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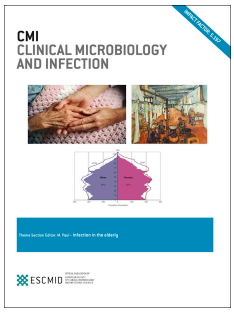


Predicting critical illness on initial diagnosis of COVID-19 based on easily-obtained clinical variables: development and validation of the PRIORITY model

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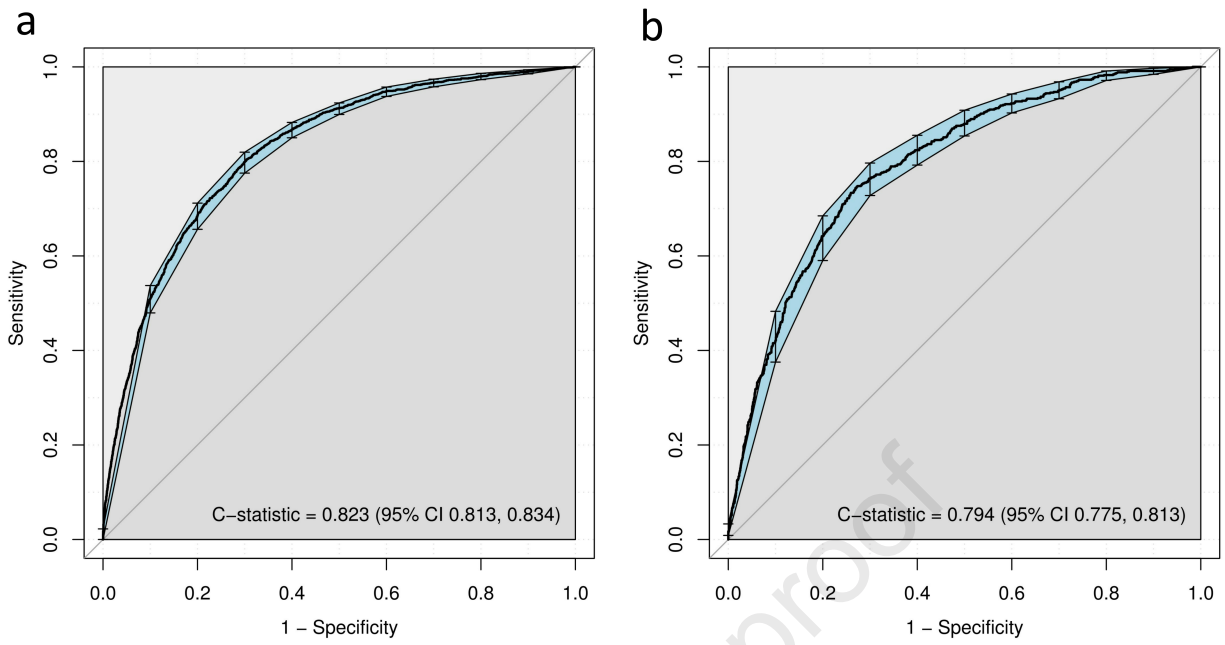

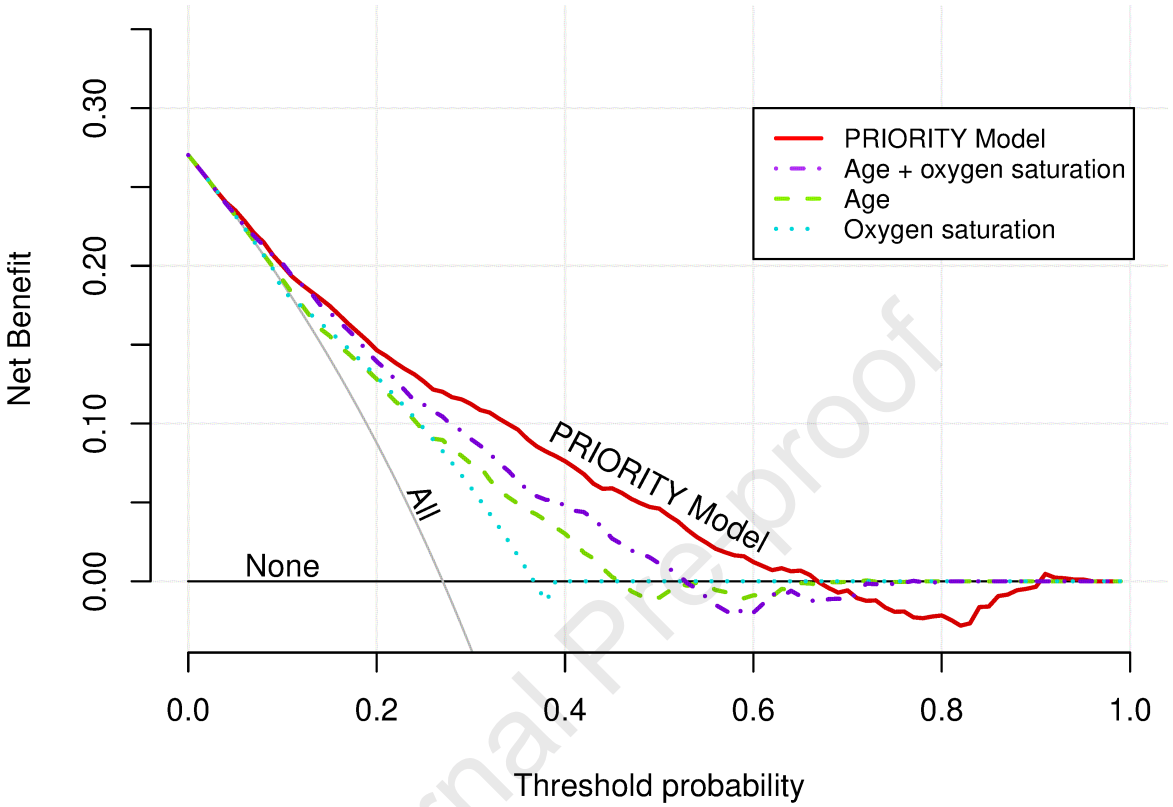

**TITLE**

# Predicting critical illness on initial diagnosis of COVID-19 based on easily-obtained clinical variables: Development and validation of the PRIORITY model

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Drs. Martinez-Lacalzada and Viteri-Noël contributed equally to the manuscript.

**Objectives**

We aimed to develop and validate a prediction model, based on clinical history and examination findings on initial diagnosis of COVID-19, to identify patients at risk of critical outcomes.

**Methods**

We used data from the SEMI-COVID-19 Registry, a cohort of consecutive patients hospitalized for COVID-19 from 132 centers in Spain (23 March to 21 May, 2020). For the development cohort tertiary referral hospitals were selected, while the validation cohort included smaller hospitals. The primary outcome was a composite of in-hospital death, mechanical ventilation or admission to intensive care unit. Clinical signs and symptoms, demographics, and medical history ascertained at presentation were screened using least absolute shrinkage and selection operator, and logistic regression was used to construct the predictive model.

**Results**

There were 10,433 patients, 7,850 in the development cohort (primary outcome 25.1%, 1,967/7,850) and 2,583 in the validation cohort (outcome 27.0%, 698/2,583). The PRIORITY model included: age, cardiovascular disease, chronic kidney disease, dyspnea, tachypnea, confusion, systolic blood pressure, and $SpO_2 \leq 93\%$ or oxygen requirement. The model showed high discrimination for critical illness in both the development (C-statistic 0.823; 95% confidence interval [CI] 0.813, 0.834) and validation (C-statistic 0.794; 95% CI 0.775, 0.813) cohorts. A freely available web-based calculator was developed based on this model (https://www.evidencio.com/models/show/2344).

**Conclusions**

The PRIORITY model, based on easily-obtained clinical information, had good discrimination and generalizability for identifying COVID-19 patients at risk of critical outcomes.

## INTRODUCTION

Coronavirus disease 2019 (COVID-19) has spread globally, with a clinical spectrum ranging from an asymptomatic state to critical illness [1-3]. Notably, Spain was one of the countries with the highest incidence of COVID-19 during the first pandemic peak [4]. To optimize the use of limited healthcare resources, it would be essential to identify, as early as possible, those patients who are at high risk of progressing to critical illness.

To date, studies of COVID-19 prognostic factors have focused on laboratory measurements and radiological examinations obtained following admission [5-15], which are not available in outpatient or resource-limited settings. Recently published well-developed models tend not to include clinical variables obtained from history and examination carried out on initial assessment [9-13]. Where one machine learning model has addressed basic clinical features, it has narrowed down the prediction to the mortality outcome only and lacks wider generalizability [16]. Furthermore, a critical appraisal of the COVID-19 models has shown poor reporting and high risk of bias [14].

Prediction models based on easy-to-collect data have previously been developed for other infectious diseases, e.g. meningitis and pneumonia [17-19]. As a global health emergency, management of COVID-19 would benefit from a prediction model that could be readily applied for initial diagnosis. Therefore, we developed and externally validated a prediction model, based on easily obtained clinical measures at presentation with confirmed COVID-19 diagnosis, to identify patients at risk of developing critical outcomes.

## METHODS

### Study design and data source

This study was based on the SEMI (Sociedad Española de Medicina Interna) COVID-19 Registry [20]. It is an ongoing multicenter nationwide cohort of consecutive patients hospitalized for COVID-19 across Spain. Eligibility criteria were age ≥ 18 years, confirmed diagnosis of COVID-19, defined as a positive result on real-time reverse-transcription-polymerase-chain-reaction (RT-PCR) for the presence of SARS-CoV-2 in nasopharyngeal swab specimens or sputum samples, first hospital admission for COVID-19, and hospital discharge or in-hospital death [20]. The SEMI-COVID-19 Registry was approved by the Provincial Research Ethics Committee of Málaga (Spain) and the Institutional Research Ethics Committees of each participating hospital.

For the study, we retrieved from the Registry clinical baseline data, history of previous medication, and comorbidities collected on admission, as well as complications during hospitalization and status at discharge. We used data from patients admitted in 132 hospitals between March 23 and May 21, 2020. We chose hospital complexity as the criterion to assess the transportability of the prognostic model in a setting other than the one in which it was derived [21, 22]. Patients admitted to tertiary referral hospitals (≥300 beds, according to the Ministry of Health of Spain [23]) were selected for the development cohort, while patients from smaller hospitals (<300 beds) were included in a separate validation cohort.

**Outcome description**

The primary outcome, critical illness during hospitalization, was defined as the composite of in-hospital death, mechanical ventilation or admission to intensive care unit (ICU), according to previously published studies [10, 24-25].

**Potential predictors**

To develop a predictive model based only on easily measurable variables registered at admission, we

considered clinical signs and symptoms, demographic variables, and medical history. An initial list of 29 candidate variables was selected based on review of the existing evidence [5-16], clinical plausibility and relevance to clinical care. To improve consensus on model applicability, a 1-round online questionnaire was conducted among a multidisciplinary panel of 24 physicians involved in COVID-19 clinical management at nursing homes, emergency departments, primary care centers and hospitalization wards (6 per each setting). The panelists were asked to rate (on a 9-point Likert scale) the availability/reliability of each predictor, its ability to predict the outcome, the best way to merge predictors of rare occurrence, and the maximum number of variables the model should contain. Agreement was considered when ≤7 panelists rated outside the 3-point region containing the median [26].

**Statistical analysis**

The predictive model, called PRIORITY, was presented as the formula for estimating the probability of COVID-19 critical illness outcome, as well as an associated web-based calculator. Patients' characteristics were summarized as frequencies and percentages or mean and standard deviation. Statistical analysis was performed using R v4.0.0, with mice, mfp, glmnet, pROC, rms and rmda packages.

*Model development:* Missing values in the potential predictors were imputed using single imputation, a reasonable alternative to multiple imputation when dealing with relatively few missings [27]. A stochastic single imputation dataset was created for both cohorts (development and validation) through multiple imputation by chained equations. Quantitative variables were kept as continuous to avoid loss of prognostic information, and non-linear relationships were modelled by multivariate fractional polynomials with a maximum of 2 degrees of freedom [28]. The least absolute shrinkage and selection operator (LASSO) was the feature selection method used to reduce the number of predictors down to

the maximum agreed by the expert panel [29]. Briefly, the potential predictors were entered into the LASSO regularization process, which penalizes the coefficients by gradually shrinking them to zero. We selected the penalty parameter (λ) that minimized the deviance within the given maximum number of predictors. Those variables with non-zero coefficients were retained for risk estimation using a logistic regression model. Coefficients were presented as odds ratios (OR) and 95% confidence intervals (CI).

*Model performance:* Nagelkerke's $R^2$ and Brier score were used as overall performance measures. We assessed the discriminative ability of the model using the C-statistic, calculated as the area under the Receiver Operating Characteristic curve, with 95% CI. Calibration of the model was visually assessed by plotting deciles of predicted vs. observed probabilities, and the calibration slope with 95% CI was calculated [22].

*Model validation:* Internal validation was carried out to assess optimism-corrected performance by repeating the entire model development over 1,000 bootstrap samples drawn from the development cohort [27]. We externally validated the model in a separate cohort of patients admitted at less-complex hospitals to evaluate model transportability [21]. Within this validation cohort, we reassessed model performance and compared its discrimination ability with models based on oxygen saturation and/or age, the most discriminating univariate predictors for in-hospital mortality previously reported [15]. We also undertook a decision curve analysis, a method to ascertain the adequacy of prediction models based on the relative value of benefits (true positives) and harms (false positives) [30]. We plotted the net benefit of the models for the full range of critical illness probability thresholds.

*Sensitivity analysis:* To assess the impact of assumptions adopted in the model development, we carried out a complete-case analysis, using only those patients with complete data in the potential predictors. We also developed models without restricting the maximum number of predictors (λ at one-standard-error of the minimum) or using linear continuous predictors instead of non-linear terms.

## RESULTS

We considered data from 10,433 patients included in the SEMI-COVID-19 Registry. The development cohort included 7,850 patients, of which 1,967 (25.1%) presented critical illness (650 [8.3%] admitted to the ICU and 1,598 [20.4%] died). The mean age was 65.8 ± 16.4 years and 57.2% (4,483/7,834) were male, ageusia/anosmia, asthenia/anorexia, headache, gastrointestinal symptoms were excluded. Consensus was achieved for including a range between 5 and 9 variables in the final model. For transparency, univariate analysis is shown on *Supplementary Table S1*, even though it was not part of the model development process. The 21 potential predictors were included in the LASSO selection process, retaining a subset of 9 variables as the best predictors of critical illness (*Supplementary Figure S1*). A multivariable logistic regression model was then fitted with these 9 variables. All of them, except for moderate or severe dependency, were statistically significant (*Table 2*).

Based on the logistic regression model, the probability of critical COVID-19 illness could be calculated as:

Probability (%) = 100/(1 + exp(-z)), where z = -4.665 + 2.663·[(Age/100)$^2$] + 0.164·[Dependency] + 0.316·[Cardiovascular disease] + 0.586·[Chronic kidney disease] + 0.504·[Dyspnea] + 0.844·[1/(SBP/100)$^2$] + 0.911·[Tachypnea] + 1.200·[$SpO_2$ ≤ 93% or oxygen requirement] + 0.681·[Confusion].

All predictors were coded as binary variables (1 when present and 0 when absent) except for age (years) and systolic blood pressure (SBP, mmHg). We also developed an online calculator based on this model (*Supplementary Figure S2*), accessible at https://www.evidencio.com/models/show/2344.

In the development cohort, the PRIORITY model had an $R^2$ of 0.347 and a Brier score of 0.138. The apparent C-statistic was 0.823 (95% CI 0.813, 0.834) (*Figure 1a*). After bootstrap internal validation, optimism-corrected C-statistic was 0.821 (95% CI 0.810, 0.832). The model showed good calibration

184 across the range of predicted probabilities within the development cohort (calibration slope 0.996, 95%
185 CI 0.989, 0.999; *Supplementary Figure S3a*).

186 **External validation**

187 The validation cohort included 2,583 patients, of which 698 (27.0%) presented critical illness (200 [7.7%]
188 admitted to the ICU and 594 [23.0%] died). The mean age was 69.5 ± 16.0 years, 54.8% (1,415/2,580)
189 were male (*Table 1*). The PRIORITY model showed good discrimination for critical illness within the
190 validation cohort (C-statistic 0.794, 95% CI 0.775, 0.813) (*Figure 1b*), and a calibration slope of 0.875,
191 95% CI 0.790, 0.960 (*Supplementary Figure S3b*).

192 Our model compared well against the risk stratification based on univariate models including age (C-
193 statistic 0.707, 95% CI 0.686, 0.729) or $SpO_2$≤93%/oxygen requirement at admission (C-statistic 0.652,
194 95% CI 0.635, 0.670) as sole predictors. Likewise, the PRIORITY model had better discrimination ability
195 than the model including both age and $SpO_2$≤93%/oxygen supply (C-statistic 0.751, 95% CI 0.731, 0.771).

196 Additionally, decision curve analysis showed that the PRIORITY model had higher net benefit across a
197 wide range of threshold probabilities for developing critical illness compared to risk stratification using
198 age and/or $SpO_2$≤93%/oxygen supply (*Figure 2*).

199 **Sensitivity analysis**

200 We carried out a complete-case analysis selecting as development cohort the 5,513 patients with
201 complete data on the 21 potential predictors and the outcome. The resulting model had the same
202 predictors as the PRIORITY model with apparent C-statistic 0.813 (95% CI 0.800, 0.826) and calibration
203 slope 0.993 (95% CI 0.986, 0,997). Next, we fitted a new model with no restriction in maximum number
204 of variables, resulting in a model which added sex, diabetes mellitus, malignancy, immunocompromised

status, pulmonary rales, and heart rate cubed to the predictors in the PRIORITY model. C-statistic was 0.831 (95% CI 0.821, 0.842) and slope 0.990 (95% CI 0.986, 0,996). Likewise, we fitted an alternative model using linear continuous predictors instead of non-linear terms, which included sex but excluded the systolic blood pressure. C-statistic was 0.823 (95% CI 0.812, 0.833) and slope 0.994 (95% CI 0.988, 0.999).

## DISCUSSION

We developed and validated a new clinical risk model to predict COVID-19 critical illness based on nine simple clinical features easily available on initial assessment, which would be useful in resource-limited or out-of-hospital settings without access to other complementary tests. The model was well calibrated, had good discrimination, and performed robustly in an external validation cohort. Moreover, it showed a potential clinical benefit in a variety of scenarios covering different healthcare situations over a range of threshold probabilities for critical illness. The web-based calculator can facilitate its immediate application for frontline clinicians.

Previously, an external validation of 22 prognostic models showed that none of the multivariate models offered incremental value for patient stratification compared to oxygen saturation or age [15]. In this regard, the PRIORITY model showed higher discriminative ability and net benefit than age and/or oxygen saturation. Additionally, despite its simplicity, our model had a similar performance to previously published prognostic tools including laboratory and imaging tests [9-16].

It is worth noting that the PRIORITY model could be applied in triage, using easily measurable variables available in settings without access to laboratory or radiology tests, identifying high-risk patients for referral to hospital. This model could be useful for supporting clinical management decisions over a range of risk thresholds for critical illness which could be considered as relevant in clinical practice. The

choice of thresholds will vary across different regions, according to changing epidemiological situations and availability of health resources. For example, under pandemic peak pressure or low-resource healthcare systems, policy-makers may consider a cut-off point up to 20%, a threshold that will be associated with higher reduction in unnecessary critical care admissions. However, at low risk of overwhelming the critical care capacity, a lower threshold may be considered at the expense of unnecessary referrals. We recommend objectively defining specific cut-off points considering the circumstances and the availability of health resources.

This study has several methodological strengths maximizing internal and external validity [23]. To the best of our knowledge, this is the first generalizable COVID-19 predictive model built with simple clinical information excluding imaging and laboratory data. We developed and validated the model in a large multicenter, national cohort. The methodology was rigorous, avoiding data-driven predictor selection and biases that affected previous studies [14]. The practical application of the model was maximized by forging an agreement among an expert panel on key issues. Moreover, the model was validated in a separate cohort of patients admitted in smaller hospitals, showing transportability to a setting with a different level of healthcare [21, 22].

The strength of our findings should be interpreted in light of some limitations. First, although we carefully selected easily available clinical and demographic variables, the data were collected at the time of hospital admission, which represents an important selection bias that would require further studies in an outpatient setting. Second, it could be suggested that, taking into account the situation of healthcare pressure, data quality may be affected. In this regard, it is notable that in this study missing data were relatively low and we used imputation to reduce their impact. Third, since the COVID-19 pandemic has demonstrated significant differences between countries and time periods, it could affect the applicability of the model to other settings. However, we considered this early pandemic period in Spain

to reflect a scenario with an overwhelmed healthcare system, where our predictive model could be particularly useful. Nevertheless, further studies introducing factors such as viral strains, healthcare system actions, new treatments, or vaccination, could improve the applicability of the PRIORITY model. Lastly, even though we compared the net benefit of using the model with discrimination based on oxygen saturation and/or age, its real clinical usefulness would require comparison with the best existing scores or the clinician's decision.

In summary, we developed and validated a new prediction model, called PRIORITY, to estimate the risk of critical illness in patients with COVID-19 based on nine clinical variables easily measurable in resource-limited or out-of-hospital settings. The study could provide underpinning evidence to inform decision-making in health systems under pandemic pressure.

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## AUTHORS CONTRIBUTIONS

MML, LAVN and MFF planned, conceived the study, analysed and interpreted the data. MML, LAVN, MFF and LM wrote the original draft of the manuscript. MRR, SLG, FAF, JLBP, JAVN, ECM, ACEA, SJFC, JLA, PMPF, AP, AMAS, ASA, BGL, JLP, JSC, PCP, GMGG, JMNC, JMCR and RGH contributed to read and approved the final version of the manuscript. MML and LAVN are joint first authors. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted. LM is the guarantor.

## TRANSPARENCY DECLARATION

The correspondent author affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

## DISSEMINATION TO PARTICIPANTS AND RELATED PATIENT AND PUBLIC COMMUNITIES

Results of this study have been made available to the public through an open access preprint posted to MedRxiv (doi: 10.1101/2020.11.27.20237966). The Spanish Society of Internal Medicine (SEMI) shares the results of the studies derived from the SEMI-COVID-19 Registry through its public facing website (https://www.fesemi.org/investigacion/proyectos/registro-semi-covid-19) and its twitter account (@Sociedad_SEMI).

## DATA SHARING

The data that support the findings of this study are available on request from the SEMI-COVID-19

294 Scientific Committee and the Registry Coordinating Center.

295

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298 **DISCLOSURES**

299 The authors declare no conflict of interest.

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302 **REFERENCES:**

303 1 Docherty AB, Harrison EM, Green CA, et al. Features of 20 133 UK patients in hospital with covid-19
304 using the ISARIC WHO Clinical Characterisation Protocol: prospective observational cohort study.
305 *BMJ* 2020;369:m1985.

306 2 Guan W, Ni Z, Hu Y, et al. Clinical Characteristics of Coronavirus Disease 2019 in China. *N Engl J Med*
307 2020;382:1708-20.

308 3 WHO. COVID-19 situation reports. https://www.who.int/emergencies/diseases/novel-coronavirus-
309 2019/situation-reports. Accessed May 24, 2021.

310 4 Ministerio De Sanidad, Consumo y Bienestar Social. Enfermedad por el coronavirus (COVID-19). (in
311 Spanish).
312 https://www.mscbs.gob.es/en/profesionales/saludPublica/ccayes/alertasActual/nCov/documentos
313 /Actualizacion_288_COVID-19.pdf. Accessed May 28, 2021.

314 5 Wang D, Hu B, Hu C, et al. Clinical Characteristics of 138 Hospitalized Patients with 2019 Novel
315 Coronavirus-Infected Pneumonia in Wuhan, China. *JAMA* 2020;323:1061-9.

316 6 Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-
317 19 in Wuhan, China: a retrospective cohort study. *Lancet* 2020;395:1054-62.

318 7 Richardson S, Hirsch JS, Narasimhan M, et al. Presenting Characteristics, Comorbidities, and
319 Outcomes Among 5700 Patients Hospitalized With COVID-19 in the New York City Area. *JAMA*
320 2020;323:2052-9.

8 Berenguer J, Ryan P, Rodríguez-Baño J, et al. Characteristics and predictors of death among 4,035 consecutively hospitalized patients with COVID-19 in Spain. *Clin Microbiol Infect* 2020;26: 1525-36.

9 Fumagalli C, Rozzini R, Vannini M, Coccia F, et al. Clinical risk score to predict in-hospital mortality in COVID-19 patients: a retrospective cohort study. *BMJ Open* 2020;10:e040729.

10 Liang W, Liang H, Ou L et al. Development and Validation of a Clinical Risk Score to Predict the Occurrence of Critical Illness in Hospitalized Patients With COVID-19. *JAMA Intern Med* 2020;180:1081-9.

11 Ji D, Zhang D, Xu J, Chen Z, et al. Prediction for Progression Risk in Patients with COVID-19 Pneumonia: the CALL Score. *Clin Infect Dis* 2020;71:1393-9.

12 Knight SR, Ho A, Pius R, Buchan I et al. Risk stratification of patients admitted to hospital with covid-19 using the ISARIC WHO Clinical Characterisation Protocol: development and validation of the 4C Mortality Score. *BMJ* 2020;370:m3339.

13 Bartoletti M, Giannella M, Scudeller L, et al. Development and validation of a prediction model for severe respiratory failure in hospitalized patients with SARS-Cov-2 infection: a multicenter cohort study (PREDI-CO study). *Clin Microbiol Infect* 2020;26:1545-53.

14 Wynants L, Van Calster B, Collins GS, et al. Prediction models for diagnosis and prognosis of COVID-19 infection: systematic review and critical appraisal. *BMJ* 2020;369:m1328.

15 Gupta RK, Marks M, Samuels T, et al. Systematic Evaluation and External Validation of 22 Prognostic Models among Hospitalised Adults with COVID-19: An Observational Cohort Study. *Eur Respir Journal* 2020;56:2003498.

16 Yadaw AS, Li YC, Bose S, Iyengar R, Bunyavanich S, Pandey G. Clinical features of COVID-19 mortality: development and validation of a clinical prediction model. *Lancet Digit Health* 2020;2:e516-25.

17 Ajayi-Obe EK, Lodi E, Alkali AS et al. Prognostic scores for use in African meningococcal epidemics. *Bull World Health Organ 1*998;76:149-52.

18 Bassat Q, Lanaspa M, Machevo S, et al. Hypoxaemia in Mozambican children <5 years of age admitted to hospital with clinical severe pneumonia: clinical features and performance of predictor models. *Trop Med Int Health* 2016;21:1147-56.

19 Lanaspa M, Valim C, Acacio S, et al. High reliability in respiratory rate assessment in children with respiratory symptomatology in a rural area in Mozambique. *J Trop Pediatr* 2014;60:93-8.

20 Casas Rojo JM, Antón Santos JM, Nuñez-Cortés J, et al. Clinical characteristics of patients hospitalized with COVID-19 in Spain: Results from the SEMI-COVID-19 Network. *Rev Clin Esp* 2020;220:480-94.

21 Justice AC, Covinsky KE, Berlin JA. Assessing the generalizability of prognostic information. *Ann Intern Med* 1999;130:515-24.

22 Steyerberg E.W, Vergouwe Y. Towards better clinical prediction models: seven steps for development and an ABCD for validation. Eur Heart J 2014;35:1925-31.

23 Ministerio de Sanidad, Consumo y Bienestar Social. Certificates of Discharge of the National Health System Register. CMBD. State Regulation. (in Spanish). https://www.mscbs.gob.es/en/estadEstudios/estadisticas/cmbd.htm. Accessed May 25, 2021.

24 Metlay JP, Waterer GW, Long AC, et al. Diagnosis and treatment of adults with community-acquired pneumonia. An official clinical practice guideline of the American Thoracic Society and Infectious Diseases Society of America. *Am J Respir Crit Care Med* 2019;200:e45-67.

25 Evangelidis, Nicole Tong A, Howell M, et al. International Survey to Establish Prioritized Outcomes for Trials in People With Coronavirus Disease 2019. *Critical Care Medicine* 2020;48:1612-21.

26 Fitch K, Bernstein S, Aguilar MD, Burnand B, LaCalle JR, Lazaro P, et al. The RAND/UCLA Appropriateness Method User's Manual. 1st ed. Santa Monica, CA: RAND Corporation, 2001.

27 Steyerberg EW. Clinical Prediction Models: A Practical Approach to Development, Validation and Updating. 2nd ed. New York: Springer, 2019.

28 Royston P, Altman DG. Regression using fractional polynomials of continuous covariates: parsimonious parametric modelling. *Appl Stat* 1994;43:429–67.

29 Hastie T, Tibshirani R, Friedman JH. The elements of statistical learning: data mining, inference, and prediction. 2nd ed. New York: Springer, 2009.

30 Vickers AJ, Elkin EB. Decision curve analysis: a novel method for evaluating prediction models. *Med Decis Making* 2006;26: 565-74.

## TABLES

**Table 1. Demographic and clinical characteristics among patients included in the development and validation cohorts.**

| | | Development cohort | | Validation cohort | |
|---|---|---|---|---|---|
| | | No of patients (%) or mean ± SD | Total No (%) | No of patients (%) or mean ± SD | Total No (%) |
| **Characteristics of the population** | | | | | |
| Critical illness | | 1967 (25.1%) | 7850 (100%) | 698 (27.0%) | 2583 (100%) |
| Age [years] | | 65.8 ± 16.4 | 7816 (99.6%) | 69.5 ± 16.0 | 2575 (97.3%) |
| Male | | 4483 (57.2%) | 7834 (99.8%) | 1415 (54.8%) | 2580 (99.9%) |
| Ethnicity | Caucasian | 6836 (89.1%) | 7677 (98.8%) | 2340 (91.0%) | 2572 (99.6%) |
| | Latino | 693 (9.0%) | | 193 (7.5%) | |
| | Other | 148 (1.9%) | | 39 (1.5%) | |
| Smoking history | Never | 5270 (70.9%) | 7433 (94.7%) | 1625 (65.7%) | 2475 (95.8%) |
| | Former smoker | 1764 (23.7%) | | 718 (29.0%) | |
| | Active Smoker | 399 (5.4%) | | 139 (5.3%) | |
| **Medical history** | | | | | |
| Obesity | | 1665 (23.7%) | 7012 (89.3%) | 584 (24.3%) | 2401 (93.0%) |
| Hypertension | | 3803 (48.6%) | 7833 (99.8%) | 1444 (56.1%) | 2576 (99.7%) |
| Diabetes mellitus | | 1440 (18.4%) | 7820 (99.6%) | 509 (19.8%) | 2570 (99.5%) |
| Cardiovascular disease | | 1974 (25.3%) | 7800 (99.4%) | 806 (31.7%) | 2545 (98.5%) |
| Pulmonary diseases | | 1625 (20.9%) | 7776 (99.1%) | 576 (22.6%) | 2583 (98.9%) |
| Severe chronic kidney disease | | 488 (6.2%) | 7825 (99.7%) | 163 (6.3%) | 2583 (99.7%) |
| Malignancy | | 793 (10.2%) | 7803 (99.4%) | 259 (10.1%) | 2571 (99.5%) |
| Immunocompromised status | | 650 (8.6%) | 7549 (96.2%) | 187 (7.6%) | 2473 (95.7%) |
| Dependency (moderate/severe) | | 1129 (14.7%) | 7701 (98.1%) | 605 (23.7%) | 2555 (98.9%) |
| **Symptoms at admission** | | | | | |
| Fever | | 5138 (67.0%) | 7663 (97.6%) | 1670 (65.6%) | 2544 (98.5%) |
| Dyspnea | | 4427 (56.7%) | 7805 (99.4%) | 1523 (59.4%) | 2562 (99.2%) |
| **Clinical signs and physical exploration at admission** | | | | | |
| SBP [mmHg] | | 129.0 ± 21.5 | 7430 (94.6%) | 127.6 ± 21.0 | 2451 (94.9%) |
| HR [beats/minute] | | 88.6 ± 17.4 | 7500 (95.5%) | 87.5 ± 17.5 | 2504 (96.9%) |
| Tachypnea (> 20 breaths/min) | | 2271 (29.9%) | 7604 (96.9%) | 879 (35.1%) | 2504 (96.9%) |
| $SpO_2$ ≤ 93% or oxygen requirement at presentation | | 4152 (52.9%) | 7842(99.9%) | 1605 (62.1%) | 2583 (100%) |
| Pulmonary rales | | 4630 (60.7%) | 7626 (97.1%) | 1588 (63.6%) | 2495 (96.6%) |
| Confusion | | 849 (11.0%) | 7736 (98.5%) | 384 (15.1%) | 2546 (98.6%) |

SD: standard deviation.

Obesity is defined as Medical history or body mass index ≥ 30 kg/$m^2$.
Cardiovascular disease: history of cerebrovascular disease, peripheral arterial disease, myocardial infarction, angina pectoris, heart failure or atrial fibrillation.
Pulmonary diseases: chronic obstructive pulmonary disease, obstructive sleep apnea/hypopnea syndrome and asthma.
Severe chronic kidney disease: History of serum creatinine level > 3 mg/dl or history of dialysis.
Malignancy: History of solid tumor, leukemia or lymphoma.
Immunocompromised status: History of autoimmune diseases, solid organ transplant recipients, HIV infection or previous immunosuppressive treatment including systemic steroids.
Dependency (moderate/severe): moderate or severe dependency for activities of daily living (Barthel index score <60).Fever: Temperature ≥ 38°C or history of fever.
HR: Heart rate.
SBP: Systolic blood pressure.
$SpO_2$: Peripheral oxygen saturation.

**Table 2. Multivariate logistic regression of critical illness prediction in COVID-19.**

| Predictors | Odds ratio | 95% CI |
|---|---|---|
| $(Age/100)^2$ [Age in years]* | 14.339 | 10.054, 20.532 |
| Cardiovascular disease | 1.372 | 1.195, 1.573 |
| Severe chronic kidney disease | 1.797 | 1.433, 2.252 |
| Dyspnea | 1.655 | 1.451, 1.891 |
| $1/(SBP/100)^2$ [SBP in mmHg]* | 2.326 | 1.837, 2.951 |
| Tachypnea (>20 breaths/min) | 2.487 | 2.192, 2.824 |
| $SpO_2 \leq 93\%$ or oxygen requirement | 3.320 | 2.889, 3.819 |
| Confusion | 1.976 | 1.642, 2.380 |
| Dependency (Moderate or severe) | 1.178 | 0.989, 1.404 |

Predictors in the PRIORITY model retained after LASSO feature selection. Model coefficients were derived from a multivariate logistic regression, and presented as odds ratios (OR) and 95% confidence intervals (95% CI).
Variables entered into the LASSO feature selection process were: age as a squared term, sex, ethnicity, smoking history, obesity, hypertension, diabetes mellitus, cardiovascular disease, pulmonary diseases, severe chronic kidney disease, malignancy, immunocompromised status, dependency, fever, dyspnea, systolic blood pressure (SBP) as the inverse of a quadratic term, heart rate (HR) as a cubic term, tachypnea, peripheral oxygen saturation ($SpO_2$) ≤ 93% on room air or oxygen requirement at presentation, pulmonary rales, and confusion. All predictors were coded as binary variables (1 when present and 0 when absent) except for age (years), SBP (mmHg) and HR (bpm).
* Continuous predictors modelled as fractional polynomial terms, including rescaling when the range of values of the predictor was reasonably large. As interpretability of the effect of non-linear continuous predictors can be difficult, linear local approximations of ORs for 10-unit variations are provided at selected values.
ORs for age (10-year increments): OR (50/40) = 1.271; OR (70/60) = 1.414; OR (90/80) =1.573.
ORs for SBP (10 mmHg decreases): OR (110/120) = 1.118; OR (90/100) = 1.219; OR (70/80) = 1.497.
Approximated ORs are provided for illustrative purposes only and were not used for making predictions.

## FIGURE LEGENDS

Figure 1. Discriminatory ability of the PRIORITY model in the development (a) and validation (b) cohorts. Discriminative ability was assessed using the C-statistic, as the area under the Receiver Operating Characteristic curve, with 95% confidence intervals (CI) computed with 1,000 bootstrap replicates.

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415 Figure 2. Decision curve analysis within the validation cohort. Clinical usefulness of the PRIORITY model
416 compared to risk stratification based on oxygen saturation (binary: $SpO_2 \leq 93\%$ or oxygen requirement)
417 and/or age (quadratic term). The x-axis represents the whole range of decision threshold probabilities
418 for critical illness ($p_t$) and the y-axis the net benefit (NB). NB calculated as: True positives/N – (False
419 positives/N)*($p_t$/(1-$p_t$)), with N total sample size.

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