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Original research

Development and validation of a prediction model for 30-day mortality in hospitalised patients with COVID-19: the COVID-19 SEIMC score

Juan Berenguer ,[1] Alberto M Borobia,[2] Pablo Ryan,[3] Jesús Rodríguez-Baño,[4] Jose M Bellón,[5] Inmaculada Jarrín,[6] Jordi Carratalà,[7] Jerónimo Pachón,[8] Antonio J Carcas,[2] María Yllescas,[9] José R Arribas,[10] COVID-19@Spain and COVID@HULP Study Groups

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For numbered affiliations see end of article.

Correspondence to
Dr Juan Berenguer, Infectious Diseases, Hospital General Universitario Gregorio Marañón, Madrid 28007, Spain; jbb4@me.com

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ABSTRACT

Objective To develop and validate a prediction model of mortality in patients with COVID-19 attending hospital emergency rooms.

Design Multivariable prognostic prediction model.

Setting 127 Spanish hospitals.

Participants Derivation (DC) and external validation (VC) cohorts were obtained from multicentre and single-centre databases, including 4035 and 2126 patients with confirmed COVID-19, respectively.

Interventions Prognostic variables were identified using multivariable logistic regression.

Main outcome measures 30-day mortality.

Results Patients' characteristics in the DC and VC were median age 70 and 61 years, male sex 61.0% and 47.9%, median time from onset of symptoms to admission 5 and 8 days, and 30-day mortality 26.6% and 15.5%, respectively. Age, low age-adjusted saturation of oxygen, neutrophil-to-lymphocyte ratio, estimated glomerular filtration rate by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation, dyspnoea and sex were the strongest predictors of mortality. Calibration and discrimination were satisfactory with an area under the receiver operating characteristic curve with a 95% CI for prediction of 30-day mortality of 0.822 (0.806–0.837) in the DC and 0.845 (0.819–0.870) in the VC. A simplified score system ranging from 0 to 30 to predict 30-day mortality was also developed. The risk was considered to be low with 0–2 points (0%–2.1%), moderate with 3–5 (4.7%–6.3%), high with 6–8 (10.6%–19.5%) and very high with 9–30 (27.7%–100%).

Conclusions A simple prediction score, based on readily available clinical and laboratory data, provides a useful tool to predict 30-day mortality probability with a high degree of accuracy among hospitalised patients with COVID-19.

Key messages

What is the key question?

► The development of a predictive prognostic model is essential for improving the management of patients with severe COVID-19.

What is the bottom line?

► In a recent systematic review and critical appraisal of prediction models for COVID-19, 50 prognostic models were identified. All models were considered to have a high risk of bias, and none were recommended for clinical use.

Why read on?

► The COVID-19 SEIMC score was developed and externally validated with two large datasets from patients hospitalised with laboratory-confirmed COVID-19. The score based on age, low age-adjusted saturation of oxygen, neutrophil-to-lymphocyte ratio, estimated glomerular filtration rate by the CKD-EPI equation, dyspnoea and sex could identify the probability of 30-day mortality with a high degree of accuracy among patients with COVID-19.

INTRODUCTION

The clinical spectrum of the novel SARS-CoV-2 associated COVID-19 varies broadly, from asymptomatic disease to pneumonia and life-threatening complications, including acute respiratory distress syndrome, multisystem organ failure and death.[1–4]

The main poor prognostic factor identified in different series of COVID-19 is advanced age.[3 5 6] Other factors that have been associated with poor outcomes include male gender, several comorbidities, lymphocyte counts, high concentrations of different inflammatory or coagulation markers, serum levels of different cytokines and features derived from imaging studies.[5 7–10]

Prediction prognostic models are developed to aid healthcare providers in estimating the probability or risk that a specific event will occur, to inform their decision-making.[11] Prediction models can be based on regression or machine learning.[12] In a recent systematic review and critical appraisal of prediction models for diagnosis and prognosis of COVID-19, 50 prognostic models were identified; 23 estimated mortality risk, 8 aimed to predict severe disease or critical illness and the remaining 19 assessed other outcomes.[13] The majority of the models included in the review used clinical and laboratory data from Chinese patients. All models were considered to have a high risk of bias due

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Table 1 Comparison of participant characteristics in the derivation and external validation cohorts

	Derivation cohort (N=4035)			External validation cohort (N=2202)			
Characteristic	**Missing values**	**Valid cases**	**Value**	**Missing values**	**Valid cases**	**Value**	**P value**
Demographics							
Median age (IQR)—years	4	4031	70 (56–80)	0	2202	61 (46–78)	<0.001
Male sex—N (%)	48	3987	2433 (61.0)	1	2201	1054 (47.9))	<0.001
Comorbidity							
Current smoker—N (%)	1.118	2917	197 (6.8)	97	2105	156 (7.4)	<0.001
Hypertension—N (%)	25	4010	2052 (51.2)	17	2185	907 (41.5)	<0.001
Diabetes—N (%)	33	4002	871 (21.8)	16	2186	378 (17.3)	<0.001
Chronic kidney disease—N (%)	35	4000	199 (5.0)	2039	163	76 (46.6)	<0.001
Obesity (BMI>30)—N (%)	429	3606	497 (13.8)	61	2141	233 (10.9)	0.001
Chronic inflammatory disease—N (%)	38	3997	231 (5.8)	0	2202	255 (11.6)	<0.001
HIV/AIDS—N (%)	73	3962	26 (0.7)	20	2182	13 (0.6)	<0.001
Disease chronology							
Δt onset of symptoms to admission, days—median (IQR)	462	3573	5 (2–7)	939	1263	8 (5–11)	<0.001
Symptoms and signs							<0.001
History of fever—N (%)	35	4000	3240 (81.0)	35	2167	1568 (72.4)	<0.001
Cough—N (%)	51	3984	2862 (71.8)	36	2166	1098 (50.7)	<0.001
Malaise—N (%)	121	3914	2505 (64.0)	38	2164	907 (41.9)	<0.001
Dyspnoea—N (%)	55	3980	1953 (49.1)	37	2165	1098 (50.7)	<0.001
Myalgia/Arthralgia—N (%)	226	3809	947 (24,9)		2160	588 (27.2)	0.045
Sputum production—N (%)	72	3963	956 (24.1)	61	2141	311 (14.5)	<0.001
Vomiting/Nausea—N (%)	111	3924	488 (12.4)	0	2202	295 (13.4)	<0.001
Diarrhoea—N (%)	123	3912	471 (12.0)	37	2165	482 (22.3)	<0.001
Radiology							
Lung infiltrates on admission—N (%)	165	3870	3002 (77.6)	8	2194	1559 (71,1)	<0.001
Oxygenation							
Age adjusted low SaO_2—N (%)	490	3545	942 (26.6)	423	1779	344 (19.3)	<0.001
Laboratory parameter							
Neutrophil-to-lymphocyte ratio—Median (IQR)	90	3945	4.5 (2.7–7.7)	636	1566	4.7 (2.9–8.0)	0.013
Platelets—number×10^{12} L—Median (IQR)	75	3960	178 (139–226)	636	1566	218 (169–285)	<0.001
D-dimer—ng/mL—Median (IQR)	2472	1563	580 (339–1040)	1325	877	736 (418–1374)	<0.001
eGFR—mL/min/1.73 m^2 (CKD-EPI)—Median (IQR)	140	3895	78.4 (56.5–93.6)	645	1557	88.9 (71.5–103.1)	<0.001
ALT—U/L—Median (IQR)	796	3239	26 (18–41)	719	1483	31 (20–48)	<0.001
Serum albumin—g/dL—Median (IQR)	2624	1411	3.5 (3.2–3.9)	1071	1131	4.3 (3.9–4.5)	<0.001
Lactate dehydrogenase—U/L—Median (IQR)	1457	2578	290 (224–403)	967	1235	320 (254–404)	<0.001
C reactive protein—mg/L—Median (IQR)	358	3677	54 (20–116)	782	1420	75 (25–151)	<0.001

ALT, alanine aminotransferase; BMI, body mass index; eGFR, estimated glomerular filtration rate; SaO2, saturation of oxygen; Δt, time interval.

to a combination of poor reporting and poor methodological conduct for participant selection, predictor description and statistical methods, and none were recommended for clinical use.[13 14] Eight additional studies of prognostic prediction models for COVID-19, including predominantly participants from China, have been published.[15–22] Outcomes included mortality in five studies[16 17 19–21] and severe disease or critical illness in three.[15 18 22] The model performance was good across all studies, although the same methodological limitations found in the meta-analysis also applied.

The development of a high-quality clinical predictive model of death to stratify patients into risk groups is essential for improving the management of patients with severe COVID-19 and evaluating therapeutic interventions' efficacy. Our study's objective was to develop and validate a prediction score to estimate the probability of 30-day mortality in patients with severe COVID-19.

METHODS

The predictive model's development followed the recommendations stated in the Transparent Reporting of a multivariable prediction model for Individual Prognosis or Diagnosis (TRIPOD) Initiative[11 23] (see online supplemental appendix table 1).

Table 2 Unadjusted association between candidate predictor variables and outcome in the derivation cohort (N=4035)

Characteristic	Number/with data (%)	Death by day 30		OR (95% CI)	P value
		Yes	No		
Sex					<0.001
Female	1554/3987	341	1213	1	
Male	2433/3987	721	1712	1.5 (1.29 to 1.74)	
Age (years)					<0.001
<=40	302/4031 (7.5)	9	293	1	
40–49	374/4031 (9.3)	16	358	1.45 (0.63 to 3.34)	
50–54	266/4031 (6.6)	19	247	2.50 (1.11 to 5.63)	
55–59	279/4031 (6.9)	38	241	5.13 (2.43 to 10.8)	
60–64	356/4031 (8.8)	53	303	5.69 (2.76 to 11.7)	
65–69	401/4031 (9.9)	78	323	7.86 (3.87 to 15.0)	
70–74	522/4031 (12.9)	123	399	10.0 (5.02 to 20.1)	
75–79	521/4031 (12.9)	201	320	20.4 (10.3 to 40.6)	
80–84	410/4031 (10.2)	196	214	29.8 (14.9 to 59.5)	
85–89	379/4031 (9.4)	200	179	36.4 (18.3 to 72.8)	
>=90	221/4031 (5.5)	140	81	56.3 (27.5 to 115)	
Hypertension	2052/4010 (51.2)	764	1288	3.22 (2.76 to 3.74)	<0.001
Obesity	497/3606 (13.8)	169	328	1.57 (1.29 to 1.93)	<0.001
Liver cirrhosis	54/3998 (1.4)	23	31	2.08 (1.21 to 3.58)	0.008
Chronic neurological disorder	373/4002 (9.3)	161	212	2.31 (1.85 to 2.87)	<0.001
Neoplasm (active)	352/4035 (8.7)	152	200	2.28 (1.82 to 2.85)	<0.001
Dementia	315/3979 (7.9)	184	131	4.52 (3.57 to 5.73)	<0.001
Myalgia/Arthralgia	947/3809 (24.9)	155	792	0.49 (0.40 to 0.59)	<0.001
Cough	2862/3984 (71.8)	688	2174	0.68 (0.59 to 0.79)	<0.001
Dyspnoea	1953/3980 (49.1)	668	1285	2.19 (1.89 to 2.53)	<0.001
Altered consciousness	450/3931 (11.4)	220	230	3.15 (2.58 to 3.86)	<0.001
White cell count—cells/$\times 10^9$/L					<0.001
<=4000	666/3971	132	534	1	
4000–12 000	2993/3971	778	2215	1.42 (1.15 to 1.75)	
>12 000	312/3971	151	161	3.79 (2.83 to 5.08)	
Neutrophil-to-lymphocyte ratio					<0.001
<3.22	1316/3945	207	1109	1	
3.22–6.33	1314/3945	298	1016	1.57 (1.29 to 1.91)	
>6.33	1315/3945	547	768	3.82 (3.17 to 4.59)	
eGFR—mL/min/1.73 m^2 (CKD-EPI)					<0.001
>=60	2786/3895 (71.5)	512	2274	1	
30–59	844/3895 (21.7)	379	465	3.62 (3.07 to 4.27)	
<30	265/3895 (6.8)	153	112	6.07 (4.67 to 7.88)	
Low SaO_2 (age-adjusted)*	942/3545 (26.6)	413	529	3.44 (2.93 to 4.05)	<0.001
INR>1.1	1503/3301 (45.5)	524	979	2.20 (1.88 to 2.57)	<0.001
CRP>5 µg/L	3378/3677	939	2439	3.21 (2.21 to 4.67)	<0.001

*≤90% for patients aged >50 years and ≤93% for patients aged ≤50 years.
CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration equation; CRP, C reactive protein; INR, international normalised ratio; SaO2, saturation of oxygen.

Source of data

The data source was the databases of two large retrospective cohorts of hospitalised patients with COVID-19 in Spain in 2020. The derivation cohort (DC) was the COVID-19@Spain, a multicentre cohort of patients hospitalised from 2 February to 17 March, with 17 April as the follow-up censoring date, sponsored by the Spanish Society of Infectious Diseases and Clinical Microbiology (SEIMC), and registered in ClinicalTrials.gov (NCT04355871).[24] The external validation was COVID-19@HULP, a large single-centre cohort of patients admitted to La Paz University Hospital in Madrid (Spain) from 25 February (the first case admitted) to 19 April; and registered in the European Union Electronic Register of Post-Authorisation Studies (EUPAS34331).[25]

Table 3 Predictive model for 30-day mortality at presentation in hospitalised patients with COVID-19

Predictor variable	Coefficient	SE	OR (95% CI)	p>z
Age				<0.001
40–49 years	0.082	0.446	1.09 (0.45 to 2.6)	
50–54 years	0.471	0.448	1.60 (0.67 to 3.86)	
55–59 years	1.058	0.412	2.88 (1.28 to 6.46)	
60–64 years	1.228	0.394	3.42 (1.58 to 7.4)	
65–69 years	1.655	0.381	5.23 (2.48 to 11.04)	
70–74 years	1.772	0.372	5.88 (2.84 to 12.21)	
75–79 years	2.268	0.373	9.66 (4.65 to 20.07)	
80–84 years	2.695	0.377	14.8 (7.08 to 30.96)	
85–89 years	2.803	0.379	16.49 (7.84 to 34.67)	
≥90 years	3.103	0.397	22.26 (10.22 to 48.48)	
Low age adjusted SaO_2	0.875	0.102	2.40 (1.97 to 2.93)	<0.001
Neutrophil-to-lymphocyte ratio				<0.001
3.22–6.33	0.173	0.123	1.19 (0.93 to 1.51)	
>6.33	0.657	0.119	1.93 (1.53 to 2.44)	
eGFR (CKD-EPI)				<0.001
30–59 mL/min/1.73 m^2	0.498	0.109	1.65 (1.33 to 2.04)	
<30 mL/min/1.73 m^2	1.093	0.176	2.98 (2.11 to 4.21)	
Dyspnoea	0.414	0.097	1.51 (1.25 to 1.83)	<0.001
Male sex	0.466	0.098	1.59 (1.31 to 1.93)	<0.001
Intercept	−4.266	0.360		

CKD-PI, Chronic Kidney Disease Epidemiology Collaboration equation; eGFR, estimated glomerular filtration rate calculated by the CKD-EPI; SaO2, oxygen saturation.

Participants

The DC included the first consecutive 4035 patients with COVID-19 admitted to 127 hospitals distributed across all regions in Spain. The external validation cohort (VC) included 2126 of the 2226 patients from COVID-19@HULP after the exclusion of the 100 patients contributing to COVID-19@Spain. The eligibility criteria in the DC and external VC were hospital admission due to COVID-19 confirmed with real-time PCR for SARS-CoV-2. No age limit was required in the DC, whereas an age of 18 years or older was an eligibility criterion in the external VC. The DC and VC were identical in terms of setting and definitions for outcomes and predictors. Besides, data in both cohorts were collected using the same modified version of the case report form (CRF) of the WHO–International Severe Acute Respiratory and Emerging Infections Consortium (ISARIC) Core CRF.[26]

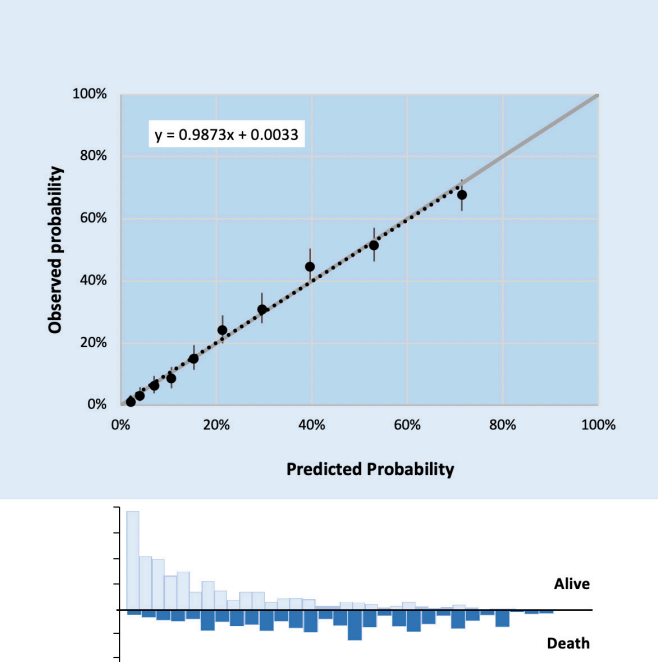

Figure 1 Calibration of the final prognostic model in the derivation cohort. Observed versus predicted risk of 30-day mortality, with estimates of the calibration slope and intercept (Hosmer-Lemeshow test=11.21, p=0.1902 vs p<0.05).

Outcome

The outcome was 30-day all-cause mortality, measured from the day of hospital admission. Patients that were discharged alive before 30 days after admission were assumed to have survived for at least 30 days.

Predictors

Predictors were preselected among the 17 baseline variables, recorded at hospital admission, independently associated with death in the COVID-19@Spain cohort by multivariable Cox regression analyses.[24] These variables were distributed in the following five clusters: (1) demographics, age in years and sex at birth; (2) comorbidities defined as diagnoses included in the medical record such as hypertension, obesity (body mass index >30), liver cirrhosis, chronic neurological disorder, active neoplasia (solid or haematologic) and dementia; (3) signs or symptoms, including dyspnoea and confusion; (4) low age-adjusted capillary oxygen saturation (SaO_2) on room air, defined as ≤90% for patients aged >50 years and ≤93% for patients

A. COVID-19 SEIMC Score

Risk factor	Addition to risk score	Risk score
Age (years)		
< 40	0	
40 – 54	1	
55 – 64	3	
65 – 74	5	
75 – 79	9	
80 – 84	14	
85 – 89	15	
≥ 90	21	
Low age adjusted Sa02*		
No	0	
Yes	2	
Neutrophil–to–lymphocyte ratio		
<3.22	0	
3.22 – 6.33	1	
>6.33	2	
eGFR mL/min/1.73 m² (CKD–EPI)		
≥60	0	
30–59	2	
<30	3	
Dyspnea		
No	0	
Yes	1	
Sex		
Female	0	
Male	1	
	Total risk score	0 to 30

*≤90% for patients aged >50 years and ≤93% for patients aged ≤50 years

B. 30-day mortality probability

		30-day mortality probability	
Total risk core	Risk category	Derivation cohort	Validation Cohort
0 – 2 points	Low	0 – 2.1 %	0 %
3 – 5 points	Moderate	4.7 – 6.3 %	0 – 3.7 %
6 – 8 points	High	10.6 – 19.5 %	4.5 – 12.7 %
9 – 30 points	Very high	27.7 – 100 %	19.0 – 100 %

Figure 2 (A) Simple scoring system to predict 30-day mortality on presentation in hospitalised patients with COVID-19. (B) 30-day mortality probability according to the total risk score in the derivation cohort and the external validation cohort. CKD–EPI, Chronic Kidney Disease Epidemiology Collaboration equation; eGFR, estimated glomerular filtration rate; SaO_2, oxygen saturation.

aged ≤50 years[27]; (5) tests results, including white cell count, neutrophil-to-lymphocyte ratio, platelet count, international normalised ratio (INR), estimated glomerular filtration rate (eGFR) measured by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation[28] and serum concentrations of C reactive protein.

Statistical analysis methods

We followed recent recommendations to calculate the minimum sample size required for prediction model development.[29] We carried out a complete-case analysis (primary analysis) and two sensitivity analyses. In the first sensitivity analysis, we included all patients and missing values for predictors were considered as a separate category (missing indicator method). In the second sensitivity analysis, we also included all patients and missing values for predictors were left blank (equivalent to the lowest risk situation). No missing values for outcomes occurred in the DC or the external VC.

Continuous variables were categorised for the analysis. As mortality from COVID-19 among hospitalised patients is highly correlated with age, this variable was divided into 11 levels: <40 years that was the reference category and after that into 11 5-year to 10-year intervals up to ≥90 years that was the last category. The neutrophil-to-lymphocyte ratio was categorised into tertiles: <3.22, which was the reference category, 3.22 to 6.33, and >6.33. The eGFR in mL/min/1.73 m^2 was grouped before the analysis into three categories: >60 (normal to mildly decreased eGFR), 30–59 (moderately to severely decreased eGFR) and <30 (severely decreased eGFR).

We used univariable and multivariable logistic regression in the derivation dataset to estimate the coefficients of each potential predictor of 30-day overall mortality. We fitted the final model by choosing predictors based on the strength of their unadjusted association with death. The model started with the predictor with the highest area under the receiver operating characteristics (AUROC) to predict 30-day mortality. Subsequently, the rest of the variables were introduced one by one, creating all the possible models of two independent variables, and the combination of higher AUROC was chosen. This process was repeated to form models of 3, 4 and more variables, always choosing the combination with the highest AUROC. The process stopped when the inclusion of a new variable in the model meant an increase lower than 0.005 unit in the AUROC.

We assessed the predictive performance of the model by examining measures of calibration and discrimination. We developed a calibration plot with estimates of the calibration slope and intercept. Calibration was also assessed using the Hosmer-Lemeshow test. Discrimination was examined by calculating its AUROC with the 95% CI. We carried out internal validation through a bootstrap with 1000 random samples with replacement to estimate the model optimism and shrinkage factor.

The logistic regression model's coefficients were converted to a simplified score to facilitate its application in clinical practice. The score was developed, dividing each coefficient by the coefficient with the lowest value and rounding to an integer. Risk groups were created using the 30-day probability of death according to the simplified score. The sensitivity, specificity, positive and negative predictive values, and likelihood ratios were calculated for different scores.

The statistical analyses were performed using Stata software (V.15.0; Stata Corporation, College Station, Texas, USA).

RESULTS

Participants

The developing cohort included 4035 patients, of which 1074 (26.6%) died and 2961 were alive within 30 days of hospital admission. The cohort size was more than twice the required for developing a clinical prognostic model (online supplemental appendix figure 1). The external VC included 2202 patients, 341 (15.5%) died and 1861 were alive within 30 days of hospital admission. The median time to death since hospital admission was 10 (IQR 6–16) days in the -DC and 5 (IQR 3–10) days in the VC.

The characteristics of the participants, including demographics, presenting signs and symptoms, presence of lung infiltrates on chest radiograph, oxygenation and laboratory parameters, are shown in table 1. Patients in the DC were, on average, 9 years older, and more frequently, males than patients in the external VC. Statistically significant differences between the cohorts were found in all the analysed variables.

In the DC, targeted viral agents were administered to 82.0% of patients, including lopinavir/ritonavir (LPV/r) (70.4%), hydroxychloroquine (65.5%) and subcutaneous interferon-beta (29.2%), usually in combination with LPV/r. In the external VC, targeted viral agents were administered to 65.3% of patients. The most frequent combination was hydroxychloroquine plus azithromycin (31.7%), followed by hydroxychloroquine alone. Host-targeted agents in the DC included systemic corticosteroids

Table 4 Prediction of 30-day mortality on presentation in hospitalised patients with COVID-19 according to the point score in the derivation cohort and in the external validation cohort

	Derivation cohort					External validation cohort				
		30-day mortality					30-day mortality			
		Yes		No			Yes		No	
Risk score	Total	N	%	N	%	Total	N	%	N	%
0	48	1	2.1	47	97.9	20	0	0.0	20	100
1	139	0	0.0	139	100	68	0	0.0	68	100
2	193	3	1.6	190	98.4	104	0	0.0	104	100
3	215	10	4.7	205	95.3	103	0	0.0	103	100
4	230	11	4.8	219	95.2	109	1	0.9	108	99.1
5	254	16	6.3	238	93.7	107	4	3.7	103	96.3
6	235	25	10.6	210	89.4	112	5	4.5	107	95.5
7	237	32	13.5	205	86.5	80	8	10.0	72	90.0
8	200	39	19.5	161	80.5	63	8	12.7	55	87.3
9	191	53	27.7	138	72.3	42	8	19.0	34	81.0
10	136	39	28.7	97	71.3	45	12	26.7	33	73.3
11	133	45	33.8	88	66.2	45	11	24.4	34	75.6
12	94	36	38.3	58	61.7	26	5	19.2	21	80.8
13	91	40	44.0	51	56.0	18	7	38.9	11	61.1
14	75	32	42.7	43	57.3	19	5	26.3	14	73.7
15	80	32	40.0	48	60.0	27	9	33.3	18	66.7
16	83	36	43.4	47	56.6	32	10	31.3	22	68.8
17	123	48	39.0	75	61.0	40	14	35.0	26	65.0
18	97	51	52.6	46	47.4	49	16	32.7	33	67.3
19	104	55	52.9	49	47.1	41	13	31.7	28	68.3
20	96	50	52.1	46	47.9	23	9	39.1	14	60.9
21	74	51	68.9	23	31.1	17	6	35.3	11	64.7
22	44	24	54.5	20	45.5	17	7	41.2	10	58.8
23	37	23	62.2	14	37.8	12	4	33.3	8	66.7
24	33	20	60.6	13	39.4	15	8	53.3	7	46.7
25	23	14	60.9	9	39.1	13	5	38.5	8	61.5
26	33	17	51.5	16	48.5	9	4	44.4	5	55.6
27	25	14	56.0	11	44.0	8	6	75.0	2	25.0
28	20	19	95.0	1	5.0	3	1	33.3	2	66.7
29	9	7	77.8	2	22.2	2	2	100	0	0.0
30	6	6	100	0	0.0	0	0	0.0	0	0.0
Total	3358	849	25.3	2509	74.7	1269	188	14.8	1081	85.2

in 28.0% patients and tocilizumab in 9.4% patients. In the VC, corticosteroids and tocilizumab were administered to 13.3% and 2.3% patients, respectively.

Model development and performance

The number of participants in the DC without missing values for each predictor, the number of outcomes per predictor and the unadjusted associations between predictors and outcomes are shown in table 2.

The final prediction model generated without recoding missing values (3358 participants) is shown in table 3. The variables used in the model to generate the score were those in table 2. The model started with the variable age since it was the one with the highest predictive capacity for death at 30 days (AUROC (95% CI) 0.768 (0.753 to 0.784)). The final input sequence of the variables to the model, following the procedure described in the Methods section, was age, low age-adjusted SaO_2, neutrophil-to-lymphocyte ratio, eGFR by the CKD-EPI equation, dyspnoea and sex.

The predicted probability of 30-day mortality was determined by the following equation:

$P_{\text{death at day 30}} = 1 / (1+\exp(-b))$,

where b=0 (if age <40)+0.082 (if age 40–49)+0.471 (if age 50–54)+1.058 (if age 55–59)+1.228 (if age 60–64)+1.655 (if age 65–69)+1.771 (if age 70–74)+2.268 (if age 75–79)+2.695 (if age 80–84)+2.803 (if age 85–89)+3.103 (if age>=90)+0.875 (if low age-adjusted SaO_2)+0.173 (if neutrophil-to-lymphocyte ratio 3.22–6.33)+0.657 (if neutrophil-to-lymphocyte ratio >6.33)+0.498 (if eGFR 30–59)+1.093 (eGFR <30)+0.414 (if dyspnoea)+0.466 (if male sex)−4.266.

Table 5 Simplified score to predict 30-day mortality in hospitalised patients with COVID-19 in the derivation cohort: sensitivity, specificity, likelihood ratios and predictive values for the different scores (0–30) in the derivation cohort

	Participants								
		Dying within 30 days							
Score	Total	N	%	Sen (%)	Spe (%)	+LR	1/-LR	PPV (%)	NPV (%)
0	48	1	2.1	100	0	1	–	25.3	–
1	139	0	0.0	99.9	1.9	1.018	15.900	25.6	97.9
2	193	3	1.6	99.9	7.4	1.079	62.940	26.7	99.5
3	215	10	4.7	99.5	15.0	1.171	31.810	28.4	98.9
4	230	11	4.8	98.4	23.2	1.280	14.040	30.2	97.6
5	254	16	6.3	97.1	31.9	1.425	10.830	32.5	97.0
6	235	25	10.6	95.2	41.4	1.623	8.567	33.5	96.2
7	237	32	13.5	92.2	49.7	1.835	6.398	38.3	95.
8	200	39	19.5	88.5	57.9	2.102	5.017	41.6	93.7
9	191	53	27.7	83.9	64.3	2.351	3.986	44.3	92.2
10	136	39	28.7	77.6	69.8	2.573	3.120	46.5	90.2
11	133	45	33.8	73.0	73.0	2.776	2.732	48.4	89.0
12	94	36	38.3	67.7	77.2	2.971	2.392	50.1	87.6
13	91	40	44.0	63.5	79.5	3.099	2.178	51.2	86.6
14	75	32	42.7	58.8	81.5	3.185	1.978	51.9	85.4
15	80	32	40.0	55.0	83.3	3.286	1.850	52.6	84.5
16	83	36	43.4	51.2	85.2	3.456	1.747	53.9	83.8
17	123	48	39.0	47.0	87.0	3.628	1.642	55.1	82.9
18	97	51	52.6	41.3	90.0	4.149	1.535	58.4	81.9
19	104	55	52.9	35.3	91.9	4.346	1.421	59.5	80.8
20	96	50	52.1	28.9	93.8	4.671	1.319	61.3	79.6
21	74	51	68.9	23.0	95.7	5.287	1.242	64.1	78.6
22	44	24	54.5	17.0	96.6	4.948	1.163	62.6	77.5
23	37	23	62.2	14.1	97.4	5.373	1.134	64.5	77.0
24	33	20	60.6	11.4	97.9	5.513	1.106	65.1	76.6
25	23	14	60.9	9.1	98.4	5.835	1.083	66.4	76.2
26	33	17	51.5	7.4	98.8	6.206	1.067	67.7	75.9
27	25	14	56.0	5.4	99.4	9.710	1.051	76.7	75.7
28	20	19	95.0	3.8	99.9	31.520	1.038	91.4	75.4
29	9	7	77.8	1.5	99.9	19.210	1.015	86.7	75.0
30	6	6	100	0.7	100	–	1.007	100	74.9

The number of individuals in different risk categories was low (0–2 points; 380 (11.3%)), medium (3–5 points; 699 (20.8%)), high (6–8 points; 672 (20.0%)) and very high (9–30 points; 1607 (47.9%)).
-LR, negative likelihood ratio; +LR, positive likelihood ratio; NPV, negative predictive value; PPV, positive predictive value; Sen, sensitivity; Spe, specificity.

The final model showed good calibration across the range of risk (figure 1), and the goodness-of-fit Hosmer-Lemeshow test was 11.21, p=0.1902 vs p<0.05, confirming the calibration of the model. Using bootstrapping techniques, an optimism of 0.006 and a shrinkage factor of 0.968 were estimated. In 600 of the samples (60%), the Hosmer-Lemeshow test was significant.

The AUROC (95% CI) of the model for prediction of 30-day mortality was 0.822 (0.806 to 0.837) in the DC and 0.845 (0.819 to 0.870) in the external VC (online supplemental appendix table 2).

Simplified score development and performance

The simplified point score (from 0 to 30) resulting from the division of the regression coefficients of predictors in the final model by the coefficient of age 40–49, which was the lowest value among all coefficients, is shown in figure 2A. The prediction of 30-day mortality on presentation in hospitalised patients with COVID-19 according to the point score in the DC and in the external VC is shown in table 4.

The AUROC (95% CI) of the simplified score for prediction of 30-day mortality was 0.806 (0.790 to 0.821) in the DC and 0.831 (0.806–0.856) in the external VC (online supplemental appendix table 2). The sensitivity, specificity, positive and negative predictive values, and likelihood ratios for the different scores in the DC and external VC are shown in table 5 and online supplemental appendix table 3, respectively.

We considered the risk of 30-day mortality as low with 0–2 points (0%–2.1%), moderate with 3–5 (4.7%–6.3%), high with 6–8 (10.6%–19.5%) and very high with 9–30 (27.7%–100.0%) (figure 2B). Kaplan-Meier survival plots for the different 30-day mortality risk categories according to the simplified score in the DC and VC are shown in online supplemental appendix figure 2.

Sensitivity analyses

Sensitivity analysis 1

When we generated the final prediction model recoding missing values for predictors as a separate category, the AUROC (95% CI) was 0.822 (0.809 to 0.836) in the DC and 0.850 (0.831 to 0.867) in the external VC. Likewise, when we applied the same approach to the simplified point score, the AUROC (95% CI) was 0.805 (0.791 to 0.820) in the DC and 0.848 (0.830 to 0.866) in the external VC (online supplemental appendix table 2).

Sensitivity analysis 2

When we applied the final prediction model to all patients, and missing values for predictors were left blank (equivalent to the lowest risk situation), the AUROC (95% CI) was 0.818 (0.805 to 0.832) in the DC and 0.859 (0.842 to 0.876) in the external VC. Likewise, when we applied the same approach to the simplified point score, the AUROC (95% CI) was 0.806 (0.791 to 0.820) in the DC and 0.849 (0.831 to 0.866) in the external VC (online supplemental appendix table 2).

DISCUSSION

The COVID-19 SEIMC score for predicting 30-day mortality of patients attending hospital emergency rooms was developed and externally validated with two large datasets from patients hospitalised with laboratory-confirmed COVID-19 in Spain. The predictors were age, low age-adjusted SaO_2, neutrophil-to-lymphocyte ratio, eGFR by the CKD-EPI equation, dyspnoea and sex. The model showed good performance in both the DC and the external VC and permitted an easy stratification of patients into four risk categories.

Our prediction model uses widely accessible clinical and laboratory data, and its simplicity would allow clinicians to perform rapid risk stratification of patients with COVID-19. Of note, our model does not take into account comorbidities, which have been associated with worse COVID-19 prognosis in descriptive studies and included in most prognostic prediction models reported to date.[13 15–22] In our study, underlying diseases such as hypertension, obesity, liver cirrhosis, chronic neurological disorder, active neoplasia and dementia were independently associated with an increased risk of 30-day mortality. However, none of these conditions improved the model's discrimination capacity and, following the principle of parsimony, were discarded.

Once again, our study highlights the extraordinary impact of age on COVID-19 mortality, which is, to the best of our knowledge, unparalleled in infectious diseases. For example, our score would classify a 65-year-old male patient attending the emergency room— regardless of the results of the other variables—as a high-risk category with a 30-day mortality probability that could reach up to 19.5%. For younger patients, our score also shows the importance of basic laboratory parameters. A 55-year-old man without dyspnoea, normal SaO_2 and normal renal function but with a neutrophil-to-lymphocyte ratio higher than 6.33 would also be classified as high risk.

At the time of writing, an eight variable mortality score developed and validated in a UK prospective cohort of 57 824 patients admitted to hospital with COVID-19, the 4C Mortality Score, has been published.[30] Some of the variables included in this score, such as respiratory rate, Glasgow Coma Scale score and urea, are not available in the COVID-19@Database precluding the cross-validation the 4C Mortality Score in our population.

Our study is limited, as is the case with other reported studies, by the retrospective capture of data. Another potential limitation is that it was based exclusively on predictors from patients attending hospital emergency rooms. However, we believe that our score could be applied in primary care settings if capillary SaO_2 and routine laboratory tests such as blood counts and serum creatinine could be determined. Finally, our score was derived from hospitalised patients in a single country, raising the question about their transportability to other countries, a common limitation to all currently described prognostic models of COVID-19. We believe that it would be of interest to carry out cross-validation between the SEIMC COVID-19 score and other scores in a large multinational dataset.

Our study has several strengths. In contrast with the majority of prior published prognostic models, ours adhere to the TRIPOD statement's recommendations. Besides, the large sample size and the high number of events in the DC minimise the risk of model overfitting, a general limitation of previous studies. Our model's strengths also include the calibration, the internal validation by bootstrapping rather than by random split of the DC and the validation in a large external cohort. Finally, the sensitivity analyses exploring different approaches for missing values for predictors did not modify the model's performance, suggesting that missing values in both cohorts occurred at random.

The SEIMC COVID-19 score could be a useful triage tool enabling quick decision-making for patients with COVID-19. For example, patients in the low-risk category are likely suitable for outpatient care, whereas hospital admission or intensive or high dependency care should be considered for patients in high and very high-risk categories. Besides, management in emergency department observation units or makeshift medicalised facilities could be considered for patients in the moderate risk category. Another potential application of the SEIMC COVID-19 score is the risk stratification of patients with COVID-19 in observational studies or clinical trials.

Our study showed that the COVID-19 SEIMC score, a simple prediction tool using readily available clinical and laboratory data results, could identify the probability of 30-day mortality with a high degree of accuracy among patients with COVID-19.

Author affiliations
[1]Clinical Microbiology and Infectious Diseases, Hospital General Universitario Gregorio Marañón, Instituto de Investigación Sanitaria Gregorio Marañón (IiSGM), Madrid, Spain
[2]Clinical Pharmacology, Hospital Universitario La Paz, Instituto de Investigación Hospital Universitario La Paz (IdiPAZ), Universidad Autónoma de Madrid, Madrid, Spain
[3]Infectious Diseases, Internal Medicine Service, Hospital Universitario Infanta Leonor, Instituto de Investigación Sanitaria Gregorio Marañón (IiSGM), Madrid, Spain
[4]Infectious Diseases and Microbiology Unit, Hospital Universitario Virgen Macarena, Instituto de Biomedicina de Sevilla (IBiS), Department of Medicine, Universidad de Sevilla, Sevilla, Spain
[5]Fundación Investigación Biomédica, Hospital General Universitario Gregorio Marañón, Instituto de Investigación Sanitaria Gregorio Marañón (IiSGM), Madrid, Spain
[6]National Centre for Epidemiology, Institute of Health Carlos III, Madrid, Comunidad de Madrid, Spain
[7]Infectious Diseases, Hospital Universitario de Bellvitge, Instituto de Investigación Biomédica de Bellvitge (IDIBELL), Universitat de Barcelona, Barcelona, Spain
[8]Infectious Diseases, Hospital Universitario Virgen del Rocío, Instituto de Biomedicina de Sevilla (IBiS), Department of Medicine, Universidad de Sevilla, Sevilla, Spain
[9]Fundación SEIMC-GESIDA, Madrid, Spain
[10]Infectious Diseases Unit, Internal Medicine Service, Hospital Universitario La Paz, Instituto de Investigación Hospital Universitario La Paz (IdiPAZ), Madrid, Spain

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Collaborators COVID-19@Spain and COVID@HULP Study Groups: Esther Aznar; Pedro Gil; Patricia Gonzalez; Clara Muñoz; Juan C López; Margarita Ramírez-Schacke; Isabel Gutiérrez; Francisco Tejerina; Teresa Aldámiz-Echevarría; Cristina Díez; Chiara Fanciulli; Leire Pérez-Latorre; Francisco Parras; Pilar Catalán; María E García-Leoni; Isabel Pérez-Tamayo; Luis Puente; Jamil Cedeño; Marta Díaz; Fernando de la Calle; Marta Arsuaga; Elena Trigo; M del Mar Lago; Rosa de Miguel; Julen Cadiñanos; Carmen Busca; Alfredo Mican; Marta Mora; Juan Carlos Ramos; Belén Loeches; José I Bernardino; Julio García; Ana Such; Elena Álvaro; Elsa Izquierdo; Juan Torres; Guillermo Cuevas; Jesús Troya; Beatriz Mestre; Eva Jiménez; Inés Fernandez; Ana J Tebar; Fátima Brañas; Jorge Valencia; Mario Pérez; Marta Alvarado; Pablo Ryan; M Antonia Sepúlveda; Carmen Yera; Pilar Toledano; Verónica Cano; Sadaf Zafar; Gema Muñiz; Inmaculada Martín; Helena Mozas; Ana Alguacil; M Paz García; Ana I Peláez; Elena Morcillo; Josune Goikoetxea; M José Blanco; Javier Nieto; Mikel del Álamo; Isabel A; Pérez; Inés Pérez; Rafael Silvariño; Jon Ugalde; Víctor Asensi; Lucia Suárez; Silvia Suárez; Carmen Yllera; Vicente Boix; Marcos Díez; Melissa Carreres; Cristina Gómez-Ayerbe; Javier Sánchez-Lora; José L Velasco; María López-Jódar; Jesús Santos; Jesús Ruiz; Ianire Virto; Vanessa Alende; Ruth Brea; Sonia Vega; Estel Pons; Oscar Del Río; Silvia Valero; Judit Villar-García; Joan Gómez-Junyent; Hernando Knobel; M Cecilia Cánepa; Silvia Castañeda; Luisa Sorli; Roberto Güerri-Fernández; María Milagro; Juan P Horcajada; Elisa García; Encarnación Moral; Alicia Hernádez; Esther García; Carmen Sáez; Zineb Karroud; José Hernández; David Vinuesa; José L García; José A Peregrina; María Novella; Cristina Hernández; José Sanz; Ramón Pérez; Rodrigo Sierra; David Alonso; Aida Gutiérrez; Alberto Arranz; Juan Cuadros; Melchor Álvarez de Mon; Vicente F Díaz De Brito; Montserrat Sanmarti; Aina Gabarrell; Daniel Molina; Sergio España; Jonathan Cámara; Albert Sabater; Laura Muñoz; Paula Sáez; Esperanza Bejaranao; Marco A Sampere; Salvador Álvarez; Ignacio De los Santos; Lucio García-Fraile; Miguel Sampedro; Ana Barrios; Carlos Rodríguez; Daniel Useros; Almudena Villa; Javier Oliver; Alexia C Espiño ; Jesús Sanz; María Rexach; Ivette Abascal; Ana del C Pérez; Clara Sala; Susana Casas; Cecilia Tortajada; Carmina Oltra; Mar Masiá; Félix Gutiérrez; Ana Ferrer; Carlos Bea; Miguel Pedromingo; M Ángeles Garcinuño; Silvana Fiorante; Sergio Pérez; Pilar Hernández; Violeta A Alastrué; M Carmen Fariñas; Claudia González; Francisco Arnaiz; Jorge Calvo; Mónica Gonzalo; Francisco Mora; Ana Milagro; Miriam Latorre-Millán; Antonio Rezusta; Ana Martínez; Yolanda Meije; Alejandra Duarte; Julia Pareja; Mercedes Clemente; Juan E Losa; Ana Vegas; M Teresa Pérez-Rodríguez; Alexandre Pérez; Moncef Belhassen-García; Beatriz Rodríguez-Alonso; Amparo López-Bernus; Cristina Carbonell; Rafael Torres; Juan Catón; Blanca Alonso; Sara L Kamal; Lucia Cajuela; David Roa; Miguel Cervero; Alberto Orejas; Juan P Avilés; Lidia Martín; Iván Pelegrín; Rosana Rouco;Jorge Parra; Violeta Ramos; Jessica Abadía; Juan Salillas; Robert Torres; Miguel Torralba; Alberto Serrano; Sergio Gilaberte; Marina Pacheco; Mónica Liébana; Sara Fernández; Álvaro Varela; Henar Calvo; Patricia Martínez; Patricia González- Ruano; Eduardo Malmierca; Isabel Rábago; Beatriz Pérez-Monte; Ángeles García; Pere Comas; Merce Sirisi; Richard Rojas; José L Díaz de Tuesta; Ruth Figueroa; Ander González; Remedios Alemán; M del Mar Alonso; Oscar Sanz; Karim M Ramírez; Melchor Riera; Helem H Vilchez; Francesc Albertí; Ana I Cañabate; Víctor J Moreno; Silvia Álvarez; Beatriz Álvarez; Alejandro García; Elena Isaba; Covadonga Morcate; Andrea Pérez; Lucía Ramos; Laura Castelo; María Rodríguez; Mónica González; Efrén Sánchez; Enrique Míguez; Javier De la Torre; José M García de Lomas; Elena Morte; Silvia Loscos; Ana Camón; Lucía Gómez; Lucia Boix; Beatriz Dietl; Iris Pedrola; Amparo Blasco; Cristina López; Esther Fraile; Tomás Tosco; María Aroca; José T Algado; Ana M Garijo; Concepción Amador; Pilar Retamar; Adoración Valiente; Luis E; López-Cortés; Jesús Sojo; Belén Gutiérrez-Gutiérrez; José Bravo-Ferrer; Elena Salamanca; Zaira R; Palacios; Patricia Pérez-Palacios; Enrique Peral; José A Pérez de León; Jesús Sánchez-Gómez; Lucía Marín-Barrera; Domingo García-Jiménez; Gabriela Abelenda-Alonso; Carmen Ardanuy ; Alba Bergas; Guillermo Cuervo; M Ángeles Domínguez; Miguel Fernández-Huerta; Carlota Gudiol ; Laia Lorenzo-Esteller; Jordi Niubó; Sandra Pérez-Recio; Daniel Podzamczer; Miquel Pujol; Alexander Rombauts; Núria Trullen; Miguel Salavert; Iván Castro; Adriana Hernández; Raquel Martínez; Marta Navarro; Sonia Calzado; Manuel Cervantes; Aina Gomila; Oriol Gasch; M Luisa Machado; Eva Van den Eynde; Luis Falgueras; M del Carmen Navarro; Esteban Martínez; M Ángeles Marcos; Mar Mosquera; José L Blanco; Montserrat Laguno; Jhon Rojas; Ana González-Cordón; Alexy Inciarte; Berta Torres; Lorena De la Mora; Alex Soriano; Olalla Martínez; Virginia Pérez; Alfonso Cabello; Nerea Carrasco; Beatriz Álvarez; Elizabet Petkova; Miguel Górgolas; Laura Prieto; Irene Carrillo; Sara Heili; Felipe Villar; Ricardo Fernández; José Milicua; Virginia Fernández; Carlos J Dueñas; Cristina Hernán; Fernando González-Romo; Paloma Merino; Alba Rueda; Jorge Martínez; Sara Medrano; Irene Díaz; Yolanda Posada; Alberto Delgado-Iribarren; Joaquín López-Contreras; Pablo Pascual; Virginia Pomar; Nuria Rabella; Natividad Benito; Pere Domingo; Xavier Bonfill; Rafael Padrós; Mireia Puig; Jordi Mancebo; Mercè Gurguí; Melania Íñigo; Alejandra Pérez; Patricia Sorní ; Nora Izko; Francisco J Membrillo; María Simón; Maribel Zamora; Yolanda Martínez; Pablo Fernández-González; Francisco Alcántara; Alejandro Aguirre; Elena López; Germán Ramírez-Olivencia; Miriam Estébanez; Ester Sáez de Adana; Joseba Portu; Juan C Gainzarain; Zuriñe Ortiz de Zárate; Miguel A Moran; Andrés Canut; Silvia Hernáez; Leire Balerdi; Cristina Morales; Miguel Corral; Zeltia Valcarce; Noelia Arenal ; Raquel E Rodríguez; Laura Iglesias; Beatriz Loureiro; Adrián Sánchez; Juan Espinosa; Benito Almirante; Marta Miarons; Júlia Sellarés; María Larrosa; Sonia García; Blanca Marzo; Miguel Villamarín; Nuria Fernández; Conchita Pérez-Jorge; Elena Resino; Andrea Espigares; Teresa Álvarez de Espejo; Iván Navas; M Isabel Quijano; Luis A Nieto; Guillermo Jiménez; Mercedes Guillamón; Josefina García; Constanza Muñoz; Ana Mariño; Nieves Valcarce; Alex Smithson; Cristina Chico; Adriana Sánchez; Eva P García; Isabel Jiménez; Guillermo Estrada; María Lorén; Nuria Parra; Carmen Martínez; Aránzazu Villasante; Teresa García; M José Ruiz; Marta Robledo; Juan C Abad; José R Muñoz ; Montaña Jiménez; Javier Coy; Inmaculada Poquet; Marta Santos; Virginia Naranjo; Tamara Manso; Delia Quilez; Gema Barbeito; M Jesús Domínguez; Laura Mao; Rodrigo Alonso; Jose D Ampuero; Raquel Barrós; M Aránzazu Galindo; Lourdes Herrera; Rocío Martínez; Sara Rodrigo; Cristóbal M Rodríguez; Eva M Romay; Roi Suárez; Maialen Ibarguren; José M Marimón; Loreto Vidaur; Xabier Kortajarena; Miriam García; Asier Aranguren; Maria Álvarez; Cintia M Martínez; Francisco Rodríguez; Francisco Muñoz; Elena Chamarro ; Merce Cardona; Ismail Zakariya-Yousef; Marta Rico; Jara Llenas; M Carmen Sánchez; Ana Fernández; Jorge Calderón; Marcos López; Antonio Ramos; Elena Múñez; Alejandro Callejas; José M Vázquez; Itziar Diego; Esther Expósito; Jorge Anel; Raquel Álvarez; Lucía Fernández; Roberto Vates; Andrés F Cardona; Pablo Marguenda; Gabriel Gaspar; Elena M Aranda; Blanca Martínez; Daniel Roger; Irene Martín; André Barbosa; Iván Piñero; Alberto Bahamonde; Paula Runza; Eva Talavera; Marta Lamata; Ainhoa Urrutia; Lorea Arteche; Elisabet Delgado; Virginia Molina; Sarah Caro; Gema Domínguez; Carolina Roldán; Carmen Herrero; Luis Force; Raquel Aranega; Arantzazu Mera; M Roca Toda; Nicolas Merchante ; Eva M León; José L Del Pozo; Josefa Serralta; Ginger G Cabrera; Mario Fernández-Ruiz; José M Aguado; Guillermo Maestro; José M Cisneros; Manuela Aguilar-Guisado; Teresa Aldabó; M Dolores Avilés; Claudio Bueno; Elisa Cordero-Matía; Ana Escoresca; Lydia Gálvez-Benítez; Carmen Infante; Guillermo Martín; Julia Praena; Cristina Roca; Celia Salamanca; Alejandro Suárez-Benjumea; Pilar Vizcarra; Carmen Quereda; Mario J Rodriguez; Francesca Gioia; Francesca Norman; Santos Del Campo; Rafael Cantón; José A Oteo; Paula Santibáñez; Cristina Cervera; Carlos Ruiz; José R; Blanco; José M Azcona; Concepción García; Jorge Alba; Valvanera Ibarra; Mercedes San Franco; Luis Metola; Héctor Meijide; Silvia Paulos; Justo Menéndez; Paula Villares; Lara Montes; Álvaro Navarro; Anna Ferrer; M de la Luz Padilla; Lucy Abella; Marcelino Hayek; Antonio García; Carolina Hernández; Andrés J Ruiz; Isabel Barrio; Alí Martakoush; Agustín Rojas-Vieyra; Sonia García; Mercedes Villarreal; Marta Vizcaíno; M Pilar García; Ana Lérida; Natalia Carrasco; Beatriz M Sanjuan; Lydia Martín; Camilo Sanz; Belén Alejos; Cristina Moreno; Marta Rava; Carlos Iniesta; Rebeca Izquierdo; Inés Suárez-García; Asunción Díaz; Marta Ruiz-Alguero; Victoria Hernando; J Frías; E Ramírez; A Martín-Quirós; M Quintana; J Mingorance; F Arnalich; F Moreno; JC Figueiras; N García-Arenzana; M Dolores Montero; MP Romero; C Toro-Rueda; S García-Bujalance; G Ruiz-Carrascoso; E Cendejas-Bueno; I Falces-Romero; F Lázaro-Perona; M Ruiz-Bastián; A Gutiérrez-Arroyo; P Girón De Velasco-Sada; E Dahdouh; B Gómez-Arroyo; C García-Sánchez; V Guedez-López; I Bloise; M Alguacil-Guillén; M Gracia Liras-Hernández; M Sánchez-Castellano; P García-Clemente; P González-Donapetry; S San José-Villar; M de Pablos; R Gómez-Gil; M Corcuera; A; Rico-Nieto; B; Loeches; J Mingorance; J García Rodríguez; F Moreno; A Herrero; D Prieto Arribas; P Oliver-Saez; R Mora; P Fernández-Calle; MJ Alcaide; J Diaz-Garzón; B Fernández-Puntero; R Nuñez; G Crespo; O Rodriguez; H Mendez; M Duque; R Gomez; M Sanz de Pedro; L Pascual; M Segovia; JM Iturzaeta; M Rodriguez; A García; MA Martinez; B Fabre; E Martinez; I Moreno; N Rodriguez; D Ortiz; M Simon; IG Tomoiu; C Pizarro; B Montero; AL Qasem; M Gomez; I Casares; A Buño; M Martí de Gracia; L Parra Gordo; A Diez Tascón; S Ossaba Vélez; I Pinilla; E Cuesta; M Fernández- Velilla; M Torres; G Garzón; V Pérez; A Quintás; I San Juan; J Cantero; C Pérez; M Castro; L Hernández; T Pedraz; E Fernández; C García; A Robustillo; I Fernández; M Noguerol; A Martínez; M González; R Cabrera; R Mayayo; R Marín; V Lo-Iacono; M Lerín; P Romero; B Reche; R Tejada; M Rico; R Deza; S Fabra; I Arroyo; L Dani; L Labajo; R Soriano; L López; E Calvin; S Martñinez; L López-Tappero; M Pilares; O González; G Bejarano; A Iglesias; Y Tung; C Maroun; R Bravo; M Silvestre; F Perdomo; B Alonso; B Antón; I Arenas; C Cabré; F Marqués; E Muñoz; MA Molina; N Cancelliere; S Pastor; L Frade; P López; I García; C Fernández Capitán; JJ González Garcia; JM Herrero; MA Quesada Simón; A Robles Marhuenda; JI Bernardino; M Mora; C Soto Abanedes; AM Noblejas Mozo; JC Ramos; B Diaz Pollán; MJ Jaras Hernandez; E Martinez Robles; A Moreno Fernandez; R Montejano; A Sanchez Purificación; JC Martin Gutiérrez; PL Martinez Hernández; F la Calle; M Arsuaga; M Diaz Menéndez; E Trigo; C Busca Arenzana; T Sancho Bueso; A Lorenzo Hernández; B Gutierrez Sancerni; G; Salgueiro; L; Martin Carbonero; J; Mostaza; R; de Miguel; M;A; Martinez-López; V; Hontañon; A; Menéndez; J; Cadiñanos; J Alvarez Troncoso; A Castellano; C Marcelo Calvo; I Vives Beltrán; L Ramos Ruperto; G Daroca Bengoa; MM Arcos Rueda; J Vasquez Manau; P Fernández Cidón; C Rosario Herrero Gil; E Palmier Peláez; Y Untoria Tabares; C; Lahoz; E; Estirado; C Hernández; F; Garcia-Iglesias; E; Monteoliva; M Martínez; M; Varas; T; González Alegre; ME Valencia; V Moreno; ML Montes; S Alcolea; J Cabanillas; C Carpio; R Casitas; J Fernández-Bujarrabal; I Fernández Navarro; J Fernández Lahera; C García Quero; M Hidalgo; R Galera; F García Río; L Gómez Carrera; M Gómez Mendieta; A Mangas; E Martínez Cerón; M Martínez Redondo; Y Martínez Abad; A Martínez-Verdasco; C Plaza; S Quirós; D Romera; D Romero; B Sánchez; A Santiago; C Villasante; E Zamarrón; V Arnalich; P Mariscal; A Falcone; D Laorden; MC Prados; R Álvarez-Sala; A García; C Arévalo; C Gutiérrez; JC Figueira; M Quintana; S Yus; MJ Asensio; M Sánchez; JM Añón; J Manzanares; A García de Lorenzo; E Perales; B Civantos; L Cachafeiro; A Agrifoglio; B Estébanez; E Flores; M Hernández; P Millán; M Rodríguez; C Gutiérrez; K Nanwani; B Arizcun; E Pérez; D Rodríguez; M Sánchez; U

Quesada; C Román; P Dorao; E Alvarez-Rojas; JJ Menendez-Suso; C Verdu; A Gómez-Zamora; C Schuffelman; B Calderón; M Laplaza; M del Rio; I Amores; M Rodriguez-Rubio; P de la Oliva;J Ruiz; S Rosillo; O González; A Iniesta; I Ponz; JM Muñoz Ramón; MC Hernández Gancedo; R Uña Orejón; P Sanabria Carretero; I Moreno Gomez-Limón; A Seiz-Martinez; E Guasch-Arévalo; C Martín-Carrasco; E Alvar; L Serrá; F Iannucelli; J Latorre; S Casares; I Valbuena; L Díaz Díez Picazo; C Rodríguez Roca: O Cervera; E García de las Heras; P Durán; C Castro; C Manrique de Lara; J Veganzones; A López Tofiño; E Fernandez-Cerezo; S Zurita; S Casares; M López-Martinez; T Prim; J Alvárez del Vayo; G Alcaraz; L Castro; J Yagüe; S Díaz-Carrasco; P González-Pizarro; A Montero; FJ Sagra; A Suárez; L Díez Porres; M Varela Cerdeira; A Alonso Babarro; F Abellán; J Alonso; A Álvarez; M Archinà; S Arribas; T Baselga; P Barco; N Barrera; L Barrera; A Bartrina; G Bassani; P Betancort; I Blanco; C Blasco; L Brieba; F Cadenas; P Carrera; C Cascajares; A Catino; R Cavallé; D Ceniza; Y Conde; L Currás; M Daltro; A Esteban; M Fernández; I Ferrer; L Regaño; P Galindo; S Garcia-Bellido; C García-Mochales; T Gómez; C Gómez; N González; S González; J Guisández; P Hernández; R Hernando; I Llorente; A Marín; P López; L Mejuto; M Palma; A Peña; L Platero; D Pujol; M Ramírez; M Redondo; F Reinoso; A Rodríguez; A Rodríguez; L Romero; S Sánchez; M Sánchez; P Serrano; H Serrano; T Silva; E Soria; A Suárez; B Tejero; A Torrecillas; J Torres; M Valentín-Pastrana; A Villanueva; M Virgós; M Yagüe; N Yustas; J Montserrat; J Queiruga; A Rodriguez Mariblanca; L Martínez de Soto; M Urroz; E Seco; M Zubimendi; S Stuart; L Díaz; I García; MT García Morales; A Martín-Vega.

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ORCID iD

Juan Berenguer http://orcid.org/0000-0001-8541-8200

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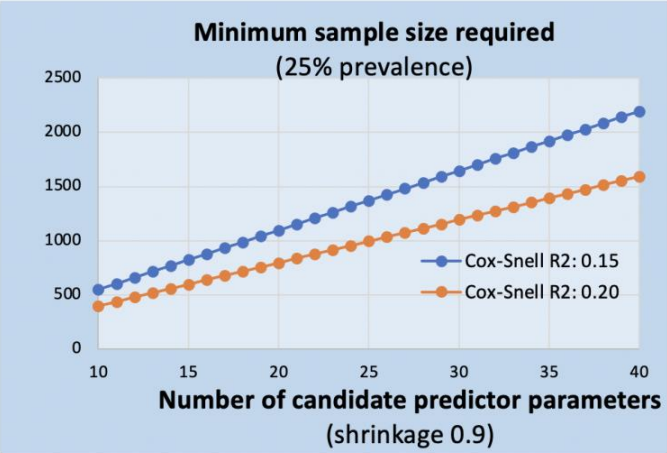
Appendix Figure 1. Sample size Calculation*

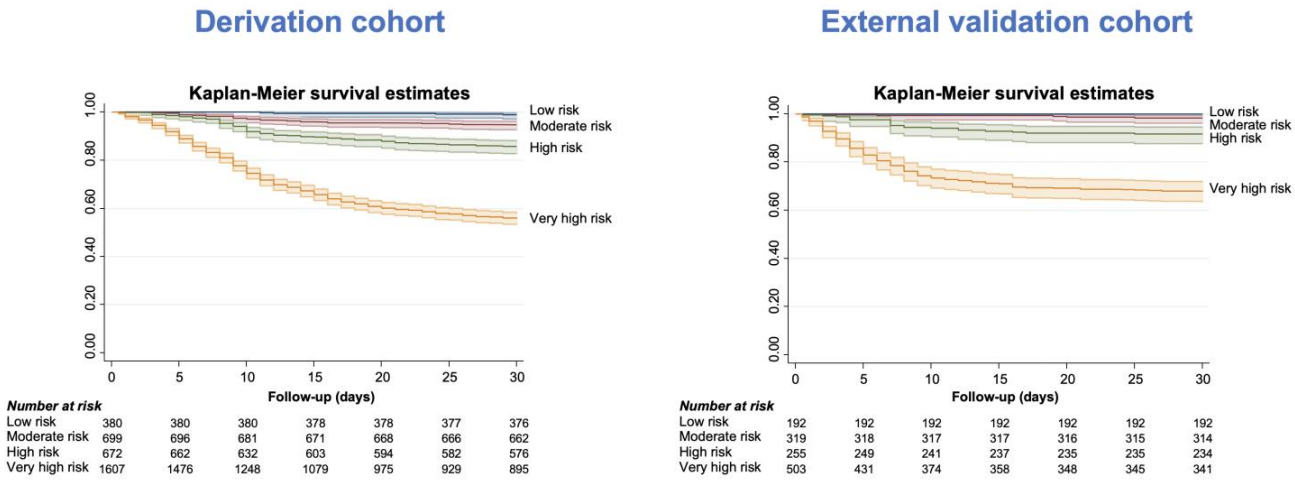


	Minimum sample size required (shrinkage of 0.9 and 25% prevalence)	
Parameters	Cox-Snell R^2: 0.15	Cox-Snell R^2: 0.20
10	549	398
15	823	597
20	1,097	796
25	1,372	995
30	1,646	1,194
35	1,920	1,393
40	2,194	1,592

To estimate a 30-parameter logistic model with a shrinkage of 0.9, a prevalence of events of 25% and assuming a Cox-Snell R^2 of 0.15, 1,646 individuals would be needed, approximately 14 events per variable. In our study, the estimated models were carried out with much higher sample size and 30 parameters were never exceeded, despite the categorization of some independent variables such as age.

*Riley RD, Ensor J, Snell KIE, Harrell FE, Jr., Martin GP, Reitsma JB, et al.
Calculating the sample size required for developing a clinical prediction model.
BMJ. 2020;368:m441. doi: 10.1136/bmj.m441.

Appendix Figure 2. Kaplan-Meier survival plots with 95% confidence intervals for the different 30-day mortality risk categories according to the simplified score in the derivation and validation cohorts.



We considered the risk of 30-day mortality as low with 0-2 points, moderate with 3-5, high with 6-8, and very high with 9-30.

Appendix Table 1. TRIPOD Checklist: Prediction Model Development and Validation

Section/Topic	Item		Checklist Item	Page
Title and abstract				
Title	1	D;V	Identify the study as developing and/or validating a multivariable prediction model, the target population, and the outcome to be predicted.	Title.
Abstract	2	D;V	Provide a summary of objectives, study design, setting, participants, sample size, predictors, outcome, statistical analysis, results, and conclusions.	Abstract.
Introduction				
Background and objectives	3a	D;V	Explain the medical context (including whether diagnostic or prognostic) and rationale for developing or validating the multivariable prediction model, including references to existing models.	Introduction paragraphs 1 to 3.
	3b	D;V	Specify the objectives, including whether the study describes the development or validation of the model or both.	Introduction paragraph 4.
Methods				
Source of data	4a	D;V	Describe the study design or source of data (e.g., randomized trial, cohort, or registry data), separately for the development and validation data sets, if applicable.	Methods section. Source of data epigraph.
	4b	D;V	Specify the key study dates, including start of accrual; end of accrual; and, if applicable, end of follow-up.	Methods section. Source of data epigraph.
Participants	5a	D;V	Specify key elements of the study setting (e.g., primary care, secondary care, general population) including number and location of centres.	Methods section. Participants epigraph.
	5b	D;V	Describe eligibility criteria for participants.	Methods section. Participants epigraph.
	5c	D;V	Give details of treatments received, if relevant.	Results section. Participants epigraph.
Outcome	6a	D;V	Clearly define the outcome that is predicted by the prediction model, including how and when assessed.	Methods section. Outcome epigraph.
	6b	D;V	Report any actions to blind assessment of the outcome to be predicted.	Non-applicable.
Predictors	7a	D;V	Clearly define all predictors used in developing the multivariable prediction model, including how and when they were measured.	Methods section. Predictors epigraph.
	7b	D;V	Report any actions to blind assessment of predictors for the outcome and other predictors.	Non-applicable.
Sample size	8	D;V	Explain how the study size was arrived at.	Methods section. Statistical analysis epigraph.
Missing data	9	D;V	Describe how missing data were handled (e.g., complete-case analysis, single imputation, multiple imputation) with details of any imputation method.	Methods section. Statistical analysis epigraph.
Statistical analysis methods	10a	D	Describe how predictors were handled in the analyses.	Methods section. Statistical analysis epigraph.
	10b	D	Specify type of model, all model-building procedures (including any predictor selection), and method for internal validation.	Methods section. Statistical analysis epigraph.
	10c	V	For validation, describe how the predictions were calculated.	Non-applicable.
	10d	D;V	Specify all measures used to assess model performance and, if relevant, to compare multiple models.	Methods section. Statistical analysis epigraph.
	10e	V	Describe any model updating (e.g., recalibration) arising from the validation, if done.	Non-applicable.
Risk groups	11	D;V	Provide details on how risk groups were created, if done.	Methods section. Statistical analysis epigraph.
Development vs. validation	12	V	For validation, identify any differences from the development data in setting, eligibility criteria, outcome, and predictors.	Results section. Participants epigraph.
Results				

Participants	13a	D;V	Describe the flow of participants through the study, including the number of participants with and without the outcome and, if applicable, a summary of the follow-up time. A diagram may be helpful.	Results. Participants epigraph.
	13b	D;V	Describe the characteristics of the participants (basic demographics, clinical features, available predictors), including the number of participants with missing data for predictors and outcome.	Results. Participants epigraph. Table 1.
	13c	V	For validation, show a comparison with the development data of the distribution of important variables (demographics, predictors and outcome).	Results. Participants epigraph. Table 1.
Model development	14a	D	Specify the number of participants and outcome events in each analysis.	Results. Model development and performance epigraph. Table 2.
	14b	D	If done, report the unadjusted association between each candidate predictor and outcome.	Results. Model development epigraph. Table 3.
Model specification	15a	D	Present the full prediction model to allow predictions for individuals (i.e., all regression coefficients, and model intercept or baseline survival at a given time point).	Results. Model development and Simplified score development epigraphs. Tables 3 and 5.
	15b	D	Explain how to use the prediction model.	Results. Model development and Simplified score development epigraphs. Table 5 and Figure 1.
Model performance	16	D;V	Report performance measures (with CIs) for the prediction model.	Results. Model development and Simplified score development epigraphs. Appendix Table 2.
Model-updating	17	V	If done, report the results from any model updating (i.e., model specification, model performance).	Non-applicable
Discussion				
Limitations	18	D;V	Discuss any limitations of the study (such as nonrepresentative sample, few events per predictor, missing data).	Discussion. Paragraph nº 4.
Interpretation	19a	V	For validation, discuss the results with reference to performance in the development data, and any other validation data.	Non-applicable.
	19b	D;V	Give an overall interpretation of the results, considering objectives, limitations, results from similar studies, and other relevant evidence.	Discussion. Paragraphs nº 1 - 3.
Implications	20	D;V	Discuss the potential clinical use of the model and implications for future research.	Discussion. Paragraphs nº 5.
Other information				
Supplementary information	21	D;V	Provide information about the availability of supplementary resources, such as study protocol, Web calculator, and data sets.	Methods section. Source of data epigraph. ClinicalTrials.gov (NCT04355871). European Union Electronic Register of Post-Authorization Studies (EUPAS34331). References section. References number 24 and 25
Funding	22	D;V	Give the source of funding and the role of the funders for the present study.	Title page and Abstract.

*Items relevant only to the development of a prediction model are denoted by D, items relating solely to a validation of a prediction model are denoted by V, and items relating to both are denoted D;V. We recommend using the TRIPOD Checklist in conjunction with the TRIPOD Explanation and Elaboration document.

Appendix Table 2. Performance of the final prediction model and the simplified score.

	Nº Participants	AUROC	95% CI
Primary analysis *			
Final prediction model			
Derivation cohort	3,358	0.822	0.806 – 0.837
External validation cohort	1,269	0.845	0.819 – 0.870
Simplified score			
Derivation cohort	3,358	0.806	0.790 – 0.821
External validation cohort	1,269	0.831	0.806 – 0.856
Sensitivity analysis 1 †			
Final prediction model			
Derivation cohort	4,031	0.822	0.809 – 0.836
External validation cohort	2,202	0.850	0.831 – 0.867
Simplified score			
Derivation cohort	4,031	0.805	0.791 – 0.820
External validation cohort	2,202	0.848	0.830 – 0.866
Sensitivity analysis 2 ‡			
Final prediction model			
Derivation cohort	4,031	0.818	0.805 – 0.832
External validation cohort	2,202	0.859	0.842 – 0.876
Simplified score			
Derivation cohort	4,031	0.806	0.791 – 0.820
External validation cohort	2,202	0.849	0.831 – 0.866

Abbreviations: AUROC; Area Under the Receiver Operating Characteristics; CI, confidence interval

* Primary analysis: Complete-case analysis without recoding missing values for predictors.
† Sensitivity analysis 1: Recoding missing values for predictors as a separate category.
‡ Sensitivity analysis 2: Missing values for predictors were given the value of the reference category for the variable.

Appendix Table 3. Simplified score to predict 30–day mortality in hospitalized patients with COVID–19 in the external validation cohort: Sensitivity, specificity, likelihood ratios, and predictive values for the different scores (0 to 30) in the validation cohort.

Score	Participants			Sen (%)	Spe (%)	+LR	1/-LR	PPV (%)	NPV (%)
	Total	Dying within 30-days							
		Nº	%						
0	20	0	0.0	100	0.0	1	.	14.8	.
1	68	0	0.0	100	1.9	1.019	.	15.1	100
2	104	0	0.0	100	8.1	1.089	.	15.9	100
3	103	0	0.0	100	17.8	1.216	.	17.5	100
4	109	1	0.9	100	27.3	1.375	.	19.3	100
5	107	4	3.74	99.5	37.3	1.586	70.090	21.6	99.8
6	112	5	4.46	97.3	46.8	1.830	17.600	24.1	99.0
7	80	8	10.0	94.7	56.7	2.187	10.660	27.6	98.4
8	63	8	12.7	90.4	63.4	2.468	6.618	30.0	97.4
9	42	8	19.1	86.2	68.5	2.732	4.950	32.2	96.6
10	45	12	26.7	81.9	71.6	2.884	3.959	33.4	95.8
11	45	11	24.4	75.5	74.7	2.980	3.051	34.1	94.6
12	26	5	19.2	69.7	77.8	3.139	2.566	35.3	93.7
13	18	7	38.9	67.0	79.7	3.308	2.418	36.5	93.3
14	19	5	26.3	63.3	80.8	3.290	2.200	36.4	92.7
15	27	9	33.3	60.6	82.1	3.379	2.085	37.0	92.3
16	32	10	31.2	55.9	83.7	3.430	1.896	37.4	91.6
17	40	14	35.0	50.5	85.8	3.547	1.734	38.2	90.9
18	49	16	32.6	43.1	88.2	3.639	1.549	38.8	89.9
19	41	13	31.7	34.6	91.2	3.934	1.394	40.6	88.9
20	23	9	39.1	27.7	93.8	4.463	1.297	43.7	88.2
21	17	6	35.3	22.9	95.1	4.665	1.233	44.8	87.6
22	17	7	41.2	19.7	96.1	5.065	1.197	46.8	87.3
23	12	4	33.3	16.0	97.0	5.391	1.155	48.4	86.9
24	15	8	53.3	13.8	97.8	6.229	1.135	52.0	86.7
25	13	5	38.5	9.6	98.4	6.088	1.088	51.4	86.2
26	9	4	44.4	6.9	99.2	8.306	1.065	59.1	86.0
27	8	6	75.0	4.8	99.6	12.940	1.046	69.2	85.7
28	3	1	33.3	1.6	99.8	8.625	1.014	60.0	85.4
29	2	2	100	1.1	100	-	1.011	100	85.3
30	0	-	-	-	-	-	-	-	-

Abbreviations: Sen, sensitivity; Spe, specificity; +LR, positive likelihood ratio; -LR, negative likelihood ratio; PPV, positive predictive value; NPV, negative predictive value.

Appendix Table 4. The COVID-19@Spain Study Group.

Fundación SEIMC-GESIDA: Esther Aznar, Pedro Gil, Patricia Gonzalez, Clara Muñoz, María Yllescas. **Hospital General Universitario Gregorio Marañón:** Juan C López, Margarita Ramírez-Schacke, Isabel Gutiérrez, Francisco Tejerina, Teresa Aldámiz-Echevarría, Cristina Díez, Chiara Fanciulli, Leire Pérez-Latorre, Francisco Parras, Pilar Catalán, María E García-Leoni, Isabel Pérez-Tamayo, Luis Puente, Jamil Cedeño, Juan Berenguer. **Hospital Universitario La Paz:** Marta Díaz, Fernando de la Calle, Marta Arsuaga, Elena Trigo, M del Mar Lago, Rosa de Miguel, Julen Cadiñaños, Carmen Busca, Alfredo Mican, Marta Mora, Juan Carlos Ramos, Belén Loeches, José I Bernardino, Julio García, José R Arribas. **Hospital Infanta Leonor:** Ana Such, Elena Álvaro, Elsa Izquierdo, Juan Torres, Guillermo Cuevas, Jesús Troya, Beatriz Mestre, Eva Jiménez, Inés Fernandez, Ana J Tebar, Fátima Brañas, Jorge Valencia, Mario Pérez, Marta Alvarado, Pablo Ryan. **Complejo Hospitalario Virgen de la Salud:** M Antonia Sepúlveda, Carmen Yera, Pilar Toledano, Verónica Cano, Sadaf Zafar, Gema Muñiz, Inmaculada Martín, Helena Mozas, Ana Alguacil, M Paz García. **Hospital Universitario Rafael Méndez:** Ana I Peláez, Elena Morcillo. **Hospital Universitario de Cruces:** Josune Goikoetxea, M José Blanco, Javier Nieto, Mikel del Álamo. **Hospital de Melilla:** Isabel A. Pérez, Inés Pérez. **Hospital San Eloy de Barakaldo:** Rafael Silvariño, Jon Ugalde. **Hospital Universitario Central de Asturias:** Víctor Asensi, Lucia Suárez, Silvia Suárez, Carmen Yllera. **Hospital General Universitario de Alicante:** Vicente Boix, Marcos Díez, Melissa Carreres. **Hospital Virgen de la Victoria:** Cristina Gómez-Ayerbe, Javier Sánchez-Lora, José L Velasco, María López-Jódar, Jesús Santos. **Hospital Universitario Puerto Real:** Jesús Ruiz, Ianire Virto. **EOXI Pontevedra e Salnés:** Vanessa Alende, Ruth Brea. **Hospital de Figueres:** Sonia Vega, Estel Pons. **Hospital Sant Jaume de Calella:** Oscar Del Río, Silvia Valero. **Hospital del Mar:** Judit Villar-García, Joan Gómez-Junyent, Hernando Knobel, M Cecilia Cánepa, Silvia Castañeda, Luisa Sorli, Roberto Güerri-Fernández, María Milagro, Juan P Horcajada. **Hospital Clínico Universitario Virgen de la Arrixaca:** Elisa García, Encarnación Moral, Alicia Hernádez. **Hospital de Can Misses:** Esther García. **Hospital de Sagunto:** Carmen Sáez, Zineb Karroud. **Hospital Clínico San Cecilio:** José Hernández, David Vinuesa, José L García, José A Peregrina. **Hospital Universitario Príncipe de Asturias:** María Novella, Cristina Hernández, José Sanz, Ramón Pérez, Rodrigo Sierra, David Alonso, Aida Gutiérrez, Alberto Arranz, Juan Cuadros, Melchor Álvarez de Mon. **Parc Sanitari Sant Joan de Déu:** Vicente F Díaz De Brito, Montserrat Sanmarti, Aina Gabarrell, Daniel Molina, Sergio España, Jonathan Cámara, Albert Sabater, Laura Muñoz. **Hospital Nuestra Señora de Gracia:** Paula Sáez, Esperanza Bejaranao. **HC Marbella Internacional Hospital:** Marco A Sampere, Salvador Álvarez. **Hospital La Princesa:** Ignacio De los Santos, Lucio García-Fraile, Miguel Sampedro, Ana Barrios, Carlos Rodríguez, Daniel Useros, Almudena Villa, Javier Oliver, Alexia C Espiño , Jesús Sanz. **Hospital Josep Trueta:** María Rexach, Ivette Abascal, Ana del C Pérez. **Hospital Dos De Maig:** Clara Sala, Susana Casas. **Hospital Arnau de Vilanova-Lliria:** Cecilia Tortajada, Carmina Oltra. **Hospital General Universitario de Elche:** Mar Masiá, Félix Gutiérrez. **Hospital Clínico Universitario de Valencia:** Ana Ferrer, Carlos Bea. **Complejo Asistencial De Ávila:** Miguel Pedromingo, M Ángeles Garcinuño, Silvana Fiorante, Sergio Pérez. **Hospital Comarcal de Alcañiz:** Pilar Hernández, Violeta A Alastrué. **Hospital Universitario Marqués de Valdecilla:** M Carmen Fariñas, Claudia González, Francisco Arnaiz, Jorge Calvo, Mónica Gonzalo. **Hospital Quiron-Salud de Torrevieja:** Francisco Mora. **Hospital Universitario Miguel Servet:** Ana Milagro, Miriam Latorre-Millán, Antonio Rezusta, Ana Martínez. **SCIAS, Hospital de Barcelona:** Yolanda Meije, Alejandra Duarte, Julia Pareja, Mercedes Clemente. **Fundación Hospital Universitario Alcorcón:** Juan E Losa, Ana Vegas. **Hospital Álvaro Cunqueiro:** M Teresa Pérez-Rodríguez, Alexandre Pérez. **Complejo Asistencial Universitario de Salamanca:** Moncef Belhassen-García, Beatriz Rodríguez-Alonso, Amparo López-Bernus, Cristina Carbonell. **Hospital Universitario Severo Ochoa:** Rafael Torres, Juan Catón, Blanca Alonso, Sara L Kamal, Lucia Cajuela, David Roa, Miguel Cervero, Alberto Orejas, Juan P Avilés, Lidia Martín. **Hospital CIMA-Sanitas:** Iván Pelegrín, Rosana Rouco. **Hospital HLA Inmaculada:** Jorge Parra, Violeta Ramos. **Hospital Universitario Rio Hortega:** Jessica Abadía. **Hospital de Guadalajara:** Juan Salillas, Robert Torres, Miguel Torralba, Alberto Serrano, Sergio Gilaberte, Marina Pacheco, Mónica Liébana, Sara Fernández, Álvaro Varela, Henar Calvo. **Hospital Universitario Infanta Sofía:** Patricia Martínez, Patricia González- Ruano, Eduardo Malmierca, Isabel Rábago, Beatriz Pérez-Monte. **Hospital Comarcal de Blanes:** Ángeles García, Pere Comas. **Hospital Universitari de Tarragona Joan XXIII:** Merce Sirisi, Richard Rojas. **Hospital Universitario Basurto:** José L Díaz de Tuesta, Ruth Figueroa, Ander González. **Hospital Universitario de Canarias:** Remedios Alemán, M del Mar Alonso. **Hospital Universitario de Gran Canaria Dr. Negrín:** Oscar Sanz, Karim M Ramírez. **Hospital Son Espases:** Melchor Riera, Helem H Vilchez, Francesc Albertí, Ana I Cañabate. **Hospital Universitario de Móstoles:** Víctor J Moreno, Silvia Álvarez, Beatriz Álvarez, Alejandro García, Elena Isaba, Covadonga Morcate, Andrea Pérez. **Complejo Hospitalario Universitario A Coruña:** Lucía Ramos, Laura Castelo, María Rodríguez, Mónica González, Efrén Sánchez, Enrique Míguez. **Hospital Costa del Sol:** Javier De la Torre, José M García de Lomas. **Hospital Clínico Universitario Lozano Blesa:** Elena Morte, Silvia Loscos, Ana Camón. **Hospital Mutua de Terrassa:** Lucía

Gómez, Lucia Boix, Beatriz Dietl. **Hospital de la Plana:** Iris Pedrola, Amparo Blasco. **Hospital Virgen de la Concha - Complejo Asistencial de Zamora:** Cristina López, Esther Fraile. **Complejo Hospitalario Universitario Insular Materno-Infantil:** Tomás Tosco, María Aroca. **Hospital de la Marina Baixa:** José T Algado, Ana M Garijo, Concepción Amador. **Hospital Universitario Virgen Macarena:** Jesús Rodriguez-Baño, Pilar Retamar, Adoración Valiente, Luis E. López-Cortés, Jesús Sojo, Belén Gutiérrez-Gutiérrez, José Bravo-Ferrer, Elena Salamanca, Zaira R. Palacios, Patricia Pérez-Palacios, Enrique Peral, José A Pérez de León, Jesús Sánchez-Gómez, Lucía Marín-Barrera, Domingo García-Jiménez. **Hospital Universitari de Bellvitge**: Jordi Carratalá, Gabriela Abelenda-Alonso, Carmen Ardanuy , Alba Bergas, Guillermo Cuervo, M Ángeles Domínguez, Miguel Fernández-Huerta, Carlota Gudiol , Laia Lorenzo-Esteller, Jordi Niubó, Sandra Pérez-Recio, Daniel Podzamczer, Miquel Pujol, Alexander Rombauts, Núria Trullen. **Hospital Universitario y Politécnico La Fe:** Miguel Salavert, Iván Castro. **Hospital Universitario del Vinalopó:** Adriana Hernández, Raquel Martínez. **Hospital de Sabadell (Parc Tauli):** Marta Navarro, Sonia Calzado, Manuel Cervantes, Aina Gomila, Oriol Gasch, M Luisa Machado, Eva Van den Eynde, Luis Falgueras, M del Carmen Navarro. **Hospital Clinic de Barcelona:** Esteban Martínez, M Ángeles Marcos, Mar Mosquera, José L Blanco, Montserrat Laguno, Jhon Rojas, Ana González-Cordón, Alexy Inciarte, Berta Torres, Lorena De la Mora, Alex Soriano. **Hospital Universitario de la Ribera:** Olalla Martínez, Virginia Pérez. **Fundación Jiménez Díaz:** Alfonso Cabello, Nerea Carrasco, Beatriz Álvarez, Elizabet Petkova, Miguel Górgolas, Laura Prieto, Irene Carrillo, Sara Heili, Felipe Villar, Ricardo Fernández, José Milicua. **Hospital Clínico Universitario de Valladolid:** Virginia Fernández, Carlos J Dueñas, Cristina Hernán. **Hospital Clínico San Carlos:** Fernando González-Romo, Paloma Merino, Alba Rueda, Jorge Martínez, Sara Medrano, Irene Díaz, Yolanda Posada, Alberto Delgado-Iribarren. **Hospital Santa Creu i Sant Pau:** Joaquín López-Contreras, Pablo Pascual, Virginia Pomar, Nuria Rabella, Natividad Benito, Pere Domingo, Xavier Bonfill, Rafael Padrós, Mireia Puig, Jordi Mancebo, Mercè Gurguí. **Clínica Universitaria de Navarra - Campus Madrid: M**elania Íñigo, Alejandra Pérez. **Hospital Son Llatzer:** Patricia Sorní , Nora Izko. **Hospital General de la Defensa Gómez Ulla:** Francisco J Membrillo, María Simón, Maribel Zamora, Yolanda Martínez, Pablo Fernández-González, Francisco Alcántara, Alejandro Aguirre, Elena López, Germán Ramírez-Olivencia, Miriam Estébanez. **Hospital Universitario de Álava:** Ester Sáez de Adana, Joseba Portu, Juan C Gainzarain, Zuriñe Ortiz de Zárate, Miguel A Moran, Andrés Canut, Silvia Hernáez, Leire Balerdi, Cristina Morales, Miguel Corral, Zeltia Valcarce. **Hospital Santos Reyes:** Noelia Arenal , Raquel E Rodríguez. **Hospital Dr. José Molina Orosa:** Laura Iglesias, Beatriz Loureiro. **Hospital Vall d´Hebrón:** Adrián Sánchez, Juan Espinosa, Benito Almirante, Marta Miarons, Júlia Sellarés, María Larrosa, Sonia García, Blanca Marzo, Miguel Villamarín, Nuria Fernández. **Hospital Universitario Rey Juan Carlos:** Conchita Pérez-Jorge, Elena Resino, Andrea Espigares, Teresa Álvarez de Espejo, Iván Navas, M Isabel Quijano, Luis A Nieto, Guillermo Jiménez. **Complejo Hospitalario Universitario Santa Lucía:** Mercedes Guillamón, Josefina García. **Hospital Santa Bárbara:** Constanza Muñoz. **Complejo Hospitalario Universitario de Ferrol:** Ana Mariño, Nieves Valcarce. **Hospital de l'Esperit Sant:** Alex Smithson, Cristina Chico. **Hospital Universitario los Arcos del Mar Menor:** Adriana Sánchez, Eva P García. **Hospital HLA Universitario Moncloa:** Isabel Jiménez, Guillermo Estrada, María Lorén, Nuria Parra, Carmen Martínez, Aránzazu Villasante, Teresa García, M José Ruiz, Marta Robledo, Juan C Abad. **Hospital Virgen del Puerto:** José R Muñoz , Montaña Jiménez. **Hospital Marina Salud de Dénia:** Javier Coy, Inmaculada Poquet. **Hospital Universitario de Jerez:** Marta Santos, Virginia Naranjo. **Hospital Reina Sofía de Tudela:** Tamara Manso, Delia Quilez. **Hospital Clínico Universitario de Santiago de Compostela:** Gema Barbeito, M Jesús Domínguez. **Hospital Universitario del Henares:** Laura Mao, Rodrigo Alonso, Jose D Ampuero, Raquel Barrós, M Aránzazu Galindo, Lourdes Herrera, Rocío Martínez, Sara Rodrigo, Cristóbal M Rodríguez. **Hospital Universitario Lucus Augusti:** Eva M Romay, Roi Suárez. **Hospital de Donostia:** Maialen Ibarguren, José M Marimón, Loreto Vidaur, Xabier Kortajarena. **Hospital de Urduliz Alfredo Espinosa:** Miriam García, Asier Aranguren. **Hospital de Mendaro:** Maria Álvarez, Cintia M Martínez. **Hospital Juan Ramón Jiménez:** Francisco Rodríguez, Francisco Muñoz. **Hospital de Tortosa Virgen de la Cinta:** Elena Chamarro , Merce Cardona. **Hospital Riotinto:** Ismail Zakariya-Yousef, Marta Rico. **Hospital Vega Baja:** Jara Llenas, M Carmen Sánchez. **Hospital Puerta de Hierro:** Ana Fernández, Jorge Calderón, Marcos López, Antonio Ramos, Elena Múñez, Alejandro Callejas, José M Vázquez, Itziar Diego, Esther Expósito, Jorge Anel. **Hospital Universitario de Getafe:** Raquel Álvarez, Lucía Fernández, Roberto Vates, Andrés F Cardona, Pablo Marguenda, Gabriel Gaspar, Elena M Aranda, Blanca Martínez, Daniel Roger, Irene Martín. **Hospital General de la Palma:** André Barbosa, Iván Piñero. **Hospital El Bierzo:** Alberto Bahamonde, Paula Runza. **Fundación Hospital de Calahorra:** Eva Talavera, Marta Lamata. **Hospital Alto Deba:** Ainhoa Urrutia, Lorea Arteche. **Hospital Universitario San Juan de Alicante:** Elisabet Delgado, Virginia Molina. **Hospital de Guadarrama:** Sarah Caro, Gema Domínguez. **Hospital Universitario de Jaén:** Carolina Roldán, Carmen Herrero. **Hospital de Mataró:** Luis Force, Raquel Aranega. **Hospital de Palamós:** Arantzazu Mera, M Roca Toda. **Hospital Universitario de Valme:** Nicolas Merchante , Eva M León. **Clínica Universitaria de Navarra - Campus Navarra:** José L Del Pozo. **Hospital Clínica Benidorm:** Josefa Serralta, Ginger G Cabrera. **Hospital Doce de Octubre:** Mario Fernández-Ruiz, José M Aguado, Guillermo Maestro. **Hospital Universitario Virgen del Rocío:**

José M Cisneros, Jerónimo Pachón, Manuela Aguilar-Guisado, Teresa Aldabó, M Dolores Avilés, Claudio Bueno, Elisa Cordero-Matía, Ana Escoresca, Lydia Gálvez-Benítez, Carmen Infante, Guillermo Martín, Julia Praena, Cristina Roca, Celia Salamanca, Alejandro Suárez-Benjumea. **Hospital Universitario Ramón y Cajal:** Pilar Vizcarra, Carmen Quereda, Mario J Rodriguez, Francesca Gioia, Francesca Norman, Santos Del Campo, Rafael Cantón. **Hospital Universitario San Pedro:** José A Oteo, Paula Santibáñez, Cristina Cervera, Carlos Ruiz, José R. Blanco, José M Azcona, Concepción García, Jorge Alba, Valvanera Ibarra, Mercedes San Franco, Luis Metola. **Hospital Quirón A Coruña:** Héctor Meijide, Silvia Paulos. **HM Sanchinarro:** Justo Menéndez, Paula Villares, Lara Montes. **Hospital Francesc de Borja:** Álvaro Navarro, Anna Ferrer. **Complejo Hospitalario Universitario Nuestra Señora de La Candelaria:** M de la Luz Padilla, Lucy Abella, Marcelino Hayek, Antonio García, Carolina Hernández. **Hospital Universitario HM Montepríncipe:** Andrés J Ruiz, Isabel Barrio. **Hospital Universitario HM Puerta del Sur:** Alí Martakoush. **Hospital Universitario HM Torrelodones:** Agustín Rojas-Vieyra. **Hospital Universitario HM Madrid:** Sonia García, Mercedes Villarreal. **Hospital Don Benito-Villanueva de la Serena:** Marta Vizcaíno, M Pilar García. **Hospital de Viladecans:** Ana Lérida, Natalia Carrasco, Beatriz M Sanjuan, Lydia Martín, Camilo Sanz. **Centro Nacional de Epidemiología:** Inmaculada Jarrín, Belén Alejos, Cristina Moreno, Marta Rava, Carlos Iniesta, Rebeca Izquierdo, Inés Suárez-García, Asunción Díaz, Marta Ruiz-Alguero, Victoria Hernando.

Appendix Table 5. COVID@HULP Working Group

Scientific Committee: J Frías, AJ Carcas, E Ramírez, A Martín-Quirós, M Quintana, J Mingorance, F Arnalich, F Moreno, JC Figueiras, N García-Arenzana, JR Arribas, AM Borobia.

Microbiology Department: M Dolores Montero, MP Romero, C Toro-Rueda, S García-Bujalance, G Ruiz-Carrascoso, E Cendejas-Bueno, I Falces-Romero, F Lázaro-Perona, M Ruiz-Bastián, A Gutiérrez-Arroyo, P Girón De Velasco-Sada, E Dahdouh, B Gómez-Arroyo, C García-Sánchez, V Guedez-López, I Bloise, M Alguacil-Guillén, M Gracia Liras-Hernández, M Sánchez-Castellano, P García-Clemente, P González-Donapetry, S San José-Villar, M de Pablos, R Gómez-Gil, M Corcuera, A. Rico-Nieto, B. Loeches, J Mingorance, J García Rodríguez.

Pharmacy Department: F Moreno, A Herrero.

Laboratory Medicine Department: D Prieto Arribas, P Oliver-Saez, R Mora, P Fernández-Calle, MJ Alcaide, J Diaz-Garzón, B Fernández-Puntero, R Nuñez, G Crespo, O Rodriguez, H Mendez, M Duque, R Gomez, M Sanz de Pedro, L Pascual, M Segovia, JM Iturzaeta, M Rodriguez, A García, MA Martinez, B Fabre, E Martinez, I Moreno, N Rodriguez, D Ortiz, M Simon, IG Tomoiu, C Pizarro, B Montero, AL Qasem, M Gomez, I Casares, A Buño.

Radiology Department: M Martí de Gracia, L Parra Gordo, A Diez Tascón, S Ossaba Vélez, I Pinilla, E Cuesta, M Fernández- Velilla, M Torres, G Garzón.

Preventive Medicine Department: V Pérez, A Quintás, I San Juan, J Cantero, C Pérez, M Castro, L Hernández, T Pedraz, E Fernández, C García, A Robustillo.

Emergency Medicine Department: I Fernández, M Noguerol, A Martínez, M González, R Cabrera, R Mayayo, R Marín, V Lo-Iacono, M Lerín, P Romero, B Reche, R Tejada, M Rico, R Deza, S Fabra, I Arroyo, L Dani, L Labajo, R Soriano, L López, E Calvin, S Martñinez, L López-Tappero, M Pilares, O González, G Bejarano, A Iglesias, Y Tung, C Maroun, R Bravo, M Silvestre, F Perdomo, B Alonso, B Antón, I Arenas, C Cabré, F Marqués, E Muñoz, MA Molina, N Cancelliere, S Pastor, L Frade, P López, I García.

Internal Medicine Department: F Arnalich, C Fernández Capitán, JJ González Garcia, JM Herrero, MA Quesada Simón, A Robles Marhuenda, JI Bernardino, M Mora, C Soto Abanedes, AM Noblejas Mozo, JC Ramos, B Diaz Pollán, MJ Jaras Hernandez, E Martinez Robles, A Moreno Fernandez, R Montejano, A Sanchez Purificación, JC Martin Gutiérrez, PL Martinez Hernández, F la Calle, M Arsuaga, M Diaz Menéndez, E Trigo, C Busca Arenzana, T Sancho Bueso, A Lorenzo Hernández, B Gutierrez Sancerni, G. Salgueiro, L. Martin Carbonero, J. Mostaza, R. de Miguel, M.A. Martinez-López, V. Hontañon, A. Menéndez, J. Cadiñanos, J Alvarez Troncoso, A Castellano, C Marcelo Calvo, I Vives Beltrán, L Ramos Ruperto, G Daroca Bengoa, MM Arcos Rueda, J Vasquez Manau, P Fernández Cidón, C Rosario Herrero Gil, E Palmier Peláez, Y Untoria Tabares, C. Lahoz, E. Estirado, C Hernández, F. Garcia-Iglesias, E. Monteoliva, M Martínez, M. Varas, T. González Alegre, ME Valencia, V Moreno, ML Montes.

Neumology Department: S Alcolea, J Cabanillas, C Carpio, R Casitas, J Fernández-Bujarrabal, I Fernández Navarro, J Fernández Lahera, C García Quero, M Hidalgo, R Galera, F García Río, L Gómez Carrera, M Gómez Mendieta, A Mangas, E Martínez Cerón, M Martínez Redondo, Y Martínez Abad, A Martínez-Verdasco, C Plaza, S Quirós, D Romera, D Romero, B Sánchez, A Santiago, C Villasante, E Zamarrón, V Arnalich, P Mariscal, A Falcone, D Laorden, MC Prados, R Álvarez-Sala

Intensive Care Department: A García, C Arévalo, C Gutiérrez, JC Figueira, M Quintana, S Yus, MJ Asensio, M Sánchez, JM Añón, J Manzanares, A García de Lorenzo, E Perales, B Civantos, L Cachafeiro, A Agrifoglio, B Estébanez, E Flores, M Hernández, P Millán, M Rodríguez, C Gutiérrez, K Nanwani

Pediatric Intensive Care Department: B Arizcun, E Pérez, D Rodríguez, M Sánchez, U Quesada, C Román, P Dorao, E Alvarez-Rojas, JJ Menendez-Suso, C Verdu, A Gómez-Zamora, C Schuffelman, B Calderón, M Laplaza, M del Rio, I Amores, M Rodriguez-Rubio, P de la Oliva

Cardiology Department: J Ruiz, S Rosillo, O González, A Iniesta, I Ponz.

Anesthesiology Department: JM Muñoz Ramón, MC Hernández Gancedo, R Uña Orejón, P Sanabria Carretero, I Moreno Gomez-Limón, A Seiz-Martinez, E Guasch-Arévalo, C Martín-Carrasco, E Alvar, L Serrá, F Iannucelli, J Latorre, S Casares, I Valbuena, L Díaz Díez Picazo, C Rodríguez Roca: O Cervera, E García de las Heras, P Durán, C Castro, C Manrique de Lara, J Veganzones, A López Tofiño, E Fernandez-Cerezo, S Zurita, S Casares, M López-Martinez, T Prim, J Alvárez del Vayo, G Alcaraz, L Castro, J Yagüe, S Díaz-Carrasco, P González-Pizarro, A Montero, FJ Sagra, A Suárez.

Palliative Care Unit: L Díez Porres, M Varela Cerdeira, A Alonso Babarro.

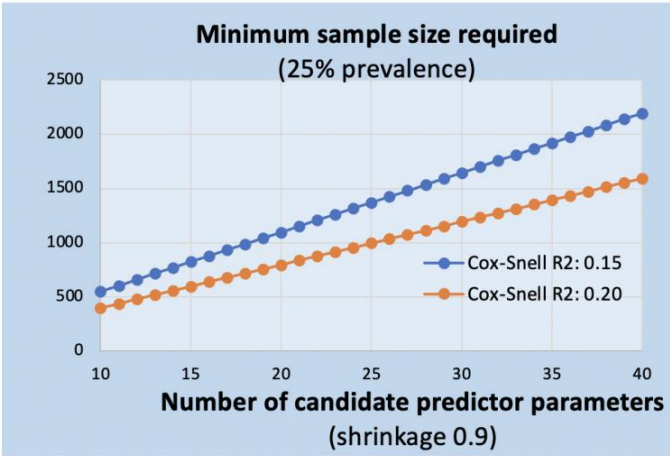
Data Entry (Medical Students): F Abellán, J Alonso, A Álvarez, M Archinà, S Arribas, T Baselga, P Barco, N Barrera, L Barrera, A Bartrina, G Bassani, P Betancort, I Blanco, C Blasco, L Brieba, F Cadenas, P Carrera, C Cascajares, A Catino, R Cavallé, D Ceniza, Y Conde, L Currás, M Daltro, A Esteban, M Fernández, I Ferrer, L Regaño, P Galindo, S Garcia-Bellido, C García-Mochales, T Gómez, C Gómez, N González, S González, J Guisández,

P Hernández, R Hernando, I Llorente, A Marín, P López, L Mejuto, M Palma, A Peña, L Platero, D Pujol, M Ramírez, M Redondo, F Reinoso, A Rodríguez, A Rodríguez, L Romero, S Sánchez, M Sánchez, P Serrano, H Serrano, T Silva, E Soria, A Suárez, B Tejero, A Torrecillas, J Torres, M Valentín-Pastrana, A Villanueva, M Virgós, M Yagüe, N Yustas.

Clinical Pharmacology Department: J Montserrat, J Queiruga, A Rodriguez Mariblanca, L Martínez de Soto, M Urroz, E Seco, M Zubimendi, S Stuart, L Díaz, I García.

Data management: MT García Morales, A Martín-Vega

Appendix Figure 1. Sample size Calculation*



	Minimum sample size required (shrinkage of 0.9 and 25% prevalence)	
Parameters	Cox-Snell R^2: 0.15	Cox-Snell R^2: 0.20
10	549	398
15	823	597
20	1,097	796
25	1,372	995
30	1,646	1,194
35	1,920	1,393
40	2,194	1,592

To estimate a 30-parameter logistic model with a shrinkage of 0.9, a prevalence of events of 25% and assuming a Cox-Snell R^2 of 0.15, 1,646 individuals would be needed, approximately 14 events per variable. In our study, the estimated models were carried out with much higher sample size and 30 parameters were never exceeded, despite the categorization of some independent variables such as age.

*Riley RD, Ensor J, Snell KIE, Harrell FE, Jr., Martin GP, Reitsma JB, et al.
Calculating the sample size required for developing a clinical prediction model.
BMJ. 2020;368:m441.
Epub 2020/03/20. doi: 10.1136/bmj.m441. PubMed PMID: 32188600.

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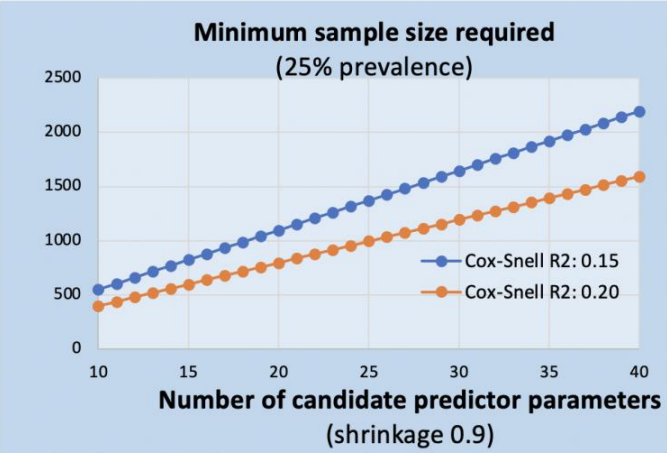

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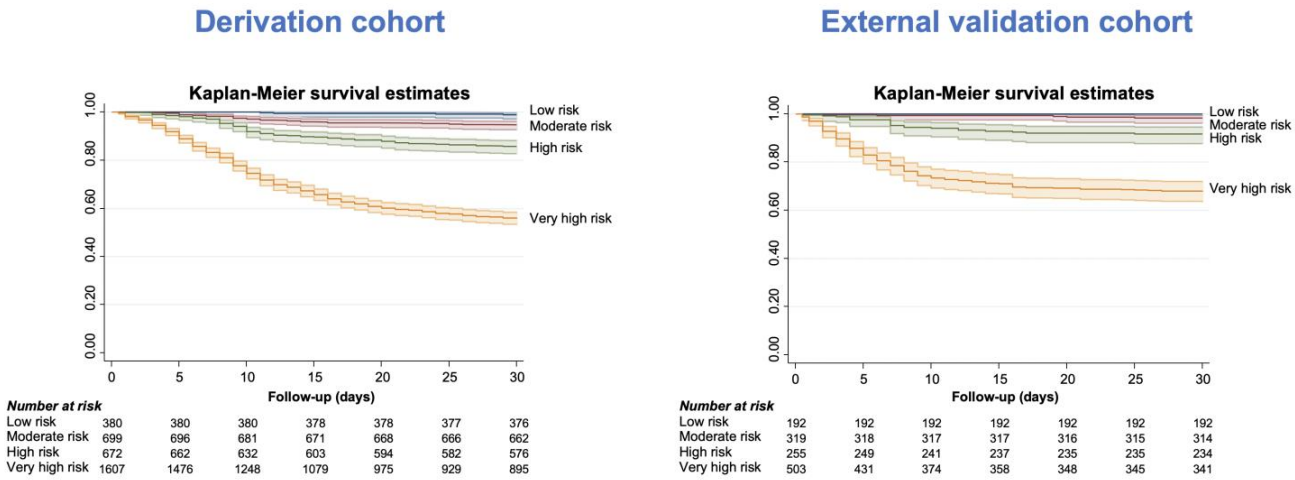
35	1,920	1,393
40	2,194	1,592

To estimate a 30-parameter logistic model with a shrinkage of 0.9, a prevalence of events of 25% and assuming a Cox-Snell R^2 of 0.15, 1,646 individuals would be needed, approximately 14 events per variable. In our study, the estimated models were carried out with much higher sample size and 30 parameters were never exceeded, despite the categorization of some independent variables such as age.

*Riley RD, Ensor J, Snell KIE, Harrell FE, Jr., Martin GP, Reitsma JB, et al.
Calculating the sample size required for developing a clinical prediction model.
BMJ. 2020;368:m441. doi: 10.1136/bmj.m441.

Appendix Figure 2. Kaplan-Meier survival plots with 95% confidence intervals for the different 30-day mortality risk categories according to the simplified score in the derivation and validation cohorts.



We considered the risk of 30-day mortality as low with 0-2 points, moderate with 3-5, high with 6-8, and very high with 9-30.

Appendix Table 1. TRIPOD Checklist: Prediction Model Development and Validation

Section/Topic	Item		Checklist Item	Page
Title and abstract				
Title	1	D;V	Identify the study as developing and/or validating a multivariable prediction model, the target population, and the outcome to be predicted.	Title.
Abstract	2	D;V	Provide a summary of objectives, study design, setting, participants, sample size, predictors, outcome, statistical analysis, results, and conclusions.	Abstract.
Introduction				
Background and objectives	3a	D;V	Explain the medical context (including whether diagnostic or prognostic) and rationale for developing or validating the multivariable prediction model, including references to existing models.	Introduction paragraphs 1 to 3.
	3b	D;V	Specify the objectives, including whether the study describes the development or validation of the model or both.	Introduction paragraph 4.
Methods				
Source of data	4a	D;V	Describe the study design or source of data (e.g., randomized trial, cohort, or registry data), separately for the development and validation data sets, if applicable.	Methods section. Source of data epigraph.
	4b	D;V	Specify the key study dates, including start of accrual; end of accrual; and, if applicable, end of follow-up.	Methods section. Source of data epigraph.
Participants	5a	D;V	Specify key elements of the study setting (e.g., primary care, secondary care, general population) including number and location of centres.	Methods section. Participants epigraph.
	5b	D;V	Describe eligibility criteria for participants.	Methods section. Participants epigraph.
	5c	D;V	Give details of treatments received, if relevant.	Results section. Participants epigraph.
Outcome	6a	D;V	Clearly define the outcome that is predicted by the prediction model, including how and when assessed.	Methods section. Outcome epigraph.
	6b	D;V	Report any actions to blind assessment of the outcome to be predicted.	Non-applicable.
Predictors	7a	D;V	Clearly define all predictors used in developing the multivariable prediction model, including how and when they were measured.	Methods section. Predictors epigraph.
	7b	D;V	Report any actions to blind assessment of predictors for the outcome and other predictors.	Non-applicable.
Sample size	8	D;V	Explain how the study size was arrived at.	Methods section. Statistical analysis epigraph.
Missing data	9	D;V	Describe how missing data were handled (e.g., complete-case analysis, single imputation, multiple imputation) with details of any imputation method.	Methods section. Statistical analysis epigraph.
Statistical analysis methods	10a	D	Describe how predictors were handled in the analyses.	Methods section. Statistical analysis epigraph.
	10b	D	Specify type of model, all model-building procedures (including any predictor selection), and method for internal validation.	Methods section. Statistical analysis epigraph.
	10c	V	For validation, describe how the predictions were calculated.	Non-applicable.
	10d	D;V	Specify all measures used to assess model performance and, if relevant, to compare multiple models.	Methods section. Statistical analysis epigraph.
	10e	V	Describe any model updating (e.g., recalibration) arising from the validation, if done.	Non-applicable.
Risk groups	11	D;V	Provide details on how risk groups were created, if done.	Methods section. Statistical analysis epigraph.
Development vs. validation	12	V	For validation, identify any differences from the development data in setting, eligibility criteria, outcome, and predictors.	Results section. Participants epigraph.
Results				

Participants	13a	D;V	Describe the flow of participants through the study, including the number of participants with and without the outcome and, if applicable, a summary of the follow-up time. A diagram may be helpful.	Results. Participants epigraph.
	13b	D;V	Describe the characteristics of the participants (basic demographics, clinical features, available predictors), including the number of participants with missing data for predictors and outcome.	Results. Participants epigraph. Table 1.
	13c	V	For validation, show a comparison with the development data of the distribution of important variables (demographics, predictors and outcome).	Results. Participants epigraph. Table 1.
Model development	14a	D	Specify the number of participants and outcome events in each analysis.	Results. Model development and performance epigraph. Table 2.
	14b	D	If done, report the unadjusted association between each candidate predictor and outcome.	Results. Model development epigraph. Table 3.
Model specification	15a	D	Present the full prediction model to allow predictions for individuals (i.e., all regression coefficients, and model intercept or baseline survival at a given time point).	Results. Model development and Simplified score development epigraphs. Tables 3 and 5.
	15b	D	Explain how to use the prediction model.	Results. Model development and Simplified score development epigraphs. Table 5 and Figure 1.
Model performance	16	D;V	Report performance measures (with CIs) for the prediction model.	Results. Model development and Simplified score development epigraphs. Appendix Table 2.
Model-updating	17	V	If done, report the results from any model updating (i.e., model specification, model performance).	Non-applicable
Discussion				
Limitations	18	D;V	Discuss any limitations of the study (such as nonrepresentative sample, few events per predictor, missing data).	Discussion. Paragraph nº 4.
Interpretation	19a	V	For validation, discuss the results with reference to performance in the development data, and any other validation data.	Non-applicable.
	19b	D;V	Give an overall interpretation of the results, considering objectives, limitations, results from similar studies, and other relevant evidence.	Discussion. Paragraphs nº 1 - 3.
Implications	20	D;V	Discuss the potential clinical use of the model and implications for future research.	Discussion. Paragraphs nº 5.
Other information				
Supplementary information	21	D;V	Provide information about the availability of supplementary resources, such as study protocol, Web calculator, and data sets.	Methods section. Source of data epigraph. ClinicalTrials.gov (NCT04355871). European Union Electronic Register of Post-Authorization Studies (EUPAS34331). References section. References number 24 and 25
Funding	22	D;V	Give the source of funding and the role of the funders for the present study.	Title page and Abstract.

*Items relevant only to the development of a prediction model are denoted by D, items relating solely to a validation of a prediction model are denoted by V, and items relating to both are denoted D;V. We recommend using the TRIPOD Checklist in conjunction with the TRIPOD Explanation and Elaboration document.

Appendix Table 2. Performance of the final prediction model and the simplified score.

	Nº Participants	AUROC	95% CI
Primary analysis *			
Final prediction model			
Derivation cohort	3,358	0.822	0.806 – 0.837
External validation cohort	1,269	0.845	0.819 – 0.870
Simplified score			
Derivation cohort	3,358	0.806	0.790 – 0.821
External validation cohort	1,269	0.831	0.806 – 0.856
Sensitivity analysis 1 †			
Final prediction model			
Derivation cohort	4,031	0.822	0.809 – 0.836
External validation cohort	2,202	0.850	0.831 – 0.867
Simplified score			
Derivation cohort	4,031	0.805	0.791 – 0.820
External validation cohort	2,202	0.848	0.830 – 0.866
Sensitivity analysis 2 ‡			
Final prediction model			
Derivation cohort	4,031	0.818	0.805 – 0.832
External validation cohort	2,202	0.859	0.842 – 0.876
Simplified score			
Derivation cohort	4,031	0.806	0.791 – 0.820
External validation cohort	2,202	0.849	0.831 – 0.866

Abbreviations: AUROC; Area Under the Receiver Operating Characteristics; CI, confidence interval

* Primary analysis: Complete-case analysis without recoding missing values for predictors.
† Sensitivity analysis 1: Recoding missing values for predictors as a separate category.
‡ Sensitivity analysis 2: Missing values for predictors were given the value of the reference category for the variable.

Appendix Table 3. Simplified score to predict 30–day mortality in hospitalized patients with COVID–19 in the external validation cohort: Sensitivity, specificity, likelihood ratios, and predictive values for the different scores (0 to 30) in the validation cohort.

Score	Participants			Sen (%)	Spe (%)	+LR	1/-LR	PPV (%)	NPV (%)
	Total	Dying within 30-days							
		Nº	%						
0	20	0	0.0	100	0.0	1	.	14.8	.
1	68	0	0.0	100	1.9	1.019	.	15.1	100
2	104	0	0.0	100	8.1	1.089	.	15.9	100
3	103	0	0.0	100	17.8	1.216	.	17.5	100
4	109	1	0.9	100	27.3	1.375	.	19.3	100
5	107	4	3.74	99.5	37.3	1.586	70.090	21.6	99.8
6	112	5	4.46	97.3	46.8	1.830	17.600	24.1	99.0
7	80	8	10.0	94.7	56.7	2.187	10.660	27.6	98.4
8	63	8	12.7	90.4	63.4	2.468	6.618	30.0	97.4
9	42	8	19.1	86.2	68.5	2.732	4.950	32.2	96.6
10	45	12	26.7	81.9	71.6	2.884	3.959	33.4	95.8
11	45	11	24.4	75.5	74.7	2.980	3.051	34.1	94.6
12	26	5	19.2	69.7	77.8	3.139	2.566	35.3	93.7
13	18	7	38.9	67.0	79.7	3.308	2.418	36.5	93.3
14	19	5	26.3	63.3	80.8	3.290	2.200	36.4	92.7
15	27	9	33.3	60.6	82.1	3.379	2.085	37.0	92.3
16	32	10	31.2	55.9	83.7	3.430	1.896	37.4	91.6
17	40	14	35.0	50.5	85.8	3.547	1.734	38.2	90.9
18	49	16	32.6	43.1	88.2	3.639	1.549	38.8	89.9
19	41	13	31.7	34.6	91.2	3.934	1.394	40.6	88.9
20	23	9	39.1	27.7	93.8	4.463	1.297	43.7	88.2
21	17	6	35.3	22.9	95.1	4.665	1.233	44.8	87.6
22	17	7	41.2	19.7	96.1	5.065	1.197	46.8	87.3
23	12	4	33.3	16.0	97.0	5.391	1.155	48.4	86.9
24	15	8	53.3	13.8	97.8	6.229	1.135	52.0	86.7
25	13	5	38.5	9.6	98.4	6.088	1.088	51.4	86.2
26	9	4	44.4	6.9	99.2	8.306	1.065	59.1	86.0
27	8	6	75.0	4.8	99.6	12.940	1.046	69.2	85.7
28	3	1	33.3	1.6	99.8	8.625	1.014	60.0	85.4
29	2	2	100	1.1	100	-	1.011	100	85.3
30	0	-	-	-	-	-	-	-	-

Abbreviations: Sen, sensitivity; Spe, specificity; +LR, positive likelihood ratio; -LR, negative likelihood ratio; PPV, positive predictive value; NPV, negative predictive value.

Appendix Table 4. The COVID-19@Spain Study Group.

Fundación SEIMC-GESIDA: Esther Aznar, Pedro Gil, Patricia Gonzalez, Clara Muñoz, María Yllescas. **Hospital General Universitario Gregorio Marañón:** Juan C López, Margarita Ramírez-Schacke, Isabel Gutiérrez, Francisco Tejerina, Teresa Aldámiz-Echevarría, Cristina Díez, Chiara Fanciulli, Leire Pérez-Latorre, Francisco Parras, Pilar Catalán, María E García-Leoni, Isabel Pérez-Tamayo, Luis Puente, Jamil Cedeño, Juan Berenguer. **Hospital Universitario La Paz:** Marta Díaz, Fernando de la Calle, Marta Arsuaga, Elena Trigo, M del Mar Lago, Rosa de Miguel, Julen Cadiñaños, Carmen Busca, Alfredo Mican, Marta Mora, Juan Carlos Ramos, Belén Loeches, José I Bernardino, Julio García, José R Arribas. **Hospital Infanta Leonor:** Ana Such, Elena Álvaro, Elsa Izquierdo, Juan Torres, Guillermo Cuevas, Jesús Troya, Beatriz Mestre, Eva Jiménez, Inés Fernandez, Ana J Tebar, Fátima Brañas, Jorge Valencia, Mario Pérez, Marta Alvarado, Pablo Ryan. **Complejo Hospitalario Virgen de la Salud:** M Antonia Sepúlveda, Carmen Yera, Pilar Toledano, Verónica Cano, Sadaf Zafar, Gema Muñiz, Inmaculada Martín, Helena Mozas, Ana Alguacil, M Paz García. **Hospital Universitario Rafael Méndez:** Ana I Peláez, Elena Morcillo. **Hospital Universitario de Cruces:** Josune Goikoetxea, M José Blanco, Javier Nieto, Mikel del Álamo. **Hospital de Melilla:** Isabel A. Pérez, Inés Pérez. **Hospital San Eloy de Barakaldo:** Rafael Silvariño, Jon Ugalde. **Hospital Universitario Central de Asturias:** Víctor Asensi, Lucia Suárez, Silvia Suárez, Carmen Yllera. **Hospital General Universitario de Alicante:** Vicente Boix, Marcos Díez, Melissa Carreres. **Hospital Virgen de la Victoria:** Cristina Gómez-Ayerbe, Javier Sánchez-Lora, José L Velasco, María López-Jódar, Jesús Santos. **Hospital Universitario Puerto Real:** Jesús Ruiz, Ianire Virto. **EOXI Pontevedra e Salnés:** Vanessa Alende, Ruth Brea. **Hospital de Figueres:** Sonia Vega, Estel Pons. **Hospital Sant Jaume de Calella:** Oscar Del Río, Silvia Valero. **Hospital del Mar:** Judit Villar-García, Joan Gómez-Junyent, Hernando Knobel, M Cecilia Cánepa, Silvia Castañeda, Luisa Sorli, Roberto Güerri-Fernández, María Milagro, Juan P Horcajada. **Hospital Clínico Universitario Virgen de la Arrixaca:** Elisa García, Encarnación Moral, Alicia Hernádez. **Hospital de Can Misses:** Esther García. **Hospital de Sagunto:** Carmen Sáez, Zineb Karroud. **Hospital Clínico San Cecilio:** José Hernández, David Vinuesa, José L García, José A Peregrina. **Hospital Universitario Príncipe de Asturias:** María Novella, Cristina Hernández, José Sanz, Ramón Pérez, Rodrigo Sierra, David Alonso, Aida Gutiérrez, Alberto Arranz, Juan Cuadros, Melchor Álvarez de Mon. **Parc Sanitari Sant Joan de Déu:** Vicente F Díaz De Brito, Montserrat Sanmarti, Aina Gabarrell, Daniel Molina, Sergio España, Jonathan Cámara, Albert Sabater, Laura Muñoz. **Hospital Nuestra Señora de Gracia:** Paula Sáez, Esperanza Bejaranao. **HC Marbella Internacional Hospital:** Marco A Sampere, Salvador Álvarez. **Hospital La Princesa:** Ignacio De los Santos, Lucio García-Fraile, Miguel Sampedro, Ana Barrios, Carlos Rodríguez, Daniel Useros, Almudena Villa, Javier Oliver, Alexia C Espiño , Jesús Sanz. **Hospital Josep Trueta:** María Rexach, Ivette Abascal, Ana del C Pérez. **Hospital Dos De Maig:** Clara Sala, Susana Casas. **Hospital Arnau de Vilanova-Lliria:** Cecilia Tortajada, Carmina Oltra. **Hospital General Universitario de Elche:** Mar Masiá, Félix Gutiérrez. **Hospital Clínico Universitario de Valencia:** Ana Ferrer, Carlos Bea. **Complejo Asistencial De Ávila:** Miguel Pedromingo, M Ángeles Garcinuño, Silvana Fiorante, Sergio Pérez. **Hospital Comarcal de Alcañiz:** Pilar Hernández, Violeta A Alastrué. **Hospital Universitario Marqués de Valdecilla:** M Carmen Fariñas, Claudia González, Francisco Arnaiz, Jorge Calvo, Mónica Gonzalo. **Hospital Quiron-Salud de Torrevieja:** Francisco Mora. **Hospital Universitario Miguel Servet:** Ana Milagro, Miriam Latorre-Millán, Antonio Rezusta, Ana Martínez. **SCIAS, Hospital de Barcelona:** Yolanda Meije, Alejandra Duarte, Julia Pareja, Mercedes Clemente. **Fundación Hospital Universitario Alcorcón:** Juan E Losa, Ana Vegas. **Hospital Álvaro Cunqueiro:** M Teresa Pérez-Rodríguez, Alexandre Pérez. **Complejo Asistencial Universitario de Salamanca:** Moncef Belhassen-García, Beatriz Rodríguez-Alonso, Amparo López-Bernus, Cristina Carbonell. **Hospital Universitario Severo Ochoa:** Rafael Torres, Juan Catón, Blanca Alonso, Sara L Kamal, Lucia Cajuela, David Roa, Miguel Cervero, Alberto Orejas, Juan P Avilés, Lidia Martín. **Hospital CIMA-Sanitas:** Iván Pelegrín, Rosana Rouco. **Hospital HLA Inmaculada:** Jorge Parra, Violeta Ramos. **Hospital Universitario Rio Hortega:** Jessica Abadía. **Hospital de Guadalajara:** Juan Salillas, Robert Torres, Miguel Torralba, Alberto Serrano, Sergio Gilaberte, Marina Pacheco, Mónica Liébana, Sara Fernández, Álvaro Varela, Henar Calvo. **Hospital Universitario Infanta Sofía:** Patricia Martínez, Patricia González- Ruano, Eduardo Malmierca, Isabel Rábago, Beatriz Pérez-Monte. **Hospital Comarcal de Blanes:** Ángeles García, Pere Comas. **Hospital Universitari de Tarragona Joan XXIII:** Merce Sirisi, Richard Rojas. **Hospital Universitario Basurto:** José L Díaz de Tuesta, Ruth Figueroa, Ander González. **Hospital Universitario de Canarias:** Remedios Alemán, M del Mar Alonso. **Hospital Universitario de Gran Canaria Dr. Negrín:** Oscar Sanz, Karim M Ramírez. **Hospital Son Espases:** Melchor Riera, Helem H Vilchez, Francesc Albertí, Ana I Cañabate. **Hospital Universitario de Móstoles:** Víctor J Moreno, Silvia Álvarez, Beatriz Álvarez, Alejandro García, Elena Isaba, Covadonga Morcate, Andrea Pérez. **Complejo Hospitalario Universitario A Coruña:** Lucía Ramos, Laura Castelo, María Rodríguez, Mónica González, Efrén Sánchez, Enrique Míguez. **Hospital Costa del Sol:** Javier De la Torre, José M García de Lomas. **Hospital Clínico Universitario Lozano Blesa:** Elena Morte, Silvia Loscos, Ana Camón. **Hospital Mutua de Terrassa:** Lucía

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Campus Madrid: M**elania Íñigo, Alejandra Pérez. **Hospital Son Llatzer:** Patricia Sorní , Nora Izko. **Hospital General de la Defensa Gómez Ulla:** Francisco J Membrillo, María Simón, Maribel Zamora, Yolanda Martínez, Pablo Fernández-González, Francisco Alcántara, Alejandro Aguirre, Elena López, Germán Ramírez-Olivencia, Miriam Estébanez. **Hospital Universitario de Álava:** Ester Sáez de Adana, Joseba Portu, Juan C Gainzarain, Zuriñe Ortiz de Zárate, Miguel A Moran, Andrés Canut, Silvia Hernáez, Leire Balerdi, Cristina Morales, Miguel Corral, Zeltia Valcarce. **Hospital Santos Reyes:** Noelia Arenal , Raquel E Rodríguez. **Hospital Dr. José Molina Orosa:** Laura Iglesias, Beatriz Loureiro. **Hospital Vall d´Hebrón:** Adrián Sánchez, Juan Espinosa, Benito Almirante, Marta Miarons, Júlia Sellarés, María Larrosa, Sonia García, Blanca Marzo, Miguel Villamarín, Nuria Fernández. **Hospital Universitario Rey Juan Carlos:** Conchita Pérez-Jorge, Elena Resino, Andrea Espigares, Teresa Álvarez de Espejo, Iván Navas, M Isabel Quijano, Luis A Nieto, Guillermo Jiménez. **Complejo Hospitalario Universitario Santa Lucía:** Mercedes Guillamón, Josefina García. **Hospital Santa Bárbara:** Constanza Muñoz. **Complejo Hospitalario Universitario de Ferrol:** Ana Mariño, Nieves Valcarce. **Hospital de l'Esperit Sant:** Alex Smithson, Cristina Chico. **Hospital Universitario los Arcos del Mar Menor:** Adriana Sánchez, Eva P García. **Hospital HLA Universitario Moncloa:** Isabel Jiménez, Guillermo Estrada, María Lorén, Nuria Parra, Carmen Martínez, Aránzazu Villasante, Teresa García, M José Ruiz, Marta Robledo, Juan C Abad. **Hospital Virgen del Puerto:** José R Muñoz , Montaña Jiménez. **Hospital Marina Salud de Dénia:** Javier Coy, Inmaculada Poquet. **Hospital Universitario de Jerez:** Marta Santos, Virginia Naranjo. **Hospital Reina Sofía de Tudela:** Tamara Manso, Delia Quilez. **Hospital Clínico Universitario de Santiago de Compostela:** Gema Barbeito, M Jesús Domínguez. **Hospital Universitario del Henares:** Laura Mao, Rodrigo Alonso, Jose D Ampuero, Raquel Barrós, M Aránzazu Galindo, Lourdes Herrera, Rocío Martínez, Sara Rodrigo, Cristóbal M Rodríguez. **Hospital Universitario Lucus Augusti:** Eva M Romay, Roi Suárez. **Hospital de Donostia:** Maialen Ibarguren, José M Marimón, Loreto Vidaur, Xabier Kortajarena. **Hospital de Urduliz Alfredo Espinosa:** Miriam García, Asier Aranguren. **Hospital de Mendaro:** Maria Álvarez, Cintia M Martínez. **Hospital Juan Ramón Jiménez:** Francisco Rodríguez, Francisco Muñoz. **Hospital de Tortosa Virgen de la Cinta:** Elena Chamarro , Merce Cardona. **Hospital Riotinto:** Ismail Zakariya-Yousef, Marta Rico. **Hospital Vega Baja:** Jara Llenas, M Carmen Sánchez. **Hospital Puerta de Hierro:** Ana Fernández, Jorge Calderón, Marcos López, Antonio Ramos, Elena Múñez, Alejandro Callejas, José M Vázquez, Itziar Diego, Esther Expósito, Jorge Anel. **Hospital Universitario de Getafe:** Raquel Álvarez, Lucía Fernández, Roberto Vates, Andrés F Cardona, Pablo Marguenda, Gabriel Gaspar, Elena M Aranda, Blanca Martínez, Daniel Roger, Irene Martín. **Hospital General de la Palma:** André Barbosa, Iván Piñero. **Hospital El Bierzo:** Alberto Bahamonde, Paula Runza. **Fundación Hospital de Calahorra:** Eva Talavera, Marta Lamata. **Hospital Alto Deba:** Ainhoa Urrutia, Lorea Arteche. **Hospital Universitario San Juan de Alicante:** Elisabet Delgado, Virginia Molina. **Hospital de Guadarrama:** Sarah Caro, Gema Domínguez. **Hospital Universitario de Jaén:** Carolina Roldán, Carmen Herrero. **Hospital de Mataró:** Luis Force, Raquel Aranega. **Hospital de Palamós:** Arantzazu Mera, M Roca Toda. **Hospital Universitario de Valme:** Nicolas Merchante , Eva M León. **Clínica Universitaria de Navarra - Campus Navarra:** José L Del Pozo. **Hospital Clínica Benidorm:** Josefa Serralta, Ginger G Cabrera. **Hospital Doce de Octubre:** Mario Fernández-Ruiz, José M Aguado, Guillermo Maestro. **Hospital Universitario Virgen del Rocío:**

José M Cisneros, Jerónimo Pachón, Manuela Aguilar-Guisado, Teresa Aldabó, M Dolores Avilés, Claudio Bueno, Elisa Cordero-Matía, Ana Escoresca, Lydia Gálvez-Benítez, Carmen Infante, Guillermo Martín, Julia Praena, Cristina Roca, Celia Salamanca, Alejandro Suárez-Benjumea. **Hospital Universitario Ramón y Cajal:** Pilar Vizcarra, Carmen Quereda, Mario J Rodriguez, Francesca Gioia, Francesca Norman, Santos Del Campo, Rafael Cantón. **Hospital Universitario San Pedro:** José A Oteo, Paula Santibáñez, Cristina Cervera, Carlos Ruiz, José R. Blanco, José M Azcona, Concepción García, Jorge Alba, Valvanera Ibarra, Mercedes San Franco, Luis Metola. **Hospital Quirón A Coruña:** Héctor Meijide, Silvia Paulos. **HM Sanchinarro:** Justo Menéndez, Paula Villares, Lara Montes. **Hospital Francesc de Borja:** Álvaro Navarro, Anna Ferrer. **Complejo Hospitalario Universitario Nuestra Señora de La Candelaria:** M de la Luz Padilla, Lucy Abella, Marcelino Hayek, Antonio García, Carolina Hernández. **Hospital Universitario HM Montepríncipe:** Andrés J Ruiz, Isabel Barrio. **Hospital Universitario HM Puerta del Sur:** Alí Martakoush. **Hospital Universitario HM Torrelodones:** Agustín Rojas-Vieyra. **Hospital Universitario HM Madrid:** Sonia García, Mercedes Villarreal. **Hospital Don Benito-Villanueva de la Serena:** Marta Vizcaíno, M Pilar García. **Hospital de Viladecans:** Ana Lérida, Natalia Carrasco, Beatriz M Sanjuan, Lydia Martín, Camilo Sanz. **Centro Nacional de Epidemiología:** Inmaculada Jarrín, Belén Alejos, Cristina Moreno, Marta Rava, Carlos Iniesta, Rebeca Izquierdo, Inés Suárez-García, Asunción Díaz, Marta Ruiz-Alguero, Victoria Hernando.

Appendix Table 5. COVID@HULP Working Group

Scientific Committee: J Frías, AJ Carcas, E Ramírez, A Martín-Quirós, M Quintana, J Mingorance, F Arnalich, F Moreno, JC Figueiras, N García-Arenzana, JR Arribas, AM Borobia.

Microbiology Department: M Dolores Montero, MP Romero, C Toro-Rueda, S García-Bujalance, G Ruiz-Carrascoso, E Cendejas-Bueno, I Falces-Romero, F Lázaro-Perona, M Ruiz-Bastián, A Gutiérrez-Arroyo, P Girón De Velasco-Sada, E Dahdouh, B Gómez-Arroyo, C García-Sánchez, V Guedez-López, I Bloise, M Alguacil-Guillén, M Gracia Liras-Hernández, M Sánchez-Castellano, P García-Clemente, P González-Donapetry, S San José-Villar, M de Pablos, R Gómez-Gil, M Corcuera, A. Rico-Nieto, B. Loeches, J Mingorance, J García Rodríguez.

Pharmacy Department: F Moreno, A Herrero.

Laboratory Medicine Department: D Prieto Arribas, P Oliver-Saez, R Mora, P Fernández-Calle, MJ Alcaide, J Diaz-Garzón, B Fernández-Puntero, R Nuñez, G Crespo, O Rodriguez, H Mendez, M Duque, R Gomez, M Sanz de Pedro, L Pascual, M Segovia, JM Iturzaeta, M Rodriguez, A García, MA Martinez, B Fabre, E Martinez, I Moreno, N Rodriguez, D Ortiz, M Simon, IG Tomoiu, C Pizarro, B Montero, AL Qasem, M Gomez, I Casares, A Buño.

Radiology Department: M Martí de Gracia, L Parra Gordo, A Diez Tascón, S Ossaba Vélez, I Pinilla, E Cuesta, M Fernández- Velilla, M Torres, G Garzón.

Preventive Medicine Department: V Pérez, A Quintás, I San Juan, J Cantero, C Pérez, M Castro, L Hernández, T Pedraz, E Fernández, C García, A Robustillo.

Emergency Medicine Department: I Fernández, M Noguerol, A Martínez, M González, R Cabrera, R Mayayo, R Marín, V Lo-Iacono, M Lerín, P Romero, B Reche, R Tejada, M Rico, R Deza, S Fabra, I Arroyo, L Dani, L Labajo, R Soriano, L López, E Calvin, S Martñinez, L López-Tappero, M Pilares, O González, G Bejarano, A Iglesias, Y Tung, C Maroun, R Bravo, M Silvestre, F Perdomo, B Alonso, B Antón, I Arenas, C Cabré, F Marqués, E Muñoz, MA Molina, N Cancelliere, S Pastor, L Frade, P López, I García.

Internal Medicine Department: F Arnalich, C Fernández Capitán, JJ González Garcia, JM Herrero, MA Quesada Simón, A Robles Marhuenda, JI Bernardino, M Mora, C Soto Abanedes, AM Noblejas Mozo, JC Ramos, B Diaz Pollán, MJ Jaras Hernandez, E Martinez Robles, A Moreno Fernandez, R Montejano, A Sanchez Purificación, JC Martin Gutiérrez, PL Martinez Hernández, F la Calle, M Arsuaga, M Diaz Menéndez, E Trigo, C Busca Arenzana, T Sancho Bueso, A Lorenzo Hernández, B Gutierrez Sancerni, G. Salgueiro, L. Martin Carbonero, J. Mostaza, R. de Miguel, M.A. Martinez-López, V. Hontañon, A. Menéndez, J. Cadiñanos, J Alvarez Troncoso, A Castellano, C Marcelo Calvo, I Vives Beltrán, L Ramos Ruperto, G Daroca Bengoa, MM Arcos Rueda, J Vasquez Manau, P Fernández Cidón, C Rosario Herrero Gil, E Palmier Peláez, Y Untoria Tabares, C. Lahoz, E. Estirado, C Hernández, F. Garcia-Iglesias, E. Monteoliva, M Martínez, M. Varas, T. González Alegre, ME Valencia, V Moreno, ML Montes.

Neumology Department: S Alcolea, J Cabanillas, C Carpio, R Casitas, J Fernández-Bujarrabal, I Fernández Navarro, J Fernández Lahera, C García Quero, M Hidalgo, R Galera, F García Río, L Gómez Carrera, M Gómez Mendieta, A Mangas, E Martínez Cerón, M Martínez Redondo, Y Martínez Abad, A Martínez-Verdasco, C Plaza, S Quirós, D Romera, D Romero, B Sánchez, A Santiago, C Villasante, E Zamarrón, V Arnalich, P Mariscal, A Falcone, D Laorden, MC Prados, R Álvarez-Sala

Intensive Care Department: A García, C Arévalo, C Gutiérrez, JC Figueira, M Quintana, S Yus, MJ Asensio, M Sánchez, JM Añón, J Manzanares, A García de Lorenzo, E Perales, B Civantos, L Cachafeiro, A Agrifoglio, B Estébanez, E Flores, M Hernández, P Millán, M Rodríguez, C Gutiérrez, K Nanwani

Pediatric Intensive Care Department: B Arizcun, E Pérez, D Rodríguez, M Sánchez, U Quesada, C Román, P Dorao, E Alvarez-Rojas, JJ Menendez-Suso, C Verdu, A Gómez-Zamora, C Schuffelman, B Calderón, M Laplaza, M del Rio, I Amores, M Rodriguez-Rubio, P de la Oliva

Cardiology Department: J Ruiz, S Rosillo, O González, A Iniesta, I Ponz.

Anesthesiology Department: JM Muñoz Ramón, MC Hernández Gancedo, R Uña Orejón, P Sanabria Carretero, I Moreno Gomez-Limón, A Seiz-Martinez, E Guasch-Arévalo, C Martín-Carrasco, E Alvar, L Serrá, F Iannucelli, J Latorre, S Casares, I Valbuena, L Díaz Díez Picazo, C Rodríguez Roca: O Cervera, E García de las Heras, P Durán, C Castro, C Manrique de Lara, J Veganzones, A López Tofiño, E Fernandez-Cerezo, S Zurita, S Casares, M López-Martinez, T Prim, J Alvárez del Vayo, G Alcaraz, L Castro, J Yagüe, S Díaz-Carrasco, P González-Pizarro, A Montero, FJ Sagra, A Suárez.

Palliative Care Unit: L Díez Porres, M Varela Cerdeira, A Alonso Babarro.

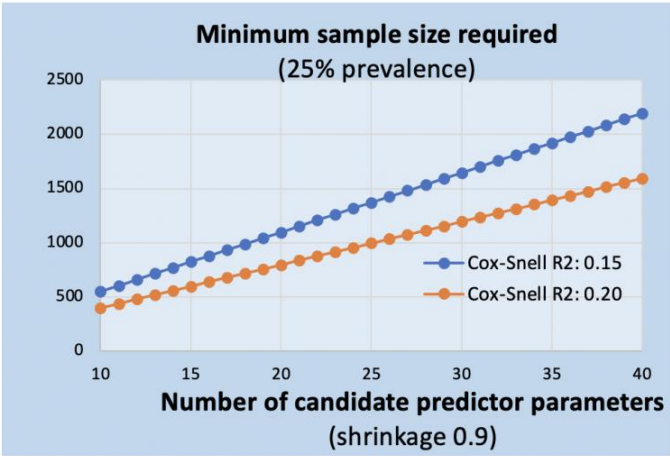
Data Entry (Medical Students): F Abellán, J Alonso, A Álvarez, M Archinà, S Arribas, T Baselga, P Barco, N Barrera, L Barrera, A Bartrina, G Bassani, P Betancort, I Blanco, C Blasco, L Brieba, F Cadenas, P Carrera, C Cascajares, A Catino, R Cavallé, D Ceniza, Y Conde, L Currás, M Daltro, A Esteban, M Fernández, I Ferrer, L Regaño, P Galindo, S Garcia-Bellido, C García-Mochales, T Gómez, C Gómez, N González, S González, J Guisández,

P Hernández, R Hernando, I Llorente, A Marín, P López, L Mejuto, M Palma, A Peña, L Platero, D Pujol, M Ramírez, M Redondo, F Reinoso, A Rodríguez, A Rodríguez, L Romero, S Sánchez, M Sánchez, P Serrano, H Serrano, T Silva, E Soria, A Suárez, B Tejero, A Torrecillas, J Torres, M Valentín-Pastrana, A Villanueva, M Virgós, M Yagüe, N Yustas.

Clinical Pharmacology Department: J Montserrat, J Queiruga, A Rodriguez Mariblanca, L Martínez de Soto, M Urroz, E Seco, M Zubimendi, S Stuart, L Díaz, I García.

Data management: MT García Morales, A Martín-Vega

Appendix Figure 1. Sample size Calculation*



	Minimum sample size required (shrinkage of 0.9 and 25% prevalence)	
Parameters	Cox-Snell R^2: 0.15	Cox-Snell R^2: 0.20
10	549	398
15	823	597
20	1,097	796
25	1,372	995
30	1,646	1,194
35	1,920	1,393
40	2,194	1,592

To estimate a 30-parameter logistic model with a shrinkage of 0.9, a prevalence of events of 25% and assuming a Cox-Snell R^2 of 0.15, 1,646 individuals would be needed, approximately 14 events per variable. In our study, the estimated models were carried out with much higher sample size and 30 parameters were never exceeded, despite the categorization of some independent variables such as age.

*Riley RD, Ensor J, Snell KIE, Harrell FE, Jr., Martin GP, Reitsma JB, et al.
Calculating the sample size required for developing a clinical prediction model.
BMJ. 2020;368:m441.
Epub 2020/03/20. doi: 10.1136/bmj.m441. PubMed PMID: 32188600.