



Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.

IL-6–based mortality risk model for hospitalized patients with COVID-19



Rocio Laguna-Goya, MD,^{a,b} Alberto Utrero-Rico, MSc,^{a,b} Paloma Talayero, PhD,^{a,b} Maria Lasa-Lazaro, BSc,^{a,b} Angel Ramirez-Fernandez, BSc,^{a,b} Laura Naranjo, BSc,^{a,b} Alejandro Segura-Tudela, BSc,^{a,b} Oscar Cabrera-Marante, MD,^{a,b} Edgar Rodriguez de Frias, MD,^{a,b} Rocio Garcia-Garcia, MD,^c Mario Fernández-Ruiz, MD,^{b,d} Jose Maria Aguado, MD,^{b,d,e} Joaquin Martinez-Lopez, MD,^{b,e,f,g,h} Elena Ana Lopez, MD,ⁱ Mercedes Catalan, MD,^j Antonio Serrano, MD,^{a,b} and Estela Paz-Artal, MD^{a,b,k}
Madrid, Spain

Background: Coronavirus disease 2019 (COVID-19) has rapidly become a global pandemic. Because the severity of the disease is highly variable, predictive models to stratify patients according to their mortality risk are needed.

Objective: Our aim was to develop a model able to predict the risk of fatal outcome in patients with COVID-19 that could be used easily at the time of patients' arrival at the hospital.

Methods: We constructed a prospective cohort with 611 adult patients in whom COVID-19 was diagnosed between March 10 and April 12, 2020, in a tertiary hospital in Madrid, Spain. The analysis included 501 patients who had been discharged or had died by April 20, 2020. The capacity of several biomarkers, measured at the beginning of hospitalization, to predict mortality was assessed individually. Those biomarkers that independently contributed to improve mortality prediction were included in a multivariable risk model.

Results: High IL-6 level, C-reactive protein level, lactate dehydrogenase (LDH) level, ferritin level, D-dimer level, neutrophil count, and neutrophil-to-lymphocyte ratio were all predictive of mortality (area under the curve >0.70), as were low

albumin level, lymphocyte count, monocyte count, and ratio of peripheral blood oxygen saturation to fraction of inspired oxygen (SpO₂/FiO₂). A multivariable mortality risk model including the SpO₂/FiO₂ ratio, neutrophil-to-lymphocyte ratio, LDH level, IL-6 level, and age was developed and showed high accuracy for the prediction of fatal outcome (area under the curve 0.94). The optimal cutoff reliably classified patients (including patients with no initial respiratory distress) as survivors and nonsurvivors with 0.88 sensitivity and 0.89 specificity.

Conclusion: This mortality risk model allows early risk stratification of hospitalized patients with COVID-19 before the appearance of obvious signs of clinical deterioration, and it can be used as a tool to guide clinical decision making. (*J Allergy Clin Immunol* 2020;146:799-807.)

Key words: COVID-19, IL-6, mortality risk, predictive model

From ^athe Department of Immunology, ^cthe Department of Pneumology, ^dthe Unit of Infectious Diseases, ^ethe Department of Hematology, ^fthe Department of Biochemistry, and ^hthe Intensive Care Unit, Hospital Universitario 12 de Octubre, Madrid; ^bInstituto de Investigación, Sanitaria Hospital 12 de Octubre (imas12), Madrid; ^gthe Department of Medicine, ^hCentro Nacional de Investigaciones Oncológicas, Madrid; ^kthe Department of Immunology, Ophthalmology and ENT, Universidad Complutense de Madrid; and ⁱCIBERONC, Madrid.

Supported by the Instituto de Salud Carlos III, Spanish Ministry of Science and Innovation (COVID-19 research call COV20/00181), and cofinanced by the European Development Regional Fund A Way to Achieve Europe, Operative Program Intelligent Growth 2014-2020. R.L.G. and O.C.M. each hold a Rio Hortega research contract (CM19/00120 and CM19/00092, respectively). P.T. holds a Juan Rodes research contract (JR19/00049), and M.F.R. holds a Miguel Servet research contract (CP18/00073), all from the Instituto de Salud Carlos III, Spanish Ministry of Science and Innovation. The funder of this study had no role in the study design, data collection, data analysis, interpretation of the data, or writing of the report. R.L.G. had full access to all the data and final responsibility to submit for publication. A.U.R. also had access to all the raw data.

Disclosure of potential conflict of interest: The authors declare that they have no relevant conflicts of interest.

Received for publication June 16, 2020; revised July 13, 2020; accepted for publication July 16, 2020.

Available online July 22, 2020.

Corresponding author: Rocio Laguna Goya, MD, Hospital 12 de Octubre, Servicio de Inmunología, Avda de Cordoba s/n, 28041, Madrid, Spain. E-mail: rociolaguna@salud.madrid.org.

The CrossMark symbol notifies online readers when updates have been made to the article such as errata or minor corrections

0091-6749/\$36.00

© 2020 Published by Elsevier Inc. on behalf of the American Academy of Allergy, Asthma & Immunology

<https://doi.org/10.1016/j.jaci.2020.07.009>

The outbreak of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection started in December 2019 in China¹ and has since spread globally, reaching more than 7 million confirmed cases and more than 400,000 reported deaths to date.² SARS-CoV-2 infection causes Coronavirus disease 2019 (COVID-19), and its severity ranges from asymptomatic to acute respiratory distress syndrome (ARDS), multiorgan failure, and eventually death.³

The overall rate of mortality due to COVID-19 has been estimated at 1% to 3%,³ whereas the reported mortality rate in hospitalized patients has varied from 6% to 34%,⁴⁻⁶ and it can exceed 50% in patients in intensive care units (ICUs).⁷ Given these differences in disease severity and the potentially high in-hospital mortality, there is a need for early predictive biomarkers able to stratify patients according to their likelihood of a fatal outcome. A few reports have described the clinical characteristics of hospitalized patients with COVID-19 and have proposed risk factors for mortality.^{4,8-10} These factors include older age; high sequential organ failure assessment (SOFA) score; high neutrophil count; high C-reactive protein (CRP), D-dimer, or lactate dehydrogenase (LDH) or IL-6 level; and low lymphocyte count and platelet count or albumin level.

IL-6 may play a relevant role in the pathophysiology of patients with severe COVID-19.¹¹ Blocking of the IL-6/IL-6R signaling pathway with tocilizumab among other drugs is currently being studied in clinical trials as a potential treatment for such patients. In this study, we analyzed the individual mortality prediction capacity of early, 1-time, readily available laboratory tests, including tests to determine IL-6 level, together with peripheral blood oxygen saturation-to-fraction of inspired oxygen (SpO₂/

Abbreviations used

ALT:	Alanine transaminase
ARDS:	Acute respiratory distress syndrome
AST:	Aspartate transaminase
AUROC:	Area under the receiver operating characteristic curve
COVID-19:	Coronavirus disease 2019
CRP:	C-reactive protein
ICU:	Intensive care unit
LDH:	Lactate dehydrogenase
N/L:	Neutrophil-to-lymphocyte
PPV:	Positive predictive value
ROC:	Receiver operating characteristic
SARS-CoV-2:	Severe acute respiratory syndrome coronavirus 2
SOFA:	Sequential organ failure assessment
SpO ₂ /FiO ₂ :	Peripheral blood oxygen saturation-to-fraction of inspired oxygen

FiO₂) ratio, and we developed a multivariable model to predict fatal outcome in hospitalized patients with COVID-19.

METHODS**Study design**

This is a single-center prospective cohort study performed at Hospital Universitario 12 de Octubre, a large tertiary hospital in Madrid (Spain). A total of 611 hospitalized adult patients in whom COVID-19 was diagnosed between March 10 and April 12, 2020, and whose IL-6 level had been measured were included in the study. SARS-CoV-2 real-time RT-PCR assay of nasopharyngeal or oropharyngeal swabs or sputum samples was performed to diagnose COVID-19. According to the local protocols during the peak of the pandemic, a COVID-19 diagnosis was assumed in 28.9% of patients with suggestive clinical and radiologic presentation and compatible epidemiologic history (Table 1). Two patients with chronic lymphocytic leukemia and a lymphocyte count higher than 70,000 cells/ μ L were excluded. Only patients who had been discharged or had died by April 20, 2020, were included in the final analysis (N = 501) (Fig 1). The institutional clinical research ethics committee approved the study protocol (reference no. 20/167).

Data collection

Clinical data (including demographics and major comorbidities; hospital admission, discharge, and death dates; time from symptom onset to hospitalization; length of hospital stay; and ICU requirement) were collected from the electronic medical records into the study database. Oxygen saturation and COVID-19 treatment were recorded on the day of the blood test. Respiratory function was assessed by measurement of SpO₂/FiO₂ ratio. The SpO₂/FiO₂ ratio shows a good correlation with the partial pressure of arterial oxygen (PaO₂)/FiO₂ ratio (SpO₂/FiO₂ = 64 + 0.84 × [PaO₂/FiO₂]),¹² and unlike the latter, it was available for all the patients. ARDS was classified according to the Berlin criteria, according to which an SpO₂/FiO₂ ratio higher than 315 indicates no ARDS, an SpO₂/FiO₂ ratio between 315 and 235 indicates mild ARDS, an SpO₂/FiO₂ ratio between 148 and 235 indicates moderate ARDS, and an SpO₂/FiO₂ ratio less than 148 indicates severe ARDS.¹³

Laboratory measurements

IL-6 level was measured with the BD CBA Human IL-6 Flex Set (BD Biosciences, San Diego, Calif) by using a BD Canto II flow cytometer. The results were analyzed with FCAP Array software, version 3.0 (BD Biosciences). IL-6 level measurements following tocilizumab therapy were not included in the study. Other laboratory parameters such as CRP level, albumin level, alanine transaminase (ALT) level, aspartate transaminase (AST) level, LDH level, ferritin level, D-dimer level, fibrinogen level, platelet count, neutrophil count, lymphocyte count, and monocyte count were measured as

part of the standard of care. All laboratory measurements were performed on the same day. Neutrophil-to-lymphocyte (N/L) ratio was calculated for every patient. High-sensitivity cardiac troponin level was not included in the analysis given the low number of patients with that measurement.

Statistical analysis

Continuous numeric data have been represented as medians and interquartile ranges and were compared by using the Mann-Whitney *U* test. Categorical variables have been represented as numbers and percentages and were compared by using the chi-square test or the Fisher exact test when appropriate. Box plots have been represented in Tukey style. Correlation was evaluated with linear regression and the Spearman rank coefficient. Univariate logistic regression was performed for each variable to test association with mortality. We evaluated each variable as a potential biomarker by using receiver operating characteristic (ROC) curves.

The Transparent Reporting of a Multivariable Prediction Model for Individual Prognosis or Diagnosis (TRIPOD) guidelines for development of multivariate prediction models were followed.¹⁴ All the variables with a significant association with fatal outcome, as tested by univariate logistic regression and an area under the ROC curve (AUROC) value higher than 0.70 were used in the backward stepwise regression. Nonsignificant variables were excluded thereafter. Random forest analysis (with 500 trees) was then used to evaluate the importance of IL-6 level, LDH level, N/L ratio, SpO₂/FiO₂ ratio, and age to the model, after which 5 sequential logistic regression models for mortality were performed. The discriminative capacity of the 5 models was estimated by using the AUROC. No imputation was performed; for every model, only patients with all the available data were included in the logistic regression. Model coefficients are shown in Table E1 (available in this article's Online Repository at www.jacionline.org). The Hosmer-Lemeshow test was used to assess the models' goodness of fit. Logistic regression models were transformed to a 0-1 scale to facilitate their interpretation. The model including 5 variables was selected as our final mortality predictive model. The final model can be calculated with the following formula: score = 1/(1 + EXP [-(7.6991 - 0.0076 × SpO₂/FiO₂ ratio + 0.0547 × N/L ratio + 0.0046 × LDH + 0.0043 × IL6 + 0.0682 × age)]). The variance inflation factor was lower than 1.2 for the 5 variables in the model, showing no collinearity. Internal validation of the selected model was performed by bootstrapping (1000 replications) of the 5 variables. The prediction model was calculated on each bootstrap sample and tested on the original sample. Optimism and optimism-adjusted discrimination were calculated.

The Youden index was used for cutoff selection. Sensitivity, specificity, negative predictive value, and positive predictive value (PPV) were calculated for each individual variable and model cutoff. Time-to-event curves were plotted by the Kaplan-Meier method, and differences were compared with the log-rank test to analyze the suitability of the score for stratification across risk categories. Throughout the analysis, only patients with available data were compared, and the number of patients is specified in the figures and tables. A *P* value less than .05 was considered statistically significant. Data sets can be made available subsequent to formal request to the corresponding author. All the analyses were performed with R software, version 3.6.1.

RESULTS

The final patient cohort included 501 patients with COVID-19 (Fig 1); their demographic and clinical characteristics are described in Table 1. In all, 36 patients (7.2%) died during follow-up and 42 patients (8.4%) required ICU admission.

The median time from arrival at the hospital to laboratory testing was 2 days (interquartile range, 1-4 days) (Table 1). Neither the time from hospital admission to laboratory testing nor the time from onset of illness to hospital admission differed between survivors and nonsurvivors (2 days vs 2 days [not significant] and 8 days vs 7 days [not significant], respectively). The laboratory test results had minimal or no correlation with the

TABLE I. Demographic and clinical characteristics of the cohort

Characteristic	Overall cohort (N = 501)	Survivors (n = 465 [92.8%])	Nonsurvivors (n = 36 [7.2%])	P value
Age (y), median (IQR)	52 (44-60)	52 (44-58)	65 (57-72)	<.0001
Gender, male, no. (%)	317 (63.3%)	292 (62.9%)	25 (69.4%)	.54
Ethnicity, no. (%)				.035
White	272 (54.3%)	241 (52.5%)	27 (75.0%)	
Hispanic	213 (42.5%)	204 (44.0%)	9 (25.0%)	
Other	16 (3.2%)	16 (3.5%)	0	
Previous comorbidities, no. (%)				
Hypertension	139 (27.7%)	117 (25.2%)	22 (61.1%)	<.0001
Diabetes mellitus	56 (11.2%)	49 (10.5%)	7 (19.4%)	.11
Dyslipidemia	125 (25.0%)	109 (23.4%)	16 (44.4%)	.008
Thromboembolic event	23 (4.6%)	20 (4.3%)	3 (8.3%)	.28
Obesity	41 (8.2%)	31 (6.7%)	10 (27.8%)	.0002
Chronic pneumopathy*	54 (10.8%)	47 (10.1%)	7 (19.4%)	.09
Neoplasia	19 (3.8%)	16 (3.4%)	3 (8.3%)	.14
Smoking	91 (18.2%)	80 (17.2%)	11 (30.6%)	.07
SARS-CoV-2 RT-PCR result, positive, no. (%)†	356 (71.1%)	327 (70.3%)	29 (80.6%)	.25
ARDS classification on test day, no. (%)‡				
None	281 (56.1%)	277 (59.6%)	4 (11.1%)	<.0001
Mild	113 (22.6%)	109 (23.4%)	4 (11.1%)	.10
Moderate	36 (7.2%)	32 (6.9%)	4 (11.1%)	.31
Severe	67 (13.4%)	43 (9.3%)	24 (66.7%)	<.0001
COVID-19 treatment on test day, no. (%)				
Hydroxychloroquine	442 (88.2%)	413 (88.8%)	29 (80.6%)	.17
Azithromycin	387 (77.2%)	362 (77.9%)	25 (69.4%)	.30
IFN-β	32 (6.4%)	26 (5.6%)	6 (16.7%)	.021
Lopinavir/ritonavir	184 (36.7%)	167 (35.9%)	17 (47.2%)	.21
Corticosteroids	123 (24.6%)	106 (22.8%)	17 (47.2%)	.002
Time from onset of illness to hospital admission (d), median (IQR)	8 (6-10)	8 (6-11)	7 (5-8)	.032
Time from hospital admission to laboratory measurements (d), median (IQR)	2 (1-4)	2 (1-4)	2 (1-4)	.87
Length of hospital stay (d), median (IQR)	8 (6-13)	8 (6-13)	7 (5-13)	.62
ICU admission, no. (%)	42 (8.4%)	28 (6.0%)	14 (38.9%)	<.0001

IQR, Interquartile range.

*Included pulmonary fibrosis, chronic obstructive pulmonary disease, bronchiectasis, and asthma.

†Real-time RT-PCR.

‡ARDS syndrome.

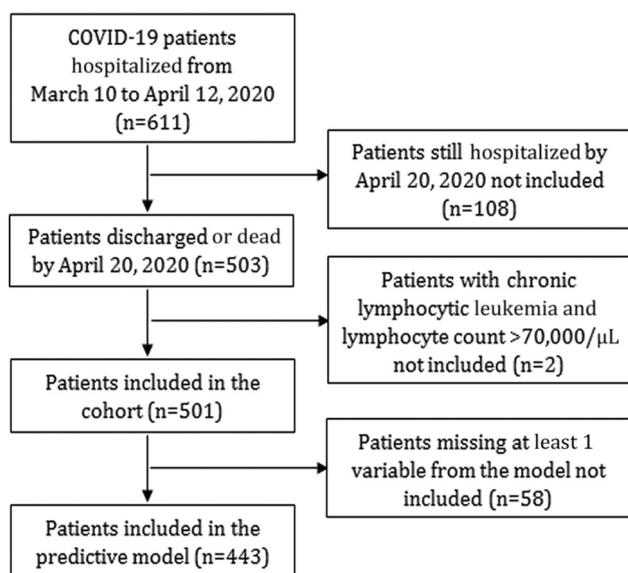


FIG 1. Flowchart of patients included in the study.

time from onset of illness (see Fig E1 in this article's Online Repository at www.jacionline.org). However, all of the recorded variables except for AST level and fibrinogen level differed between survivors and nonsurvivors (Table II). IL-6 level, CRP level, LDH level, ferritin level, D-dimer level, neutrophil count, and N/L ratio were significantly increased in deceased patients compared with in discharged patients, whereas albumin level, ALT level, platelet count, monocyte count, lymphocyte count, and SpO₂/FiO₂ ratio were decreased. Univariate logistic regression assessed the ability of each individual variable to predict mortality; the analysis showed that high IL-6 level, CRP level, LDH level, ferritin level, neutrophil count, and N/L ratio were risk factors for mortality due to COVID-19, whereas low albumin level, ALT level, platelet count, monocyte count, lymphocyte count, and SpO₂/FiO₂ ratio were also associated with higher risk of death (see the odds ratio in Table II). D-Dimer level did not reach statistical significance as a risk factor.

To evaluate the potential of these variables as predictors of mortality due to COVID-19, an AUROC analysis was performed (Table III). Several variables emerged individually as potential biomarkers, namely, IL-6 level (AUROC = 0.74), CRP

TABLE II. Variables measured in survivors and nonsurvivors and their association with mortality

Variables	Survivors (n = 465)			Nonsurvivors (n = 36)			P value	Univariate logistic regression		
	Median	IQR	n	Median	IQR	n		OR*	95% CI	P value
IL-6 level (pg/mL)	17.0	5.0-44	421	86.0	20.0-225.0	33	<.0001	1.008	1.005-1.012	<.0001
CRP level (mg/dL)	7.68	3.31-14.93	464	19.4	13.0-26.5	36	<.0001	1.105	1.069-1.145	<.0001
Albumin level (g/dL)	3.7	3.4-4.0	459	3.3	2.9-3.5	36	<.0001	0.071	0.028-0.168	<.0001
ALT level (U/L)	43.0	28.0-72.0	463	24.5	16.5-39.5	36	.0002	0.984	0.970-0.996	.016
AST level (U/L)	38.0	26.0-58.0	461	42	30.0-64.8	36	.22	1.001	0.991-1.008	.86
LDH level (U/L)	344.0	270.8-443.0	456	538.0	384.8-691.8	36	<.0001	1.007	1.005-1.009	<.0001
Ferritin level (ng/mL)	984.0	449.5-1801.2	378	2345.0	1502.0-3388.0	23	.0001	1.000	1.000-1.000	.0009
D-Dimer level (ng/mL)	550.0	354.8-935.0	304	1514.0	614.5-3367.2	26	<.0001	1.000	0.999-1.000	.052
Fibrinogen level (mg/dL)	811.0	697.0-923.0	331	845.0	776.0-960.5	27	.12	1.002	0.999-1.004	.08
Platelet count ($\times 10^3$ cells/ μ L)	277.0	211.5-372.0	463	232.5	172.8-300.8	36	.011	0.996	0.992-0.999	.017
Monocyte count ($\times 10^3$ cells/ μ L)	0.5	0.4-0.7	463	0.4	0.2-0.5	36	.002	0.084	0.015-0.398	.003
Neutrophil count ($\times 10^3$ cells/ μ L)	4.3	3.0-6.8	463	8.1	6.0-11.4	36	<.0001	1.225	1.135-1.326	<.0001
Lymphocyte count ($\times 10^3$ cells/ μ L)	1.0	0.7-1.4	464	0.6	0.3-0.9	36	<.0001	0.076	0.025-0.201	<.0001
N/L ratio	4.2	2.4-8.0	463	16.9	7.4-28.4	36	<.0001	1.097	1.065-1.133	<.0001
SpO ₂ /FiO ₂ ratio	346.4	269.4-452.4	461	106.7	101.1-212.1	36	<.0001	0.986	0.982-0.990	<.0001

*Odd ratio per unit increase.

TABLE III. Variables analyzed as potential biomarkers for mortality

Variable	ROC curve		Risk factor cutoff characterization					Cutoff univariate logistic regression			
	AUC	95% CI	Cutoff	Sensitivity	Specificity	PPV	NPV	Value	OR	95% CI	P value
IL-6 level (pg/mL)	0.74	0.64-0.84	86	0.52	0.89	0.26	0.96	≤ 86 >86	Ref 7.67	— 3.61-16.30	<.0001
CRP level (mg/dL)	0.80	0.72-0.89	8.75	0.97	0.53	0.14	0.99	≤ 8.75 >8.75	Ref 19.52	— 5.85-121.15	<.0001
Albumin level (g/dL)	0.81	0.75-0.87	3.4	0.74	0.78	0.17	0.97	≤ 3.4 >3.4	6.35 Ref	3.10-13.80 —	<.0001
ALT level (U/L)	0.69	0.61-0.77	25	0.80	0.53	0.16	0.96	≤ 25 >25	4.06 Ref	2.03-8.17 —	.0001
AST level (U/L)*	0.57	0.47-0.67	—	—	—	—	—	—	—	—	—
LDH level (U/L)	0.78	0.69-0.87	424	0.72	0.71	0.16	0.97	≤ 424 >424	Ref 5.70	— 2.79-12.38	<.0001
Ferritin level (ng/mL)	0.74	0.62-0.86	1799	0.70	0.75	0.14	0.97	≤ 1799 >1799	Ref 5.59	— 2.35-14.26	.0002
D-dimer level (ng/mL)	0.75	0.64-0.87	1386	0.62	0.84	0.23	0.96	≤ 1386 >1386	Ref 7.10	— 3.10-16.76	<.0001
Fibrinogen level (mg/dL)*	0.59	0.47-0.71	—	—	—	—	—	—	—	—	—
Platelet count ($\times 10^3$ cells/ μ L)	0.63	0.54-0.72	245	0.63	0.61	0.11	0.95	≤ 245 >245	2.61 Ref	1.31-5.35 —	.007
Monocyte count ($\times 10^3$ cells/ μ L)	0.71	0.63-0.78	0.4	0.77	0.67	0.11	0.96	≤ 0.4 >0.4	2.63 Ref	1.31-5.56 —	.008
Neutrophil count ($\times 10^3$ cells/ μ L)	0.76	0.66-0.85	5.1	0.86	0.62	0.15	0.98	≤ 5.1 >5.1	Ref 8.08	— 3.53-21.87	<.0001
Lymphocyte count ($\times 10^3$ cells/ μ L)	0.79	0.73-0.85	0.9	0.63	0.83	0.13	0.98	≤ 0.9 >0.9	6.37 Ref	2.78-17.23 —	<.0001
N/L ratio	0.83	0.74-0.91	6.5	0.86	0.68	0.17	0.98	≤ 6.5 >6.5	Ref 10.54	— 4.59-28.55	<.0001
SpO ₂ /FiO ₂ ratio	0.87	0.83-0.92	211.11	0.88	0.75	0.32	0.98	≤ 211.11 >211.11	21.26 Ref	9.86-50.04 —	<.0001

AUC, Area under the curve; NPV, negative predictive value; Ref, reference.

*Variables with an AUC less than 0.60 were not analyzed further.

level (AUROCC = 0.80), albumin level (AUROCC = 0.81), LDH level (AUROCC = 0.78), ferritin level (AUROCC = 0.74), D-dimer level (AUROCC = 0.75), monocyte count (AUROCC = 0.71), neutrophil count (AUROCC = 0.76), lymphocyte count (AUROCC = 0.79), N/L ratio (AUROCC = 0.83), and SpO₂/FiO₂ ratio (AUROCC = 0.87). Optimal cutoffs based on Youden

index were calculated for these variables to classify patients into groups at high or low risk of a fatal outcome. AUROCC and survival curves for each individual biomarker are shown in Fig E2 (in this article's Online Repository at www.jacionline.org), except for neutrophil count and lymphocyte count (which were replaced in any further analysis by N/L ratio because of its superiority as a

biomarker in this setting). The variable with the highest sensitivity was CRP level (0.97), whereas IL-6 level had the highest specificity (0.89) (Table III). Patients in our cohort with a CRP value below 8.75 mg/dL had less than a 1% probability of dying. PPVs were discrete owing to the relatively low mortality in the cohort. IL-6 level and SpO₂/FiO₂ ratio had the highest PPVs (0.26 and 0.32 respectively), which meant that having an IL-6 level higher than 86 pg/mL or an SpO₂/FiO₂ ratio lower than 211 increased the likelihood of dying from 7.2% in the overall cohort to 26% or 32%, respectively. Individually, the most robust biomarkers for predicting risk of mortality in this study were CRP level and SpO₂/FiO₂ ratio; patients with a CRP level higher than 8.75 mg/dL or an SpO₂/FiO₂ ratio less than 211 had 20 times more risk of dying than did those with values below or above the threshold.

A multivariate prediction model was developed to improve the predictive power of each individual biomarker. The independent contribution of the top 8 variables to mortality risk, as identified by significant univariate logistic regression (Table II) and ROC curve analysis result greater than 0.70 (Table III) plus age, was assessed by backward stepwise regression. Age was included in the analysis because it had been identified as one of the major risk factors in COVID-19 in previous studies.^{3,4} Of these 9 variables, only IL-6 level, LDH level, N/L ratio, SpO₂/FiO₂ level, and age showed a statistically significant individual contribution to the predictive model. Random forest analysis gave the relative levels of relevance of each of the selected variables for mortality risk stratification, which in descending order were as follows: SpO₂/FiO₂ ratio, N/L ratio, LDH level, IL-6 level, and age (see Fig 3 in this article's Online Repository at www.jacionline.org). The sequential regression models for mortality prediction in COVID-19 are shown in Table IV, and their β -coefficients are shown in Table E1. Increasing the model's complexity through the sequential addition of biomarkers improved its predictive performance up to an AUROC of 0.94 (95% CI = 0.89-1.00). This final model, which includes SpO₂/FiO₂ ratio, N/L ratio, LDH level, IL-6 level, and age, had a robust classifying accuracy (Fig 2, A). The Youden index-based cutoff generated for the model was 0.07, with a 0.88 sensitivity, 0.89 specificity, 0.38 PPV, and 0.99 negative predictive value. Kaplan-Meier analysis showed a very significant difference in survival for patients below or above the model threshold ($P < .0001$ [Fig 2, B]). Internal validation of the final model was performed by bootstrap resampling, showing maintained high accuracy (optimism-adjusted AUROC = 0.93) (see Table E2 in this article's Online Repository at www.jacionline.org). The COR+12 calculator based on the model can be found online at https://utrero-rico.shinyapps.io/COR12_Score/, thus allowing for calculation of a patient's probability of death (see the instructions at the end of this article).

The developed model detected, early after their arrival at the hospital, 88% of patients who subsequently died. Only 4 patients stratified by the model as having a low mortality risk died (12% of the deceased patients) (see Table E3 in this article's Online Repository at www.jacionline.org). Three of these patients (75%) had relevant comorbidities for mortality due to COVID-19. At the time of data collection, more than half of the patient cohort had no respiratory distress (281 [56.1%]), 113 patients (22.6%) had mild ARDS, 36 (7.2%) had moderate ARDS, and 67 (13.4%) had severe ARDS (Table I). The initial respiratory function assessment was a good predictor of mortality (SpO₂/FiO₂ ratio AUROC = 0.87); however, 12 patients with no ARDS or

mild-to-moderate ARDS in this early assessment died. Most of these patients (73%) who died without initial severe ARDS would have been classified by the model as having a high mortality risk (see Fig E4 in this article's Online Repository at www.jacionline.org).

Finally, we analyzed all of the studied variables regarding ICU admission. Patients were divided into 3 levels of severity: patients who were discharged from hospital without having needed for intensive care, patients who required ICU admission but survived, and patients who died either after ICU admission or not. There were significant differences between the severity groups with regard to all variables except for AST level (Fig 3). For some biomarkers, such as CRP level or neutrophil count, ICU patients had values similar to those of nonsurvivors, whereas for other biomarkers such as LDH level, lymphocyte count, or SpO₂/FiO₂ ratio, ICU patients had intermediate values between those of less severely ill discharged patients and nonsurvivors. Next, the capacity of the risk model to predict intensive care requirement was tested. The score was significantly higher in patients who required ICU admission than in survivors who did not require ICU admission (0.059 [interquartile range, 0.015-0.15] vs 0.007 [interquartile range, 0.002-0.024]; $P < .0001$) (Fig 4, A). The AUROC for ICU requirement was 0.82 (95% CI = 0.74-0.91), with an optimal cutoff for the model of 0.03, which had 0.77 sensitivity and specificity. The value of the model to further define disease severity and to assist in hospital resource planning was tested; a significant positive correlation was found between the model and length of hospital stay in survivors ($R^2 = 0.12$; $P < .0001$) (Fig 4, B).

DISCUSSION

We have described a predictive model to classify patients with a recent COVID-19 diagnosis according to their risk of death by using 5 early, easy-to-assess biomarkers. This study analyzed a large patient cohort at a hospital in Madrid, Spain, at the peak of the pandemic. Recently, a score to predict critical illness,¹⁵ and 2 scores to predict mortality,^{5,16} in hospitalized patients with COVID-19 have been published, with all of them analyzing patients from China. These have studies included a large number of variables in their model, and in contrast to in the present work, some of the variables, such as radiographic abnormalities or dyspnea, are relatively subjective. Additionally, a new machine learning model showed that LDH level, lymphocyte frequency, and CRP level can predict patient mortality more than 10 days in advance.¹⁷

The present cohort confirmed in a non-Asian population some of the previously identified risk factors (eg, age). The patients included in the study were mostly of white or Hispanic ethnicity. A higher mortality rate was found in white patients than in Hispanic patients, which could be partly explained by age difference (56 years [range 47-64 years] vs 48 years [range 41-54 years]; $P < .0001$). The main comorbidities associated with fatal outcome were hypertension, dyslipidemia, and obesity. Of note, the overall mortality rate of 7.2% during follow-up was lower than that reported by other hospital cohorts^{4,6} and lower than the 23% mortality rate described in the first consecutive 521 patients with COVID-19 in our hospital (from the end of February to the beginning of March, 2020) (Lalueza et al personal communication, 2020). Because it includes patients with IL-6 level measurements, the present cohort

TABLE IV. Sequential regression models for mortality prediction in COVID-19

Model	SpO ₂ /FiO ₂ ratio	N/L ratio	LDH level	IL-6 level	Age	AIC	H-L	AUC	95% CI	Cutoff	Sensitivity	Specificity	PPV	NPV
1	Yes	No	No	No	No	190.63	.05	0.87	0.80-0.95	0.12	0.75	0.88	0.32	0.98
2	Yes	Yes	No	No	No	175.14	.41	0.91	0.84-0.97	0.07	0.86	0.83	0.27	0.99
3	Yes	Yes	Yes	No	No	169.43	.57	0.91	0.84-0.97	0.11	0.81	0.88	0.34	0.98
4	Yes	Yes	Yes	Yes	No	136.41	.92	0.93	0.87-0.99	0.13	0.81	0.92	0.44	0.98
5	Yes	Yes	Yes	Yes	Yes	129.28	.93	0.94	0.89-1.00	0.07	0.88	0.89	0.38	0.99

AIC, Akaike information criterion; AUC, area under the curve; HL, Hosmer-Lemeshow test *P* value; NPV, negative predictive value.

Model 1 included 497 patients and 36 events, model 2 included 495 and 36 events, model 3 included 486 patients and 36 events, model 4 included 443 patients and 33 events, and model 5 includes 443 patients and 33 events.

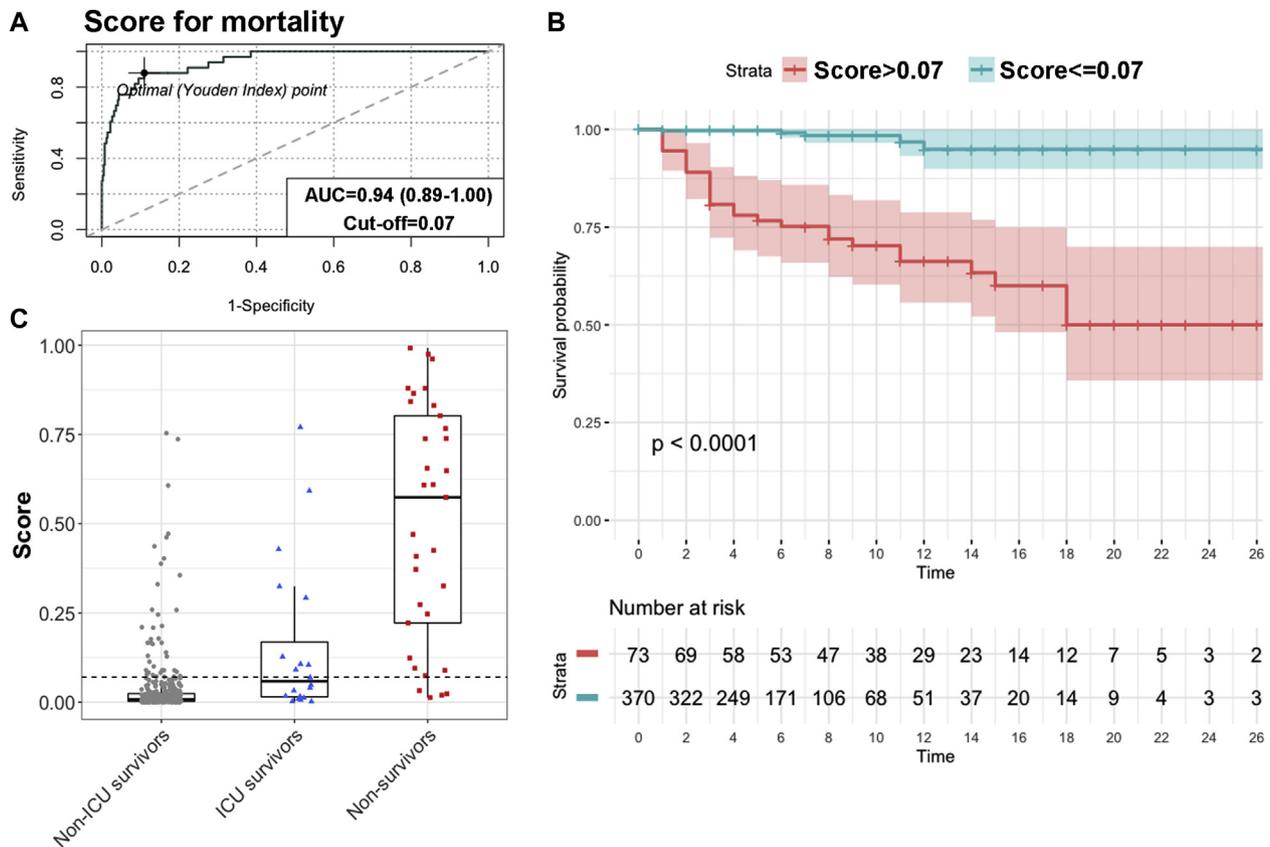


FIG 2. The mortality risk model accurately classified patients at risk of dying. **A**, The area under the curve (AUC) of the model was 0.94 (95% CI = 0.89-1.00); the optimal cutoff of 0.07 had a sensitivity of 0.88 and a specificity of 0.89. **B**, Kaplan-Meier analysis based on Youden index optimal cutoff showed a very different survival rate between the groups with low and high risk of death ($P < .0001$). Color shades represent the 95% CI. Time is indicated in days. **C**, The score obtained from the model in nonsurvivors (red) was significantly higher than that in survivors who required intensive care (blue) ($P = .0001$) and in survivors who did not require intensive care (gray) ($P = .0001$). Dashed line indicates the optimal cutoff for mortality (0.07).

is younger (52 vs 65 years) and with lower rate of comorbidities (eg, a hypertension prevalence of 27.7% vs 42%) than in the work reported in the aforementioned communication by Lalueza et al. Moreover, 195 patients in our cohort (38.9%) received tocilizumab; the potential effect of this and other treatments on the mortality rate is currently being studied. The median time from hospital admission to laboratory testing was 2 days. However, the laboratory test results had minimal or no correlation with the time from onset of illness (see Fig E1), suggesting that the variables included in the study correlated with the severity of the disease rather than with the time interval since onset of symptoms or hospital admission.

Patients who progress to severe forms of COVID-19 are thought to have hyperactivation of the immune system with uncontrolled release of inflammatory cytokines.¹⁰ Signaling of the proinflammatory cytokine IL-6 can be blocked by the humanized anti-IL-6 receptor mAb tocilizumab.¹⁸ We set up measurement of IL-6 level in patients with COVID-19 at our hospital as a biomarker for inflammation and to help guide the administration of tocilizumab together with other inflammation markers such as CRP level, lymphocyte count, and clinical evaluation results.¹⁹ In our cohort, IL-6 level was increased in nonsurvivors. This reinforces the evidence that the amount of circulating IL-6 is closely linked to the severity of COVID-19,^{4,10,20} which has been further

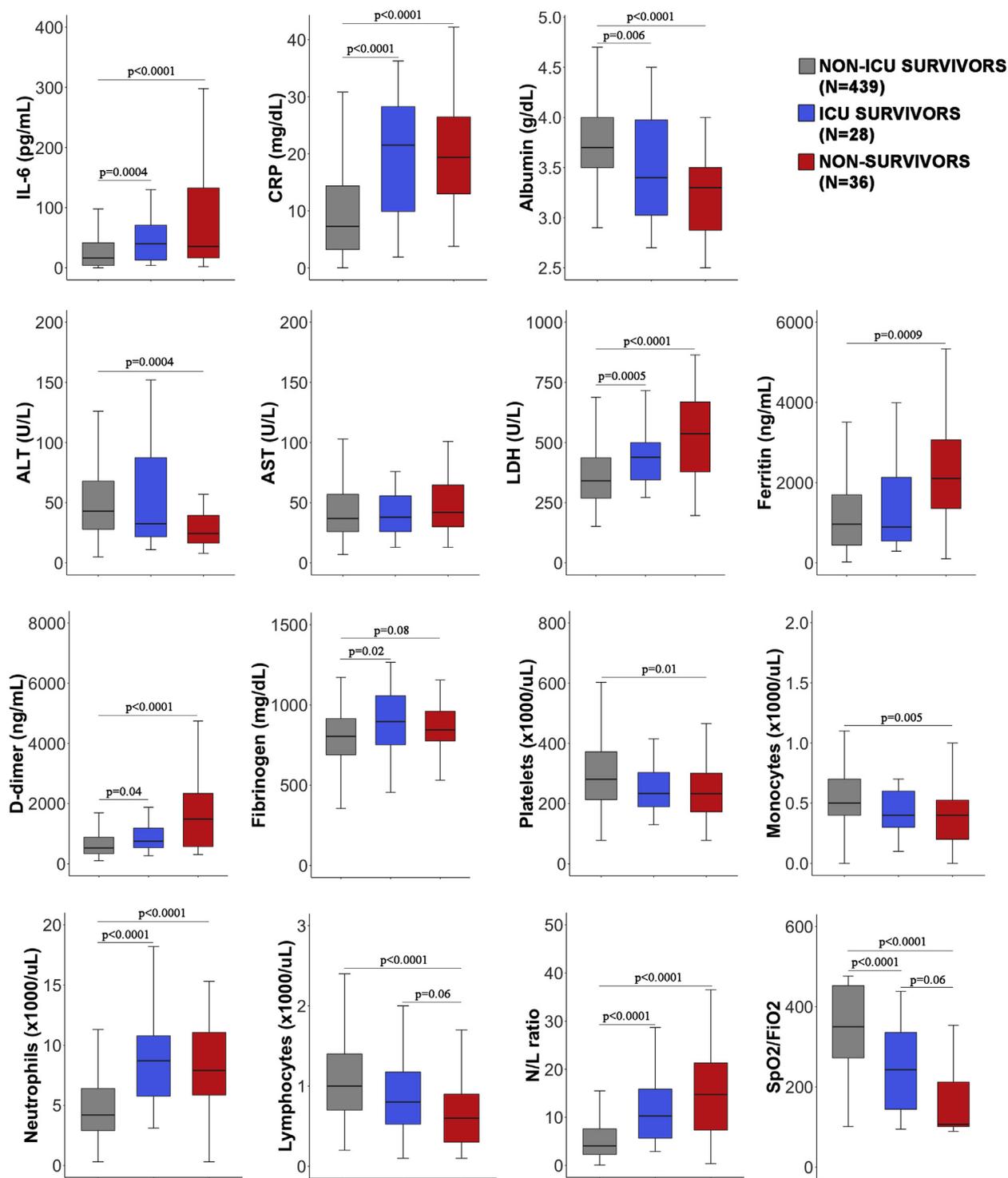


FIG 3. Comparison of variables for survivors who did not require ICU admission, survivors who required ICU admission, and nonsurvivors. There were significant differences in most of the variables between the patient groups. The ICU survivors (*blue*) were similar to the nonsurvivors (*red*) for some variables such as CRP level and neutrophil count. For other variables, however, ICU survivors had values intermediate between those for survivors who did not require ICU admission (*gray*) and those for nonsurvivors.

confirmed in a recent meta-analysis²¹ and contradicts the results reported for smaller published cohorts in which there were no differences in IL-6 level between patients with mild and severe COVID-19 cases.^{8,22} IL-6 level has also been associated with

mortality risk in patients with ARDS who do not have COVID-19.²³ Measuring IL-6 level and including it in the predictive model may not only be relevant for prognosis but could also improve therapeutic decision making. There is an increasing

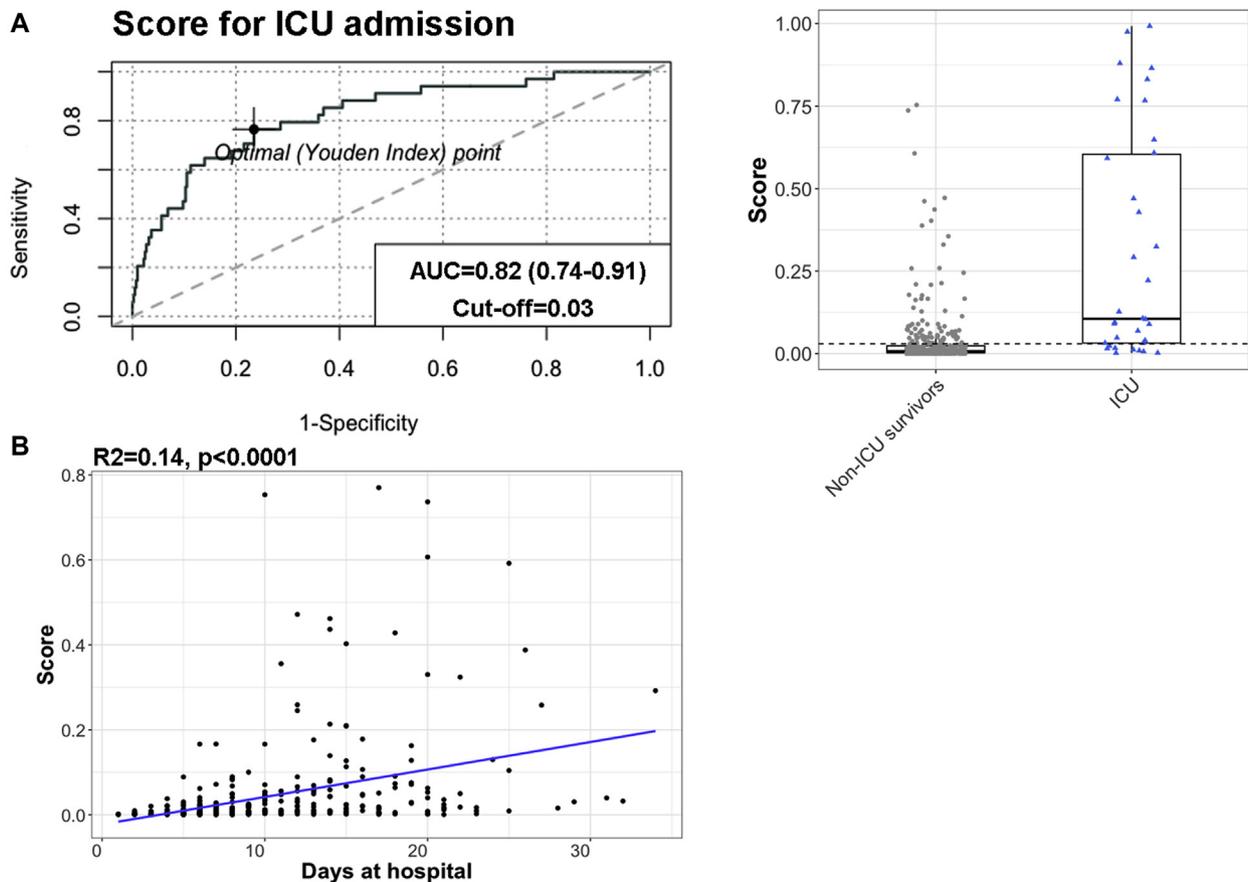


FIG 4. The mortality risk model could also be applied to other severity estimates such as ICU requirement and length of hospital stay. **A**, The model was an acceptable predictor of ICU requirement, with an area under the curve (AUC) of 0.82 (95% CI = 0.74-0.91) and optimal cutoff of 0.03, with 0.77 sensitivity and 0.77 specificity. The risk score was significantly higher for patients who required ICU admission than the score for those who did not ($P < .0001$). Dashed line represents the optimal cutoff for ICU admission (0.03). **B**, There was a positive correlation between the model and length of hospital stay by survivors ($P < .0001$).

number of studies reporting a favorable outcome from blocking IL-6 signaling in patients with COVID-19,^{19,24-26} all of them without a randomized control group. The model described here could be used as a tool to classify patients into more biologically and clinically uniform subgroups before inclusion in randomized trials for tocilizumab or other drugs. Until results from clinical trials are available, the current model can be useful to indicate those patients who could potentially benefit most from immunomodulatory treatments. Besides measuring IL-6 level, measuring the level of other cytokines could offer deeper insight into the pathophysiology of the disease or prognostic value, and it could also be targeted for therapy intervention. Notably, blocking of IL-1 with anakinra is proving beneficial in reducing the need for invasive mechanical ventilation and mortality among patients with severe COVID-19.²⁷

CRP is commonly used in clinical practice for decision making. In our study, it showed a remarkably high sensitivity for mortality prediction (0.97); however, it dropped out of the model, possibly because of its strong correlation with the variables SpO₂/FiO₂ ratio, N/L ratio, LDH level, and IL-6 level (see Fig E5 in this article's Online Repository at www.jacionline.org). In particular, CRP levels are influenced by IL-6 level, as its cellular transcription can be a direct result of IL-6 signaling. Regarding the 3 levels of disease severity in Fig 3,

CRP level appeared to be an accurate biomarker for predicting disease severity defined as ICU requirement or death.

Zhou et al highlighted D-dimer, together with age and SOFA score, as an independent risk factor for mortality.⁴ Our study did not confirm the predictive value of D-dimer level (Table II). In the study by Zhou et al, 81% of nonsurvivors had a D-dimer level higher than 1000 ng/mL, whereas in our cohort only 13% of nonsurvivors had a level above that threshold. It is plausible that this biomarker classifies a subgroup of patients with coagulopathy complications during COVID-19 and this subgroup was less represented in our cohort. Of note, D-dimer level was measured in only 330 patients, and this might have prevented its significance as biomarker. Similarly, in our cohort the transaminase ALT level was significantly lower in nonsurvivors, in contrast with the levels in previous studies in which ALT was increased in ICU patients or nonsurvivors.^{4,8} Lei et al described a delayed increase in ALT level in patients with COVID-19 compared with the increase in levels of other liver enzymes. This could partially explain why ALT level was not increased in nonsurvivors at the time of measurement.²⁸

The final model includes only 5 variables, namely, SpO₂/FiO₂ ratio, N/L ratio, LDH level, IL-6 level, and age, which are readily obtainable at hospitals and clinical laboratories and can be obtained in a short time. Their combination boosted the mortality

predictive accuracy of the model to an AUROCC of 0.94. Nevertheless, 5 sequential regression models were developed, and all of them can be used on the basis of the available data. For example, in the absence of laboratory data, SpO₂/FiO₂ ratio alone could be used as a biomarker predictive of mortality (AUROCC = 0.87), with 0.75 sensitivity and 0.88 specificity. Similarly, in a setting without measurements of IL-6 level, model 3 could be used, increasing the predictive capacity (AUROCC = 0.91) with 0.81 sensitivity and 0.88 specificity. The already published scores of patients with COVID-19 do not include IL-6 level; however, we have provided data supporting the potential relevance of this cytokine in prognosis and personalized treatment.

The potential limitations of this study include a relatively low number of deceased patients for developing the mortality risk model from a single enter. In addition, patients with measurements of IL-6 level were selected for inclusion in the cohort, which might have biased the cohort toward a younger median age. Finally, laboratory tests were performed not at time of admission but rather with a median delay of 2 days after hospitalization, and this may have limited the predictive capacity of the model. Validation of these results in other cohorts and at hospital admission is needed.

The COVID-19 pandemic has posed an enormous challenge for health care professionals and the medical systems worldwide. We have developed a risk model that could allow early identification of patients at high risk of a fatal outcome. The early identification of prognostic factors and patient groups at high risk of COVID-19 mortality could contribute to guiding medical decisions, planning for hospital resources (including intensive care), and reducing the fatality rate of this new infection.

COR+12 calculator instructions

Go to https://utrero-rico.shinyapps.io/COR12_Score/. Introduce the following 5 parameters: SpO₂/FiO₂ ratio, N/L ratio, LDH level (U/L), IL-6 level (pg/mL), and age (in years). Click the Predict button. The probability of death will appear in the graph, represented as a square with its 95% CI. By positioning the mouse over the square, the specific values for each patient can be visualized. For any issues regarding use of the COR+12 calculator, please contact R.L.G. at the e-mail address rociolagunagoya@gmail.com.

Clinical implications: This model provides a quantifiable risk of fatal outcome in patients with COVID-19, including patients without respiratory distress at the time of evaluation, which can help guide medical decisions.

REFERENCES

- 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* 2020;382:727-33.
- Johns Hopkins University: Coronavirus Resource Center. Available at: <https://coronavirus.jhu.edu/>. Accessed June 10, 2020.
- Wu Z, McGoogan JM. Characteristics of and important lessons from the Coronavirus disease 2019 (COVID-19) outbreak in China: summary of a report of 72314 cases from the Chinese Center for Disease Control and Prevention. *JAMA* 2020;323:1239-42.
- Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet* 2020;395:1054-62.
- Wang K, Zuo P, Liu Y, Zhang M, Zhao X, Xie S, et al. Clinical and laboratory predictors of in-hospital mortality in patients with COVID-19: a cohort study in Wuhan, China. *Clin Infect Dis* [Published online May 2020]. <https://doi.org/10.1093/cid/ciaa538>.
- Richardson S, Hirsch JS, Narasimhan M, Crawford JM, McGinn T, Davidson KW, et al. Presenting characteristics, comorbidities, and outcomes among 5700 patients hospitalized with COVID-19 in the New York City area. *JAMA* 2020;323:2052-9.
- Yang X, Yu Y, Xu J, Shu H, Xia J, Liu H, et al. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. *Lancet Respir Med* 2020;8:475-81.
- 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* 2020;395:497-506.
- Zhang J, Yu M, Tong S, Liu LY, Tang LV. Predictive factors for disease progression in hospitalized patients with Coronavirus disease 2019 in Wuhan, China. *J Clin Virol* 2020;127:104392.
- Chen G, Wu D, Guo W, Cao Y, Huang D, Wang H, et al. Clinical and immunological features of severe and moderate Coronavirus disease 2019. *J Clin Invest* 2020;130:2620-9.
- Blanco-Melo D, Nilsson-Payant BE, Liu WC, Uhl S, Hoagland D, Moller R, et al. Imbalanced host response to SARS-CoV-2 drives development of COVID-19. *Cell* 2020;181:1036-45.
- Rice TW, Wheeler AP, Bernard GR, Hayden DL, Schoenfeld DA, Ware LB. Comparison of the SpO₂/FIO₂ ratio and the PaO₂/FIO₂ ratio in patients with acute lung injury or ARDS. *Chest* 2007;132:410-7.
- Ranieri VM, Rubenfeld GD, Thompson BT, Ferguson ND, Caldwell E, Fan E, et al. Acute respiratory distress syndrome: the Berlin Definition. *JAMA* 2012;307:2526-33.
- Moons KG, Altman DG, Reitsma JB, Collins GS. New guideline for the reporting of studies developing, validating, or updating a multivariable clinical prediction model: The TRIPOD Statement. *Adv Anat Pathol* 2015;22:303-5.
- Liang W, Liang H, Ou L, Chen B, Chen A, Li C, et al. Development and validation of a clinical risk score to predict the occurrence of critical illness in hospitalized patients with COVID-19. *JAMA Intern Med* [Published online May 12, 2020]. <https://doi.org/10.1001/jamainternmed.2020.2033>.
- Zou X, Li S, Fang M, Hu M, Bian Y, Ling J, et al. Acute Physiology and Chronic Health Evaluation II score as a predictor of hospital mortality in patients of Coronavirus disease 2019. *Crit Care Med* 2020;48:e657-65.
- Yan L, Zhang H, Goncalves J, et al. An interpretable mortality prediction model for COVID-19 patients. *Nat Mach Intell* 2020;283-8.
- Zumla A, Hui DS, Azhar EI, Memish ZA, Maeurer M. Reducing mortality from 2019-nCoV: host-directed therapies should be an option. *Lancet* 2020;395:e35-6.
- Fernandez-Ruiz M L-MF, Perez-Jacoiste MA, et al. Tocilizumab for the treatment of adult patients with severe COVID-19 pneumonia: a single-center cohort study. *J Med Virol* [Published online July 16, 2020]. <https://doi.org/10.1002/jmv.26308>.
- Herold T, Jurinovic V, Amreich C, Lipworth BJ, Hellmuth JC, Bergwelt-Baildon MV, et al. Elevated levels of IL-6 and CRP predict the need for mechanical ventilation in COVID-19. *J Allergy Clin Immunol* 2020;146:128-36.e4.
- Aziz M, Fatima R, Assaly R. Elevated interleukin-6 and severe COVID-19: a meta-analysis. *J Med Virol* [Published online April 28, 2020]. <https://doi.org/10.1002/jmv.25948>.
- Zheng HY, Zhang M, Yang CX, Zhang N, Wang XC, Yang XP, et al. Elevated exhaustion levels and reduced functional diversity of T cells in peripheral blood may predict severe progression in COVID-19 patients. *Cell Mol Immunol* 2020;17:541-3.
- Bime C, Casanova N, Oita RC, Ndikum J, Lynn H, Camp SM, et al. Development of a biomarker mortality risk model in acute respiratory distress syndrome. *Crit Care* 2019;23:410.
- Xu X, Han M, Li T, Sun W, Wang D, Fu B, et al. Effective treatment of severe COVID-19 patients with tocilizumab. *Proc Natl Acad Sci U S A* 2020;117:10970-5.
- Sciascia S, Apra F, Baffa A, Baldovino S, Boaro D, Boero R, et al. Pilot prospective open, single-arm multicentre study on off-label use of tocilizumab in patients with severe COVID-19. *Clin Exp Rheumatol* 2020;38:529-32.
- Klopfenstein T, Zayet S, Lohse A, Balblanc JC, Badie J, Royer PY, et al. Tocilizumab therapy reduced intensive care unit admissions and/or mortality in COVID-19 patients. *Med Mal Infect* 2020;50:397-400; <https://doi.org/10.1016/j.medmal.2020.05.001>.
- Huet TBH, Voisin O, Jouvesshomme S, Dauriat G, Lazareth I, Sacco E, et al. Anakinra for severe forms of COVID-19: a cohort study. *Lancet Rheumatol* 2020;2:E393-400.
- Lei F, Liu YM, Zhou F, Qin JJ, Zhang P, Zhu L, et al. Longitudinal association between markers of liver injury and mortality in COVID-19 in China. *Hepatology* [Published online May 2, 2020]. <https://doi.org/10.1002/hep.31301>.

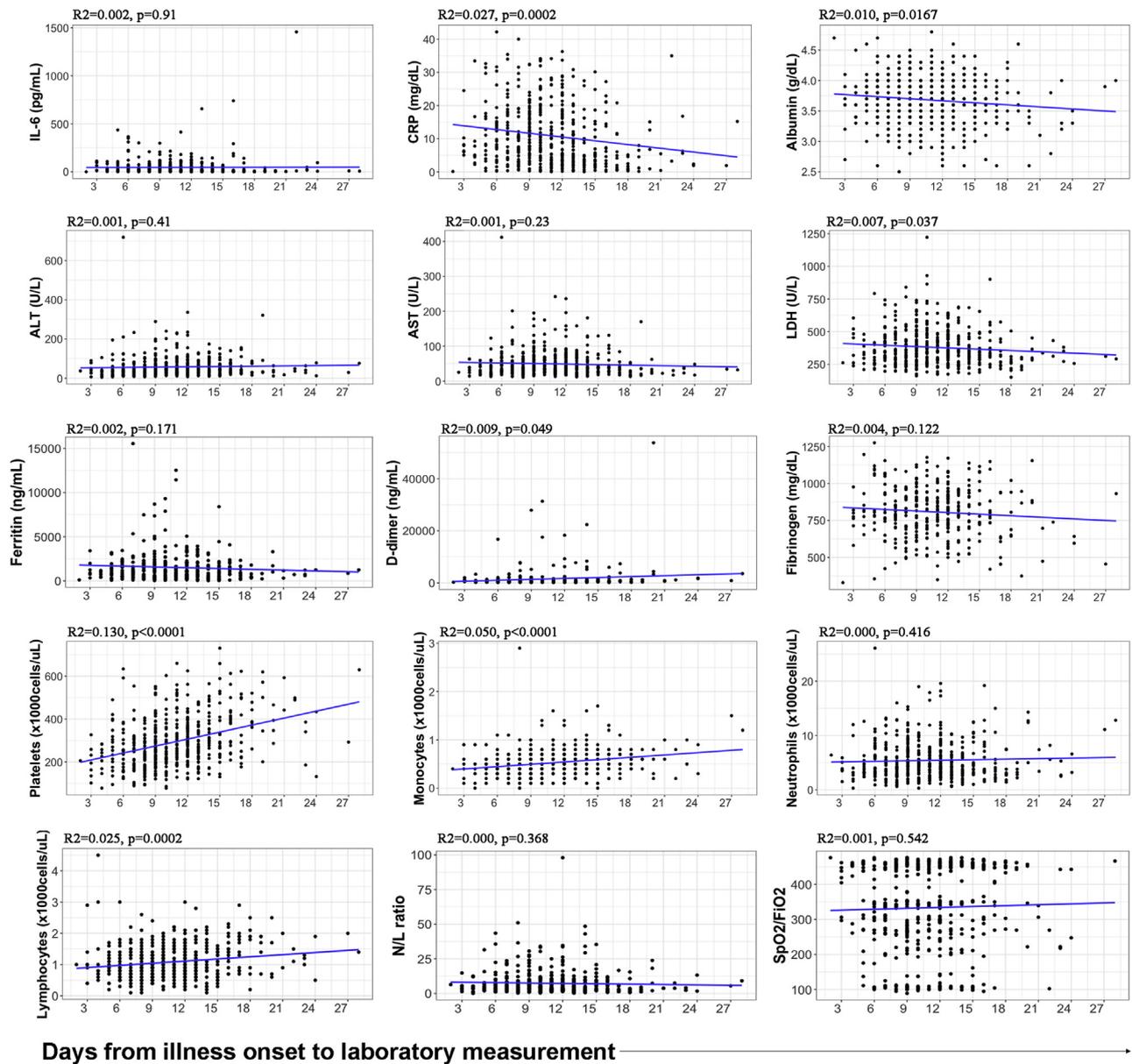


FIG E1. Laboratory values and SpO₂/FiO₂ ratio did not correlate with the time from onset of illness to the measurement. Most variables did not correlate, and for those that did, the impact of days from onset of illness was minimal (very low R²). This implied that the values obtained depended not on the number of days with symptoms until the measurement but rather on the severity of each particular patient.

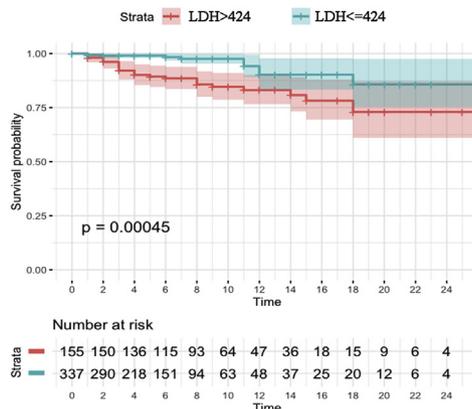
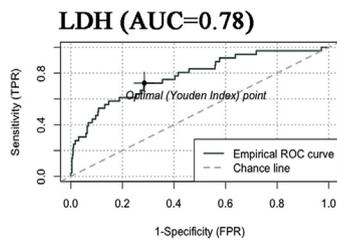
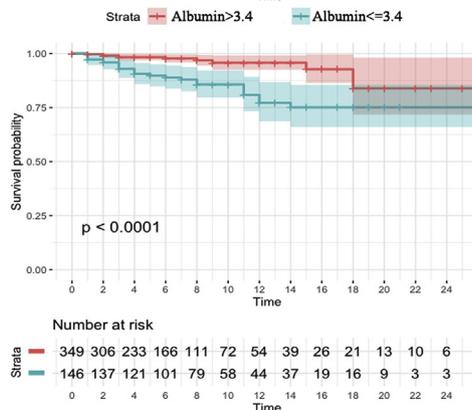
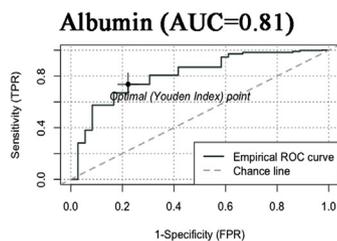
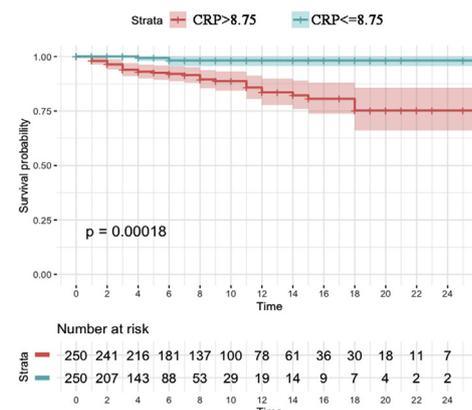
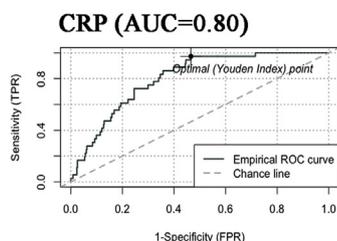
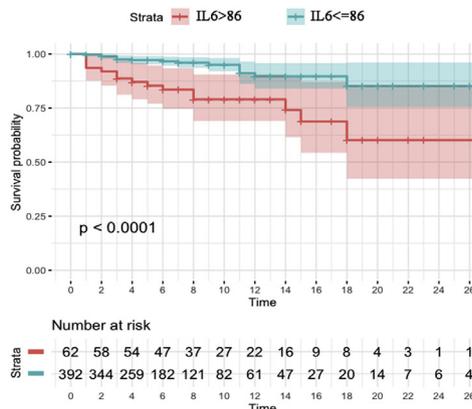
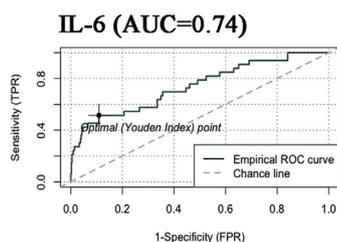


FIG E2. ROC and Kaplan-Meier analysis of individual variables with an area under the curve (AUC) greater than 0.70 and with a *P* value less than .05 in univariate logistic regression. Color shades represent the 95% CI. Time is indicated in days.

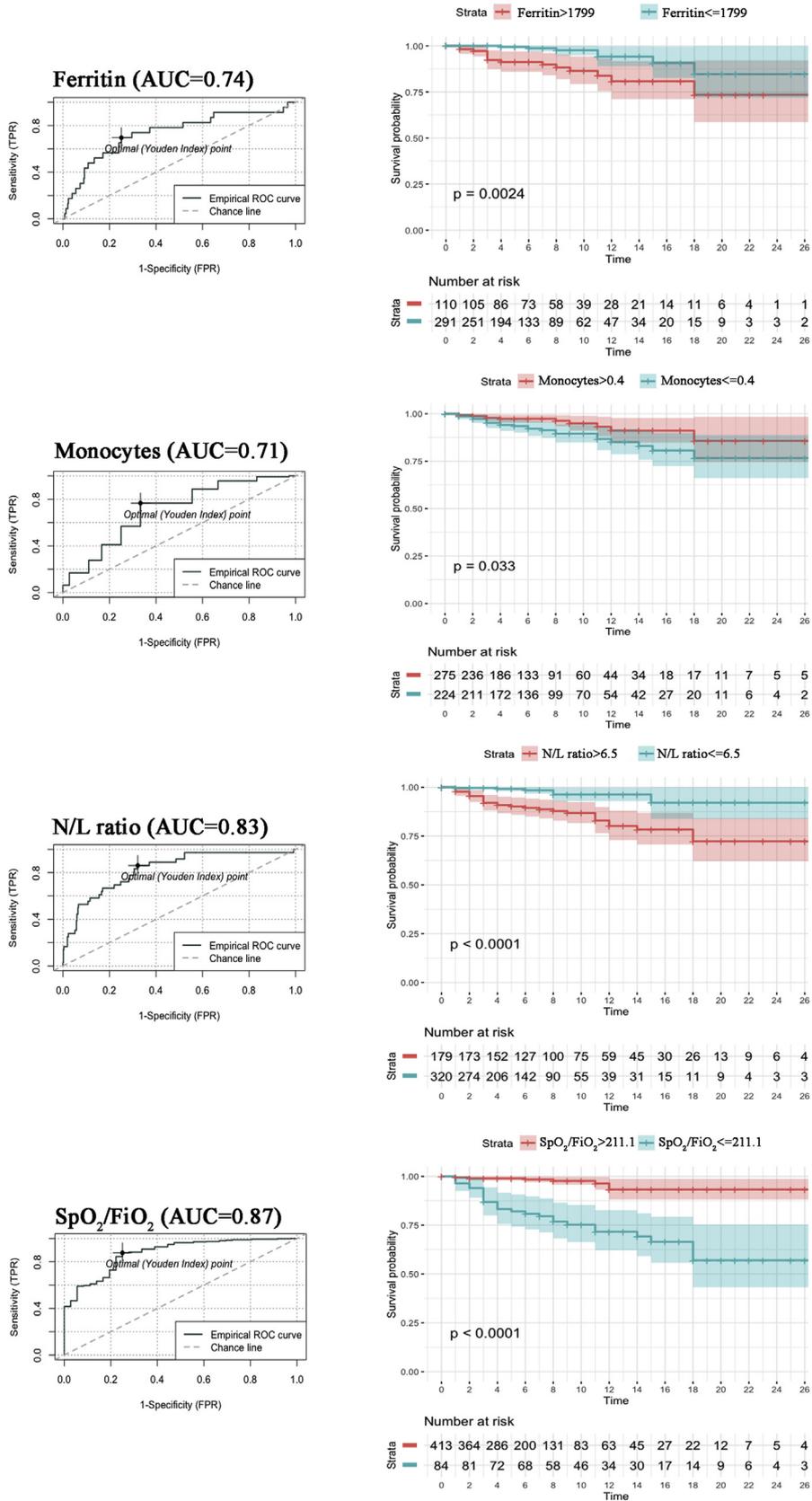


FIG E2. Continued

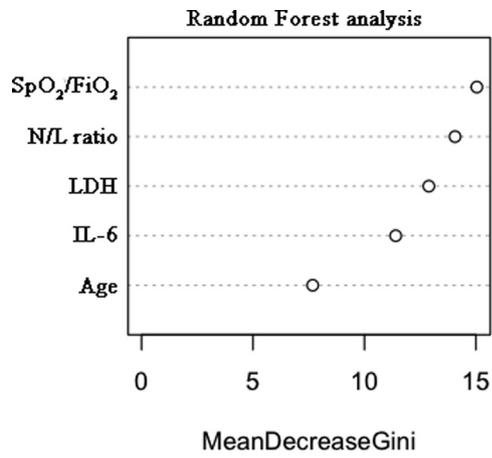


FIG E3. Determination of the importance of each significant variable in the multivariate logistic regression by random forest analysis. The relative weights of each variable, from highest to lowest, were as follows: SpO₂/FiO₂ ratio, N/L ratio, LDH level, IL-6 level, and age.

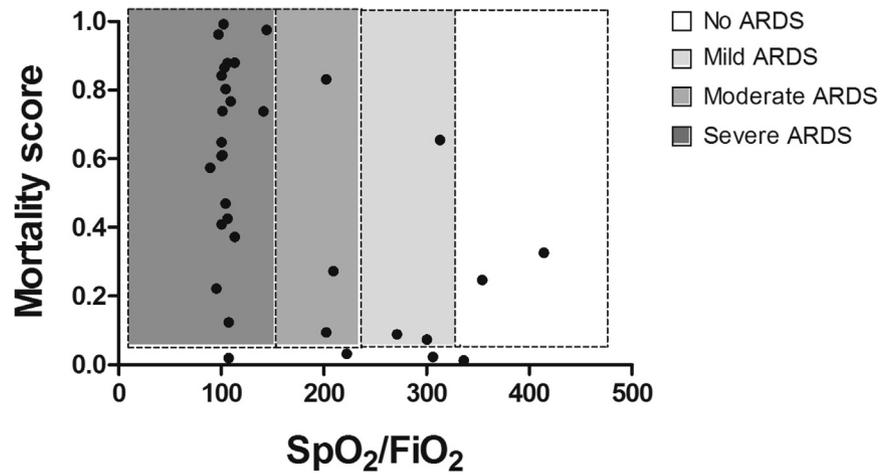


FIG E4. Contribution of the model to prediction of patient mortality in addition to their initial respiratory function assessment. SpO₂/FiO₂ ratio and mortality score are represented for every deceased patient in the cohort, except for 3 of 36 patients who died (1 indicates no ARDS, and 2 indicates severe ARDS), and no score was available. Of the 11 patients without severe ARDS who died, 8 (73%) had a high mortality score in the beginning of their hospitalization. The lower limit of the color shade corresponds to the model cutoff 0.07.

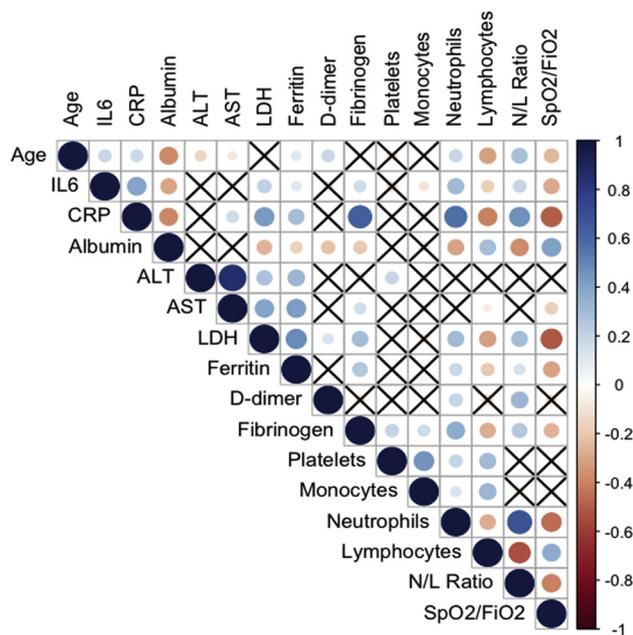


FIG E5. Correlation plot of all the variables assessed as potential predictive biomarkers of mortality due to COVID-19. Positive correlations appear in blue, and negative correlations appear in red. The size of the circle corresponds to the magnitude of the correlation. The cross indicates no correlation.

TABLE E1. β -Coefficients of sequential regression models for mortality prediction in COVID-19

Model	Intercept	SpO ₂ /FiO ₂ ratio	N/L ratio	LDH level	IL-6 level	Age
1	0.8415	-0.0136	—	—	—	—
2	-0.3353	-0.0121	0.0660	—	—	—
3	-2.2212	-0.0103	0.0604	0.0034	—	—
4	-3.2413	-0.0091	0.0675	0.0038	0.0046	—
5	-7.6991	-0.0076	0.0547	0.0046	0.0043	0.0682

TABLE E2. Internal validation of the model by bootstrapping

	Risk model	Optimism	Optimism-adjusted
AUROC	0.944	0.017	0.927
Calibration intercept	0.000	0.121	-0.121
Calibration slope	1.000	0.096	0.904

TABLE E3. Mortality score in the 36 deceased patients and clinical characteristics of the patients who had a low mortality risk score but died

Initial respiratory function	High score	Low score	No score available	Characteristics of the deceased patients with a low score
No ARDS (n = 4)	2	1	1	Kidney transplantation, hypertension, dyslipidemia, previous thromboembolic event, smoking
Mild ARDS (n = 4)	3	1	—	No comorbidities
Moderate ARDS (n = 4)	3	1	—	Hypertension, dyslipidemia, obesity, benign prostatic hyperplasia, steatosis
Severe ARDS n = 24)	21	1	2	HIV-HCV coinfection

HCV, Hepatitis C virus.