additionally, we excluded patients with missing data on ARDS or any of the predictor variables (Supplementary Table 1). Patients reported from France, Portugal, and Germany were excluded because of the unavailability of data on ARDS or smoking status.

**Outcome.** ARDS was the outcome and the event being predicted in this study. A diagnosis of COVID-19–related ARDS was indicated by the reporting clinician at the point of data entry and in almost all cases reflected a diagnosis given to the patient by the inpatient team (eg, pulmonologists, critical care specialists, or internists directly caring for the patient).

**Predictors.** ARDS was predicted using 83 predictor variables related to patient demographics, rheumatic disease diagnoses and activity, immunomodulatory medications used for the treatment of rheumatic disease, and comorbidities (Supplementary Table 2). All variables reflect data at the time of COVID-19 diagnosis.

**Training, test, and validation sets.** Construction of the training, test, and validation sets is depicted in Figure 1. Patients reported from the United States (except those reported from Mass General Brigham in Massachusetts and Mayo Clinic in Minnesota and Florida) and all other countries that directly reported to the GRA registry were included in the training set (n = 5673). The test set comprised all patients reported from Mass General Brigham in Massachusetts and Mayo Clinic in Minnesota and Florida (n = 891). We used this approach to address any potential for provider reporting bias and to improve the generalizability of our findings by testing on a subset of data that most closely represent the underlying spectrum of COVID-19 severity among patients with pre-existing rheumatic diseases. Additionally, patients reported from these health systems had low rates of missing data (<10% of patients excluded because of incomplete data) permitting complete-case analyses. Patients reported from countries with independent registries were used as validation sets (n = 2069). We used four validation sets in total, corresponding to patients reported from Italy (n = 1060), Sweden (n = 225), Brazil (n = 201), and Argentina (n = 583). The amount of missing data varied considerably between the validation sets (Supplementary Table 1). Italy had the lowest rates of missing data (<10% of patients excluded because of incomplete data) and was therefore considered the primary validation set.

**Prediction algorithms.** Because ARDS is relatively rare and many predictors are potentially relevant to predicting this severe outcome, we used a machine learning approach for predictor selection, which is suited to data with high dimensionality. To identify the most important predictors of ARDS, we compared predictive performance of seven supervised machine learning

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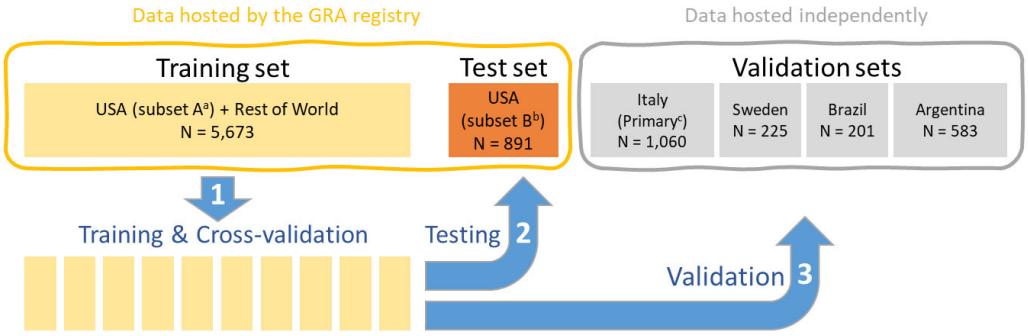



**Figure 1.** Data set partitioning into training, test, and validation sets. 1) Seven supervised machine learning algorithms were trained on acute respiratory distress syndrome outcomes using three repeats of 10-fold cross-validation. 2) Predictive performance was assessed in the test set. 3) Predictive performance was further assessed in the validation sets. [a]Subset A included all patients reported from the United States, except patients reported from Mass General Brigham in Massachusetts and Mayo Clinics in Minnesota and Florida. [b]Subset B included all patients reported from Mass General Brigham in Massachusetts and Mayo Clinics in Minnesota and Florida. These health systems systematically reported all coronavirus disease 2019 (COVID-19) diagnoses, irrespective of severity. [c]Italy had the lowest rates of unknown data (<7% in any variable and <10% of patients excluded because of incomplete data) among all validation sets and was therefore considered the primary validation set. GRA, Global Rheumatology Alliance.

classifiers commonly applied in the setting of rare clinical outcomes (29). The classifiers were trained on ARDS outcomes using three repeats of 10-fold cross-validation. Prediction algorithms used instance-based learning (k-nearest neighbors and support vector machines), regularization (the lasso and elastic-net regularized generalized linear models), Bayesian regression (Bayesian generalized linear models), additive models (generalized additive models), ensemble learning (gradient boosting machines [GBM]), and deep learning (neural networks). All analyses were performed in R version 3.6.1, using the Classification and Regression Training (30) package.

**Model performance.** Model performance was assessed using accuracy, sensitivity, specificity, and area under the curve (AUC). The prediction algorithm with the highest AUC in the test set was selected as the best performing classifier. AUC is an aggregate measure of the receiver operating characteristic curve and, unlike accuracy, does not depend on a classification threshold value. For each prediction algorithm and data set, separately, classification threshold values were selected to reduce the absolute difference between sensitivity and specificity (31). This approach was taken to maximize both metrics (Supplementary Figure 1) and to account for potential country-level differences in health system structure, health care access, and use. Mean classification thresholds, mean performance metrics, and corresponding 95% confidence intervals (CIs) were derived from 1000 samples of 500 randomly selected patients from the test set and each validation set using bootstrapping and sampling with replacement.

**Risk score calculator development.** The risk score calculator was derived from a multivariable logistic regression incorporating the most influential predictors from the best performing classifier (32). We used logistic regression to develop a risk score calculator that was interpretable, user friendly, and readily accessible for potential use in clinical settings across health systems. To determine the optimum number of items in the risk score calculator, a series of regressions with varying numbers of predictors (ranging from top five predictors to top n predictors, in which the importance score associated with nth predictor was >0) were trained on ARDS outcomes using 10 repeats of 10-fold cross-validation. To balance the calculator's ease of use in clinical settings (33,34) with predictive performance, our final regression model incorporated the lowest number of predictors associated with the highest mean AUC. To improve regression fit, we assessed linearity in the relationship between continuous predictors and the outcome and accounted for nonlinear relationships using interaction terms. Direction, magnitude, and statistical significance of key risk factors associated with ARDS were reported from the final regression model using adjusted odds ratios (ORs). The predictive performance of the regression model was evaluated in the test set and validation sets using the aforementioned performance metrics and methods. Additionally, we assessed calibration of the regression model by comparing the mean predicted ARDS probabilities with the mean observed probabilities within every decile of predicted risk in the test and validation sets and reported corresponding integrated calibration indices (ICIs) (35).

To aid the interpretation of predicted probabilities, risk of ARDS development was defined as "low" for predicted probabilities lower than the lowest country-specific mean classification threshold, "moderate to high" for the predicted probability region between the highest and the lowest country-specific mean classification thresholds, and "high" for predicted probabilities equal to or higher than the highest country-specific mean classification threshold.

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A point-based scoring system was developed in which points were assigned to each item by multiplying each β coefficient (log OR) from the regression model by a constant arbitrary number and rounding (to the nearest integer for points 1-5 and to the nearest fifth integer for points >5) to facilitate total risk score calculation. A total risk score was assigned to each patient by summing the points for each item in the risk score calculator. Mean predicted ARDS probabilities and 95% CIs corresponding to each total risk score within the "moderate to high" category of risk are reported.

**Table 1.** Demographic and clinical characteristics of the study population

| | | | Validation sets | | | |
|---|---|---|---|---|---|---|
| | | | Primary | Other | | |
| | Training set n = 5673 | Test set n = 891 | Italy n = 1060 | Sweden n = 225 | Brazil n = 201 | Argentina n = 583 |
| Age, years, mean (SD) | 53.2 (15.2) | 58.0 (17.1) | 56.6 (14.6) | 53.5 (14.7) | 47.8 (14.1) | 49.2 (14.2) |
| Sex, n (%) | | | | | | |
| Male | 1585 (27.9) | 236 (26.5) | 311 (29.3) | 88 (39.1) | 57 (28.4) | 126 (21.6) |
| Female | 4088 (72.1) | 655 (73.5) | 749 (70.7) | 137 (60.9) | 144 (71.6) | 457 (78.4) |
| Smoking status, n (%) | | | | | | |
| Never smoker | 4212 (74.2) | 543 (60.9) | 752 (70.9) | 127 (56.4) | 188 (93.5) | 395 (67.8) |
| Former smoker | 1152 (20.3) | 307 (34.5) | 199 (18.8) | 88 (39.1) | 5 (2.5) | 154 (26.4) |
| Current smoker | 309 (5.4) | 41 (4.6) | 109 (10.3) | 10 (4.4) | 8 (4) | 34 (5.8) |
| Most common diagnoses, n (%) | | | | | | |
| Rheumatoid arthritis | 2472 (43.6) | 322 (36.1) | 360 (34) | 100 (44.4) | 60 (29.9) | 299 (51.3) |
| Psoriatic arthritis | 569 (10) | 81 (9.1) | 220 (20.8) | 46 (20.4) | 23 (11.4) | 47 (8.1) |
| Spondyloarthritis | 554 (9.8) | 45 (5.1) | 108 (10.2) | 40 (17.8) | 54 (26.9) | 48 (8.2) |
| Other inflammatory arthritis | 145 (2.6) | 63 (7.1) | 12 (1.1) | 12 (5.3) | 0 (0) | 0 (0) |
| Systemic lupus erythematosus | 689 (12.1) | 99 (11.1) | 80 (7.5) | 5 (2.2) | 25 (12.4) | 110 (18.9) |
| Vasculitis | 171 (3) | 49 (5.5) | 40 (3.8) | 8 (3.6) | 1 (.5) | 23 (3.9) |
| Sjogren syndrome | 195 (3.4) | 34 (3.8) | 29 (2.7) | 0 (0) | 9 (4.5) | 31 (5.3) |
| Polymyalgia rheumatica | 102 (1.8) | 47 (5.3) | 25 (2.4) | 0 (0) | 0 (0) | 3 (.5) |
| Systemic sclerosis | 165 (2.9) | 23 (2.6) | 63 (5.9) | 1 (.4) | 11 (5.5) | 20 (3.4) |
| Disease activity, n (%) | | | | | | |
| Remission or low | 4554 (80.3) | 695 (78) | 894 (84.3) | 194 (86.2) | 166 (82.6) | 457 (78.4) |
| Moderate or high | 1119 (19.7) | 196 (22) | 166 (15.7) | 31 (13.8) | 35 (17.4) | 126 (21.6) |
| Most common comorbidities, n (%) | | | | | | |
| None | 2040 (36) | 182 (20.4) | 315 (29.7) | 102 (45.3) | 81 (40.3) | 317 (54.4) |
| At least one comorbidity | 3633 (64) | 709 (79.6) | 745 (70.3) | 123 (54.7) | 120 (59.7) | 266 (45.6) |
| Interstitial lung disease | 288 (5.1) | 42 (4.7) | 70 (6.6) | 5 (2.2) | 6 (3) | 33 (5.7) |
| Obstructive lung disease | 433 (7.6) | 145 (16.3) | 69 (6.5) | 28 (12.4) | 6 (3) | 9 (1.5) |
| Obesity | 926 (16.3) | 273 (30.6) | 131 (12.4) | 16 (7.1) | 26 (12.9) | 93 (16) |
| Diabetes | 786 (13.9) | 167 (18.7) | 102 (9.6) | 15 (6.7) | 20 (10) | 52 (8.9) |
| Hypertension | 1921 (33.9) | 412 (46.2) | 365 (34.4) | 56 (24.9) | 67 (33.3) | 161 (27.6) |
| Cardiovascular disease | 463 (8.2) | 129 (14.5) | 169 (15.9) | 21 (9.3) | 13 (6.5) | 19 (3.3) |
| Chronic kidney disease | 274 (4.8) | 114 (12.8) | 66 (6.2) | 3 (1.3) | 8 (4) | 17 (2.9) |
| Cancer | 191 (3.4) | 70 (7.9) | 64 (6) | 4 (1.8) | 4 (2) | 12 (2.1) |
| Liver disease | 156 (2.7) | 24 (2.7) | 66 (6.2) | 1 (.4) | 0 (0) | 8 (1.4) |
| Neurological or neuromuscular disease | 77 (1.4) | 40 (4.5) | 53 (5) | 6 (2.7) | 0 (0) | 5 (.9) |
| Psychiatric disease | 91 (1.6) | 44 (4.9) | 27 (2.5) | 2 (.9) | 2 (1) | 22 (3.8) |
| Psoriasis | 291 (5.1) | 54 (6.1) | 184 (17.4) | 13 (5.8) | 6 (3) | 28 (4.8) |
| Medications, n (%) | | | | | | |
| No DMARDs | 939 (16.6) | 265 (29.7) | 175 (16.5) | 13 (5.8) | 25 (12.4) | 5 (.9) |
| csDMARDs alone | 2501 (44.1) | 338 (37.9) | 396 (37.4) | 77 (34.2) | 80 (39.8) | 405 (69.5) |
| b/tsDMARDs alone | 1196 (21.1) | 193 (21.7) | 278 (26.2) | 85 (37.8) | 64 (31.8) | 91 (15.6) |
| csDMARDs + b/tsDMARDs | 1037 (18.3) | 95 (10.7) | 211 (19.9) | 50 (22.2) | 32 (15.9) | 82 (14.1) |
| GC use | | | | | | |
| No use, n (%) | 3942 (69.5) | 635 (71.3) | 659 (62.2) | 172 (76.4) | 180 (89.6) | 335 (57.5) |
| GC user, n (%) | 1731 (30.5) | 256 (28.7) | 401 (37.8) | 53 (23.6) | 21 (10.4) | 248 (42.5) |
| GC dose,[a] mg, median (IQR) | 5 (5) | 5 (5) | 5 (0) | 5 (2.5) | 10 (5) | 5 (5) |
| ARDS, n (%) | | | | | | |
| Yes | 355 (6.3) | 35 (3.9) | 57 (5.4) | 12 (5.3) | 17 (8.5) | 47 (8.1) |
| No | 5318 (93.7) | 856 (96.1) | 1003 (94.6) | 213 (94.7) | 184 (91.5) | 536 (91.9) |

Abbreviations: ARDS, acute respiratory distress syndrome; b/tsDMARDs, biologic or targeted synthetic DMARDs; csDMARDs, conventional systemic DMARDs; DMARD, disease-modifying antirheumatic drug; GC, glucocorticoid; IQR, interquartile range.
[a]Average daily prednisone-equivalent dose among GC users.

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## RESULTS

**Characteristics of the study population.** A total of 8633 patients reported from 74 countries were included in the study. Of these, 5673 were partitioned into the training set and 891 and 2069 into the test set and validation sets, respectively, as described in Methods. Among patients composing the training set, the mean (SD) age was 53.2 (15.2) years, 4088 (72.1%) were female, and 4212 (74.2%) were nonsmokers. RA, reported among 2472 (43.6%) individuals, was the most common diagnosis, followed by systemic lupus erythematosus (12.1%) and psoriatic arthritis (10.0%). Treatment with conventional synthetic disease-modifying antirheumatic drugs alone was the most common treatment modality (44.1%). A majority of individuals were in remission or had low disease activity (80.3%; Table 1). ARDS was reported among 355 (6.3%) patients in the training set, 35 (3.9%) patients in the test set, and 57 (5.4%) patients in the primary validation set (Italy). In the other validation sets, the prevalence of ARDS ranged from 3.3% (Sweden) to 8.5% (Brazil).

**Predictive performance of machine learning algorithms.** Among the seven machine learning classifiers, GBM had the highest AUC in the test set (mean: 0.78; 95% CI: 0.67-0.88) and was considered the top performing model (Supplementary Table 3). In the test set, at the optimum classification threshold, GBM had a mean accuracy, sensitivity, and specificity of 0.70. In the primary validation set, GBM had a mean AUC of 0.79 (95% CI: 0.70-0.87) and a mean accuracy, sensitivity, and specificity of 0.73 at the optimum classification threshold (Supplementary Table 4). In other validation sets, GBM's mean AUC ranged from 0.74 to 0.85, with mean sensitivity and mean specificity ranging from 0.65 to 0.78 and 0.66 to 0.78, respectively. In order of predictor importance, age, average daily prednisone-equivalent glucocorticoid dose, and pulmonary hypertension were the most influential predictors identified by GBM (Supplementary Figure 2).

**Important risk factors and risk score calculator.** The risk score calculator was derived from a multivariable logistic regression model incorporating the 10 most influential predictors from GBM because 10 was the smallest number of predictors that corresponded to the highest mean AUC (0.77) in cross-validation (Supplementary Materials). Average daily prednisone-equivalent glucocorticoid doses greater than 60 mg were considered clinically high doses. We fitted an interaction term to account for the potential effect modification in dose response in patients receiving glucocorticoid doses greater than 60 mg. The resulting regression was equivalent to a simpler regression that winsorized glucocorticoid

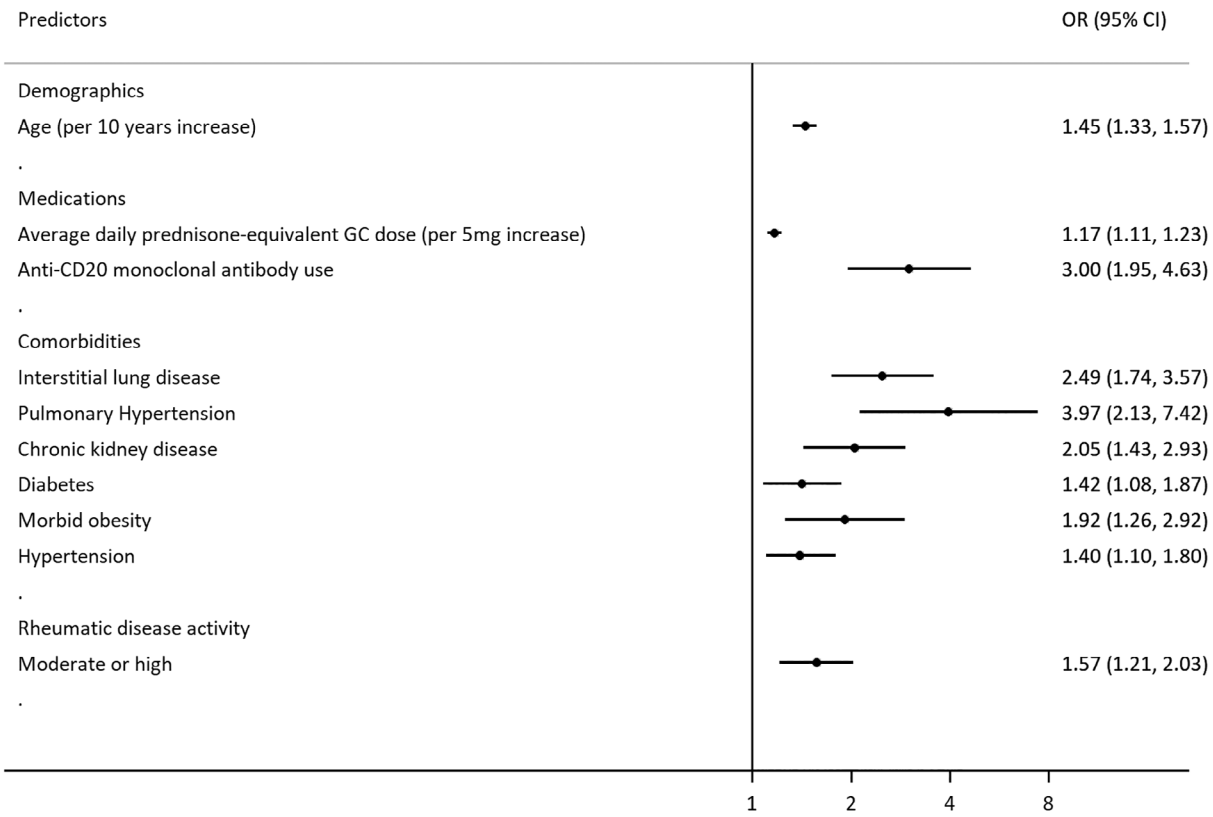



**Figure 2.** Adjusted odds ratios (ORs) obtained from the multivariable logistic regression model. Top 10 most influential predictors identified by the gradient boosting machine. CI, confidence interval; GC, glucocorticoid.

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**Table 2.** Predictive performance of the multivariable logistic regression model in the test set and across validation sets

| | Classification threshold, mean (95% CI) | Percentile of predicted risk[a] | Performance metrics, mean (95% CI) | | | |
|---|---|---|---|---|---|---|
| | | | AUC | Accuracy | Sensitivity | Specificity |
| Test set | 0.096 (0.074-0.128) | 71.1 (58.8-80.4) | 0.79 (0.68-0.88) | 0.71 (0.62-0.82) | 0.71 (0.61-0.83) | 0.71 (0.62-0.82) |
| Primary validation set | | | | | | |
| Italy | 0.069 (0.056-0.085) | 70.7 (61.9-77.8) | 0.77 (0.68-0.86) | 0.73 (0.65-0.80) | 0.73 (0.64-0.81) | 0.73 (0.65-0.80) |
| Other validation sets | | | | | | |
| Sweden | 0.058 (0.044-0.081) | 70.7 (60.9-81.8) | 0.82 (0.72-0.92) | 0.74 (0.62-0.84) | 0.74 (0.59-0.85) | 0.74 (0.62-0.84) |
| Brazil | 0.036 (0.033-0.041) | 60.2 (54.2-67.7) | 0.71 (0.63-0.78) | 0.61 (0.55-0.70) | 0.61 (0.52-0.71) | 0.61 (0.55-0.70) |
| Argentina | 0.060 (0.053-0.069) | 75.5 (70.5-79.9) | 0.85 (0.79-0.91) | 0.80 (0.75-0.85) | 0.80 (0.74-0.86) | 0.80 (0.75-0.85) |

Abbreviations: AUC, area under curve; CI, confidence interval.
[a]Percentiles of predicted risk correspond to the mean (95% CI) classification thresholds. Classification thresholds, performance metrics, and corresponding 95% CIs were derived from 1000 random samples of 500 patients from each data set using bootstrapping and sampling with replacement.

doses greater than 60 to 60 mg (calibration slope: 0.99 [1.00 indicating perfect calibration]; calibration intercept: 0.00; correlation coefficient: 0.99; $P < 0.0001$). We therefore opted for the simpler regression model in creating the risk score calculator. All 10 predictors were independently and statistically significantly associated with the development of ARDS (Figure 2): older age (OR 1.45; 95% CI: 1.33-1.57, per decade increase in age), higher average daily prednisone-equivalent glucocorticoid doses (1.17; 95% CI: 1.11-1.23, per 5-mg increase in dose), pulmonary hypertension (3.97; 95% CI: 2.13-7.42), interstitial lung disease (2.49; 95% CI: 1.74-3.57), chronic renal insufficiency or end-stage renal disease (2.05; 95% CI: 1.43-2.93), anti-CD20 monoclonal antibody use (3.00; 95% CI: 1.95-4.63), diabetes (1.42; 95% CI: 1.08-1.87), hypertension (1.40; 95% CI: 1.10-1.80), moderate or high rheumatic disease activity (1.57; 95% CI: 1.21-2.03), and morbid obesity (1.92; 95% CI: 1.26-2.92).

Predictive performance of the final regression model was assessed in the test set and each validation set from countries

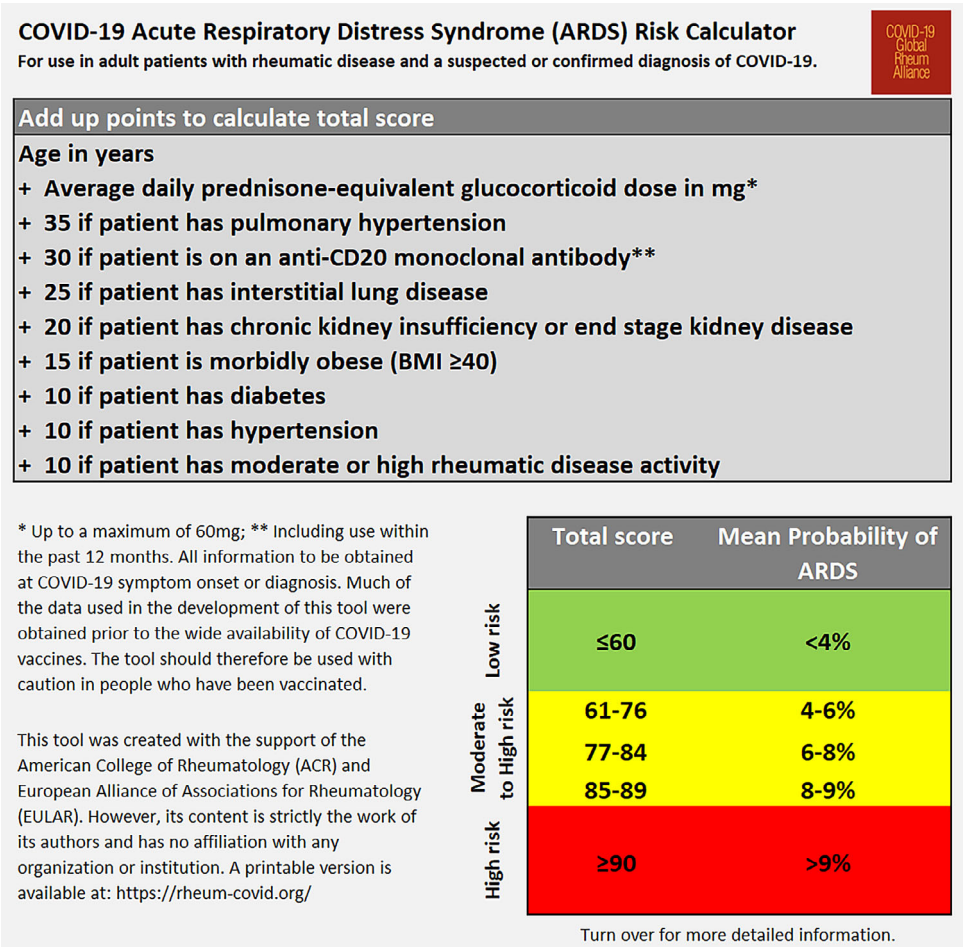
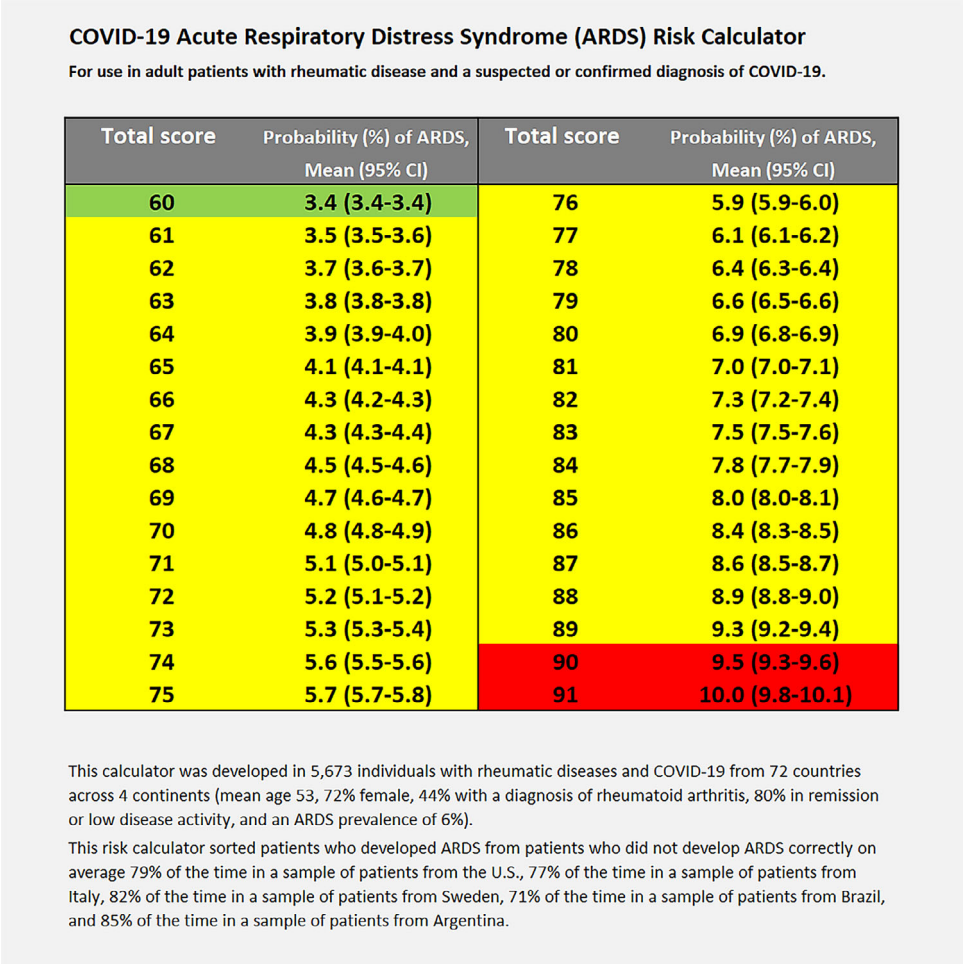



**Figure 3.** The risk score calculator pocket care side 1. BMI, body mass index; COVID-19, coronavirus disease 2019.

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**COVID-19 Acute Respiratory Distress Syndrome (ARDS) Risk Calculator**

**For use in adult patients with rheumatic disease and a suspected or confirmed diagnosis of COVID-19.**

| Total score | Probability (%) of ARDS, Mean (95% CI) | Total score | Probability (%) of ARDS, Mean (95% CI) |
|---|---|---|---|
| 60 | 3.4 (3.4-3.4) | 76 | 5.9 (5.9-6.0) |
| 61 | 3.5 (3.5-3.6) | 77 | 6.1 (6.1-6.2) |
| 62 | 3.7 (3.6-3.7) | 78 | 6.4 (6.3-6.4) |
| 63 | 3.8 (3.8-3.8) | 79 | 6.6 (6.5-6.6) |
| 64 | 3.9 (3.9-4.0) | 80 | 6.9 (6.8-6.9) |
| 65 | 4.1 (4.1-4.1) | 81 | 7.0 (7.0-7.1) |
| 66 | 4.3 (4.2-4.3) | 82 | 7.3 (7.2-7.4) |
| 67 | 4.3 (4.3-4.4) | 83 | 7.5 (7.5-7.6) |
| 68 | 4.5 (4.5-4.6) | 84 | 7.8 (7.7-7.9) |
| 69 | 4.7 (4.6-4.7) | 85 | 8.0 (8.0-8.1) |
| 70 | 4.8 (4.8-4.9) | 86 | 8.4 (8.3-8.5) |
| 71 | 5.1 (5.0-5.1) | 87 | 8.6 (8.5-8.7) |
| 72 | 5.2 (5.1-5.2) | 88 | 8.9 (8.8-9.0) |
| 73 | 5.3 (5.3-5.4) | 89 | 9.3 (9.2-9.4) |
| 74 | 5.6 (5.5-5.6) | 90 | 9.5 (9.3-9.6) |
| 75 | 5.7 (5.7-5.8) | 91 | 10.0 (9.8-10.1) |

This calculator was developed in 5,673 individuals with rheumatic diseases and COVID-19 from 72 countries across 4 continents (mean age 53, 72% female, 44% with a diagnosis of rheumatoid arthritis, 80% in remission or low disease activity, and an ARDS prevalence of 6%).

This risk calculator sorted patients who developed ARDS from patients who did not develop ARDS correctly on average 79% of the time in a sample of patients from the U.S., 77% of the time in a sample of patients from Italy, 82% of the time in a sample of patients from Sweden, 71% of the time in a sample of patients from Brazil, and 85% of the time in a sample of patients from Argentina.

**Figure 4.** The risk score calculator pocket care side 2. CI, confidence interval; COVID-19, coronavirus disease 2019.

with independent registries. In the test set, the model had a mean AUC of 0.79 (95% CI: 0.68-0.88) and a mean accuracy, sensitivity, and specificity of 0.71 at the optimum classification threshold (Table 2). In the primary validation set, the model had a mean AUC of 0.77 (95% CI: 0.68-0.86) and a mean accuracy, sensitivity, and specificity of 0.73 at the optimum classification threshold. In other validation sets, mean AUCs ranged from 0.71 to 0.85, with both mean sensitivity and mean specificity ranging from 0.61 to 0.80. The calibration plot showed relatively poor agreement between the observed and predicted ARDS risk in the test set (calibration slope: 0.43; intercept: 0.00; ICI: 0.056) and good agreement in the primary validation set (calibration slope: 0.80; intercept: 0.00; ICI: 0.024). The model had relatively poor to moderate calibration in other validation sets, with calibration slopes, intercepts, and ICIs ranging from 1.38 to 1.91, –0.03 to 0.01, and 0.029 to 0.049, respectively (Supplementary Figure 3).

Figures 3 and 4 provide details of the ARDS risk score calculator developed from the multivariable regression model. Predicted ARDS probabilities less than 4% (corresponding to total scores ≤60) were defined as "low" risk, predicted ARDS probabilities between 4% and 9% (corresponding to total scores 61-89) were defined as "moderate to high" risk, and predicted ARDS probabilities greater than 9% were defined as "high" risk. As described in methods, these thresholds were not quantitatively derived but instead reflect probabilities that were felt to be clinically meaningful.

## DISCUSSION

In this global sample of patients with rheumatic diseases, we developed a simple ARDS risk score calculator that has the potential for risk stratification and to guide management of COVID-19 among individuals with rheumatic diseases in routine clinical settings. A machine learning classifier, GBM, predicted the onset of ARDS with 70% sensitivity in the test set and with 73% sensitivity in the primary validation set using information obtained at COVID-19 diagnosis. A multivariable regression model using the 10 most influential predictors from GBM predicted ARDS with 71% sensitivity in the test set and with 73% sensitivity in the primary validation set. Rheumatic disease characteristics and medications identified as important risk factors in predicting COVID-19 ARDS align with previously reported factors

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associated with COVID-19 hospitalization or death in patients with immune-mediated inflammatory diseases (36–41). Other risk factors, including older age, obesity, chronic lung disease, and chronic kidney disease, were also consistent with risk factors identified by a recently published prognostic model for adverse COVID-19 outcomes using information obtained at diagnosis in a general population-based cohort from Iceland (42).

Our study findings help identify patients with underlying rheumatic diseases who may be at a higher risk for ARDS from COVID-19. Use of baseline information at COVID-19 symptom onset or at COVID-19 exposure or diagnosis in asymptomatic patients facilitates early triage of high-risk patients for monitoring, prophylaxis, or treatment interventions. For example, with the recent Food and Drug Administration Emergency Use Authorizations (43,44) for the use of monoclonal antibodies for the treatment of ambulatory patients with COVID-19 or as postexposure prophylaxis for high-risk individuals exposed to the virus, a risk calculator coupled with clinical judgment can prioritize which patients are most likely to derive benefit from this therapy. Our findings also identify potentially modifiable risk factors that rheumatologists can consider when making patient care decisions to minimize the risk of adverse COVID-19 outcomes, namely, glucocorticoid dose, rituximab use (45), and rheumatic disease activity.

With only 10 items, the proposed calculator is simple to use and can be easily implemented in clinical settings. Additionally, information required for the scoring system is available in both outpatient and inpatient settings or even remotely without the need for close contact, which is not the case with existing ARDS prediction models that require physical examination, laboratory measurements, and imaging data (46–48). In classification, there is typically an inverse relationship between sensitivity and specificity. In this study, we selected classification thresholds that maximized both sensitivity and specificity by minimizing the absolute difference between them. This choice is somewhat arbitrary; in practice, the trade-off between specificity and sensitivity must account for the underlying population risk for ARDS, health gains from available treatment or monitoring interventions, and the regional health system structure that governs the availability and access to health resources.

With the exception of Brazil, both GBM and the GBM-based regression model performed slightly better in validation sets than the test set. This may be explained by the fact that the training set was more similar in nature to the validation sets than the test set, such that provider reporting bias affecting the training set was of a similar magnitude of the bias affecting the validation sets. It is plausible that rheumatology practices that systematically reported all COVID-19 diagnoses and composed the test set also captured information on important risk factors, such as comorbidities, more comprehensively than practices that composed the training set and validation sets. Calibration plots support this hypothesis: predicted probabilities of ARDS were higher than the observed risk in the test set, whereas they were largely comparable in Italy, Sweden, and Argentina and lower than the observed risk in Brazil. Without processes in place to systematically report all COVID-19 diagnoses and capture complete information on baseline characteristics, it is possible that provider reporting patterns were influenced by COVID-19 severity, provider perceptions of factors related to COVID-19 severity, and availability of information through direct interactions between the patient and their rheumatologist during the pandemic. Other factors that may have impacted calibration include nature of the institutions included in the test versus training sets, capabilities of care teams (eg, presence of dedicated COVID-19 care teams and units), and characteristics of the study populations beyond those that we were able to account for. Furthermore, patients may underreport important social and behavioral factors, such as smoking. This social desirability bias can vary across countries and cultures (49) and may additionally explain the discordances observed in predictive performance.

This study has important strengths. First, to our knowledge, this is the first study predicting COVID-19 ARDS among individuals with rheumatic diseases. Second, the prediction models were trained on a global sample of individuals with rheumatic disease, thus increasing the heterogeneity and likely generalizability of patient characteristics. This has the potential to improve prediction accuracy by increasing the number of potential predictors and accounting for complex high-dimensional relationships between them. Importantly, active rheumatic disease status was captured as a predictor. The registry is unique among other data sources in rheumatic diseases in being able to capture data on disease activity that are not typically available in administrative data or EHRs. Furthermore, reporting occurred directly via rheumatology clinicians, which likely increased the accuracy of the information. Third, we tested the performance of prediction models in a subset of practices that had processes in place to minimize potential provider reporting bias. Maximizing the heterogeneity of COVID-19 outcomes in the test set improves the generalizability of our findings to the target population of individuals with pre-existing rheumatic diseases with COVID-19. Fourth, the external validity of our prediction models was assessed using external data sets from Europe and Latin America.

Limitations of this work include potential provider reporting bias and missing data in the training set and external validation sets; the tool should therefore be used with caution outside the United States. Assessments of calibration showed relatively poor agreement between observed and predicted probabilities of ARDS in the test set and in external validation sets; we therefore recommend that the tool be used as a guide for COVID-19 prognosis and in conjunction with clinical judgement. Although we attempted to account for country-level differences in health system structure, health care access, and use through optimizing ARDS classification thresholds at the regional level, a residual impact by these factors may remain. Additionally, we were unable

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to account for other important clinical, sociodemographic, or environmental factors, such as the continuation or withholding of rheumatic disease treatments at the time of COVID-19 diagnosis, race and ethnicity, alcohol consumption, occupation, poverty, housing conditions, or air pollution, all of which may influence the outcomes of COVID-19, including the development of ARDS. Much of the data were obtained prior to the wide availability of COVID-19 vaccines, which may lower risk of developing severe COVID-19 outcomes, such as ARDS. However, vaccinated patients with COVID-19 with rheumatic diseases have been reported to experience breakthrough infection possibly because of inadequate humoral vaccine immune response associated with some immunosuppressors (50).

In summary, a GBM-based regression model predicted COVID-19 ARDS with good sensitivity and specificity in patients with pre-existing rheumatic diseases using demographics and basic clinical characteristics that can be easily obtained at COVID-19 exposure or onset. Prediction accuracies were largely comparable or better in external data sets from four countries that hosted independent COVID-19 registries. Age, daily glucocorticoid dose, pulmonary hypertension, interstitial lung disease, chronic kidney disease, anti-CD20 monoclonal antibody use, diabetes, hypertension, active rheumatic disease, and morbid obesity were the most influential factors in predicting the onset of ARDS. Further studies including vaccinated individuals and more recent COVID-19 variants (such as omicron) are needed to prospectively evaluate the clinical utility of the proposed risk score calculator for its potential to guide risk stratification, prophylaxis with monoclonal antibodies, and treatment of COVID-19 in high-risk patients with rheumatic diseases.

## AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Izadi had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

**Study conception and design.** Izadi.
**Acquisition of data.** All authors.
**Analysis and interpretation of data.** Izadi, Gianfrancesco, Yazdany.

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