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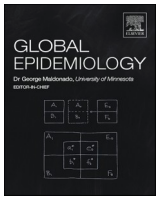

ACCREDIT: Validation of clinical score for progression of COVID-19 while hospitalized

Vinicius Lins Costa Ok Melo , Pedro Emmanuel Alvarenga Americano do Brasil, PhD *

Instituto Nacional de Infectologia Evandro Chagas, Fundação Oswaldo Cruz, Brazil

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ABSTRACT

COVID-19 is no longer a global health emergency, but it remains challenging to predict its prognosis.
Objective: To develop and validate an instrument to predict COVID-19 progression for critically ill hospitalized patients in a Brazilian population.
Methodology: Observational study with retrospective follow-up. Participants were consecutively enrolled for treatment in non-critical units between January 1, 2021, to February 28, 2022. They were included if they were adults, with a positive RT-PCR result, history of exposure, or clinical or radiological image findings compatible with COVID-19. The outcome was characterized as either transfer to critical care or death. Predictors such as demographic, clinical, comorbidities, laboratory, and imaging data were collected at hospitalization. A logistic model with lasso or elastic net regularization, a random forest classification model, and a random forest regression model were developed and validated to estimate the risk of disease progression.
Results: Out of 301 individuals, the outcome was 41.8 %. The majority of the patients in the study lacked a COVID-19 vaccination. Diabetes mellitus and systemic arterial hypertension were the most common comorbidities. After model development and cross-validation, the Random Forest regression was considered the best approach, and the following eight predictors were retained: D-dimer, Urea, Charlson comorbidity index, pulse oximetry, respiratory frequency, Lactic Dehydrogenase, RDW, and Radiologic RALE score. The model's bias-corrected intercept and slope were − 0.0004 and 1.079 respectively, the average prediction error was 0.028. The ROC AUC curve was 0.795, and the variance explained was 0.289.
Conclusion: The prognostic model was considered good enough to be recommended for clinical use in patients during hospitalization (https://pedrobrasil.shinyapps.io/INDWELL/). The clinical benefit and the performance in different scenarios are yet to be known.

Introduction

COVID-19 may be asymptomatic to severe and lead to death [1]. From December 2019 up to December 2022, 601 million cases and 6.4 million deaths occurred worldwide and health systems around the world were overwhelmed [2,3], especially due to its behavior in waves [4]. COVID-19 progression rate to critically ill among not vaccinated was estimated to be 22.9 % [5]. Estimated risk among those not vaccinated for intensive care unit (ICU) admission, mechanical ventilation, and overall mortality were 10.96 %, 7.1 %, and 5.6 % respectively [5].

There are different time trends of hospitalizations, critical care admissions, and deaths from COVID-19 throughout the pandemic. After population vaccination, there was a decrease in critical unit admissions and deaths [6]. In adults over 50 years, there was a lower relative risk of intensive care unit (ICU) admission of 23.3 % and 24.3 % when comparing the peaks of Ômicron vs Alpha and Ômicron vs Delta variants, respectively. When comparing the Ômicron to previous waves, deaths and, ICU admissions were 4.5 % vs 21.3 % and 1 % vs 4.3 % respectively [7], changing to a profile of high dissemination and a decreasing number of hospitalizations and deaths [6]. However, this interpretation is confounded mainly by age and the number and type of comorbidities, and vaccines seem to not affect hospital outcomes in adjusted analysis from primary data [8,9] and from secondary data [10]. Hospital prognosis may also be confounded by vaccine doses, vaccine types, and SARS-CoV-2 variants [11].

Early identification of patients at higher risk for disease progression at the first evaluation despite the vaccination status, or antiviral use could aid decision-making. Diagnostic and prognostic tools were

* Corresponding author at: Av. Brasil, 4365 - Manguinhos, Rio de Janeiro CEP: 21040-360, Brazil.
E-mail address: pedro.brasil@fiocruz.br (P.E.A.A. do Brasil).

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developed, validated, and used in different settings around the world, for early identification of potentially serious or critical patients [12–22], many with promising applicability [23]. A prognostic score for in-hospital death with Brazilian participants estimated 20.3 % mortality, and this score was later validated in Barcelona, Spain [24]. Nevertheless, there isn't much research comparing prognostic scores with the Brazilian population. This study aimed to develop and internally validate a prognostic instrument to predict COVID-19 progression to a severe condition in a sample of Brazilian patients.

Materials and methods

Ethics

The study was conducted in compliance with ethical guidelines in the Regulatory Guidelines and Standards for Research Involving Human Beings (Resolution CNS/MS No. 466/2012). All participants signed a written consent. The Ethics Committee of the INI-Fiocruz registry and approval can be accessed at https://plataformabrasil.saude.gov.br/login.jsf with number CAAE 39520820.7.0000.5262.

Source data and settings

Part of this research was reported elsewhere, therefore we followed the same methods previously published. [25] Briefly, this is a retrospective observational follow-up study carried out at Niterói / Rio de Janeiro state – Brazil, at Hospital Santa Martha and Hospital Niterói D'Or. Enrollment was sequential from January and April 2021, and from September 2021 to February 2022 in the different participant health units.

Study participants

The inclusion criteria were: patients hospitalized with flu-like syndrome (COVID-19 compatible clinical findings), history of exposure, or radiological image compatible with COVID-19 according to Ministry of Health criteria at that time [26] (see hospitalization criteria below); patients with a completed hospitalization guide in the emergency room, or allocated in non-critical sectors; adult patients (18 years or older); a positive RT-PCR result for COVID-19, derived from a respiratory swab or viable biological material indicative of active disease, collected between 3 and 10 days after symptom start, at any time during hospitalization. The exclusion criteria were: absence of clinical evaluation in the first 48 h; discharge or death before completing 24 h of hospitalization; critical conditions at admission or directly admitted to intensive support units. Critical conditions were considered as (1) Glasgow coma scale <8; (2) need to use vasoactive amines; (3) need intubation and mechanical ventilation support; (4) need for acute dialysis therapy.

Criteria and measurements

The predictors' assessments were performed at hospital admission, and eventually considered up to 48 h after admission. Patients underwent a protocol consisting of (1) clinical examination to identify pertinent clinical features (e.g. fever, headache, coryza, sore throat, myalgia, dry cough, exposure risk); (2) laboratory testing; and (3) chest imaging by computed tomography.

The criteria used for hospital admission at the time followed the parameters defined by the Brazilian Ministry of Health, which were: (1) moderate cases: patient with clinical or radiological evidence of respiratory disease and SatO2 $\geq$ 94 % in room air; (2) Severe cases: patient with respiratory rate $>$ 30 bpm, or O2 saturation $<$ 94 % on room air (or, in patients with chronic hypoxia, a $>$ 3 % reduction from baseline), or PaO2/FiO2 ratio $<$ 300 mmHg, or opacities in $>$50 % of the lung [26]. Standard treatment was offered according to each hospital's protocol based on guidelines at the time, therefore no antiviral treatment was offered as they were not available.

Medical records and consulting assistants were the sources of the data. One of the authors (VLCM) and an undergraduate trainee under the supervision of the second author (PEAAB) extracted data from medical records to an electronic standard data collection device. At first, there was some instruction in data extraction and the enhancement of research forms. No extractor interrater agreement was measured, and the extractors were not blinded to the study premise.

Outcomes

In this study, the outcome of interest was the progression to a critically ill condition defined as a composite of intensive care unit admission during hospital stay or death.

Potential predictors for the outcomes

The predictors tested were selected because they were present in previously developed and validated models for COVID-19 prognosis. [25] They were: age at admission, sex at birth, tobacco use, vaccination status, days with symptoms on admission, hemoptysis, dyspnea, respiratory frequency, pulse oximetry (0–100 %), oxygen flow (L/min), systolic blood pressure (mmHg), Charlson Comorbidity Index, RDW (%), leukocyte count (x10^9/L), neutrophil count (x10^9/L), lymphocyte count (x10.9/L), monocyte count (x10^9/L), glucose (mg/dL), C-reactive protein - CRP (mg/L), D-dimer (mg/mL), lactic dehydrogenase - LDH (U/L), urea (mg/dL), creatinine (mg/dL), AST (U/L), direct bilirubin (mg/dL), procalcitonin (ng/ml), ultra-sensitive troponin (ng/L), concomitant bacterial infection, Radiological RALE Score (0–8) [27], image findings, multilobe infiltrates.

Data analysis

The outcome prevalence estimated from administrative data before the study ranged from 50 % to 72 %. Therefore, 300 subjects would be enough to reach 100 subjects with events and 100 subjects without the events for minimum sample size purposes [28].

Data analysis was conducted in R software (packages: mice, glmnet, glmnetUtils, randomForest, rfUtilities, givitiR, UncertainInterval) following the steps: description of possible predictors to be explored; exploration of missing data patterns and the need for data imputation; verification of the need for recoding of the predictors; exploration of different types of models and validation (discrimination and calibration), when applicable either internal cross-validation or penalization were performed. Missing data was imputed with multiple imputation procedures. All the continuous predictors were tested as such (with no categorization such as normal vs. abnormal values limits) or with functional forms transformations. The following approaches were tested: general linear logistic model (GLM) with lasso or elastic net regularization with cross-validation, a random forest classification, and a random forest regression with cross-validation. The validity was accessed by (discrimination) the area under the ROC curve, mean of squared residuals and variance explained, (calibration) calibration belt, model's intercept and slope (including bias-corrected,) and prediction errors were used (average, maximum, and percentile 90) [29]. Decision limits were estimated with the "uncertain interval" method [30] to allow the interpretation of different courses of action, for example, (a) low risk recommending discharge, (b) moderate risk recommending monitoring, (c) high risk recommending early transfer to critical care.

Results

Participants descriptions are described elsewhere. [25]. Briefly, 301 participants were included and analyzed from both health units, Hospital Santa Martha and Hospital Niterói D'Or. The composite outcome overall prevalence was 41.86 %. The overall mortality rate was 16.61 %

and the overall intensive care admission rate was 41.86 %. Median age was higher, and males were more frequent in the outcome group. Most participants were not vaccinated. Participants with worse respiratory parameters were more often in the outcome group [25]. A higher Charlson comorbidity score was observed in the outcome group. Laboratory markers that initially seemed clinically relevant were C-reactive protein (CRP), D-dimer and concomitant bacterial infection, and imaging score [25].

The final penalized logistic model had the following 28 predictors: age at admission, smoking, immunization, days with symptoms on admission, dyspnea, respiratory frequency, pulse oximetry, systolic blood pressure (mmHg), diabetes, obesity, history of cancer, chronic cardiopathy, cerebrovascular disease, malignancy for at least 6 months, RDW (%), lymphocyte count (x10.9/L), monocyte count (x10^9/L), glucose (mg/dL), C-reactive protein (mg/L), D-dimer (mg/mL), urea (mg/dL), creatinine (mg/dL), procalcitonin (ng/ml), ultra-sensitive troponin (ng/L), FiO2 (F) (%), concomitant bacterial infection, Radiological RALE Score (0–8), image findings. The following predictors had nonlinear effects detected by polynomial transformation within the model: systolic blood pressure, RDW, Monocyte count, FiO2, and Radiological RALE Score. Additionally, interactions of pulse oximetry (0–100 %) with FiO2 (F) (%), and interactions of Radiological RALE Score (0–8) and image findings were detected. (Table 1) It had good discrimination with a below-desired calibration, with an area under the ROC curve of 0.882, a R2 of 0.518, an Intercept of 0.266, a Slope of 1.63, a maximum error of 0.097, a percentile 90 of error 0.095, an average error of 0.064. It underestimates in the lower range and overestimates in the higher range of predictions. (Fig. 1).

The Random Forest classification development and cross-validation returned the following 8 predictors: D-dimer, Urea, Charlson comorbidity index, pulse oximetry, respiratory frequency, Lactic Dehydrogenase, RDW, and C-reactive protein. One may see that the important variables represent disturbances of clotting, previous comorbidities, renal function, respiratory function, and general inflammation intensity. (Fig. 2) The Random Forest classification model retained fewer predictors compared with the penalized logistic regression approach. Its classification returns reasonable likelihood and predictive values, however, it has moderate to poor sensitivity, specificity, and area under the ROC curve. (Table 2).

Random Forest regression development and cross-validation also returned 8 predictors but with one (the less important) different from the classification approach, they were: D-dimer, Urea, Charlson comorbidity index, pulse oximetry, respiratory frequency, Lactic Dehydrogenase, RDW, and Radiologic RALE score. (Fig. 3) By far, D-dimer was the most important predictor. Five of the eight predictors retained in the final model had very similar crude distribution values among those with and without the outcome, therefore confounding and interactions are likely present. This phenomenon may also be involved in the understanding that predictors previously identified in the literature were not retained in the final model.

The bias-corrected intercept and slope were − 0.0004 and 1.079 respectively, the average prediction error was 0.028, the maximum prediction error was 0.085 and the prediction error percentile 90 was 0.054, adding the visual analysis the final model calibration was considered good. (Fig. 4). The discrimination performance was: area under the ROC curve was 0.795, mean of squared residuals was 0.173, and variance explained was 0.289. Although the discrimination was lower when compared to the penalized logistic model, the Random Forest regression was considered better balanced between discrimination and calibration with fewer predictors. The uncertain range was estimated to be from 0.43 to 0.63. (Fig. 5) There is a web tool for readers and users to make predictions with the random forest model, and some interpretation of the predictions with the suggested decision limits. This can be found at https://pedrobrasil.shinyapps.io/INDWELL/.

Table 1
Final penalized and cross-validated logistic model effects and Odds Ratios taking death or intensive care as outcome.

Variables	Categories	Coefficients	OR
Intercept		9.0333	
Age at admission		0.0037	1.0037
Smoking	No	−0.2212	0.8016
	Past	0.3195	1.3764
	Current	−0.3051	0.7370
Initial vaccination	Vaccinated	0.1011	1.1064
	Not vaccinated	−0.1741	0.8402
	Unknown	0.0889	1.0930
Days with symptoms on admission		−0.0343	0.9663
Dyspnea	No	−0.2182	0.8040
	Yes	0.2182	1.2439
Respiratory frequency		0.0455	1.0465
Pulse oximetry (0–100 %)		−0.0472	0.9539
Systolic blood pressure (mmHg)	poly(,2)1	0.2168	1.2420
	poly(, 2)2	2.8711	17.6568
Diabetes	No	−0.1401	0.8692
	Yes	0.1401	1.1504
Obesity	BMI $<$ 30	−0.2960	0.7438
	BMI $\geq$ 30	0.2960	1.3445
History of cancer	No	−0.2341	0.7913
	Yes	0.2340	1.2636
Chronic cardiopathy	No	−0.2946	0.7448
	Yes	0.2945	1.3425
Cerebrovascular disease	No	−0.5602	0.5711
	Yes	0.5600	1.7507
Malignancy for at least 6 months	No	−0.4691	0.6255
	Yes	0.4691	1.5986
RDW (%)	poly(, 2)1	−0.4942	0.6100
	poly(, 2)2	−1.1171	0.3272
Lymphocyte count (x10.9/L)		−0.0002	0.9998
Monocyte count (x10^9/L)	poly(, 2)1	0.2593	1.2961
	poly(, 2)2	1.3451	3.8385
Glucose (mg/dL)		0.0008	1.0008
C-reactive protein - CRP (mg/L)		−0.0017	0.9983
D-dimer (mg/mL)		0.0003	1.0003
Urea (mg/dL)		0.0027	1.0027
Creatinine (mg/dL)		0.1730	1.1888
Procalcitonin (ng/ml)		0.7534	2.1243
Ultra-sensitive troponin (ng/L)		0.0051	1.0051
FiO2 (F) (%)	poly(,3)1	−1.0142	0.3627
	poly(, 3)2	−0.2048	0.8148
	poly(, 3)3	1.0951	2.9896
Concomitant bacterial infection	No	−0.2471	0.7811
	Yes	0.2470	1.2802
Pulse oximetry (0–100 %)		−0.0472	0.9539
FiO2 (F) (%)	poly(, 3)1	−1.0154	0.3622
	poly(, 3)2	−0.2047	0.8149
	poly(, 3)3	1.0953	2.9899
Pulse oximetry (0–100 %): FiO2 (F) (%)	poly(, 3)1	−0.0106	0.9895
	poly(, 3)2	−0.0025	0.9975
	poly(, 3)3	0.0109	1.0110
Radiological RALE Score (0–8)	poly(, 2)1	2.0077	7.4460
	poly(, 2)2	0.6445	1.9050
Image findings	Normal	−0.1817	0.8339
	No specific signs	0.0745	1.0773
	Frosted glass opacity	−0.0371	0.9636
	Consolidation	0.0269	1.0272
Radiological RALE Score (0–8)	poly(, 2)1	2.0075	7.4444
	poly(, 2)2	0.6442	1.9044
Image findings	Normal	−0.1818	0.8338
	No specific signs	0.0743	1.0771
	Frosted glass opacity	−0.0370	0.9637
	Consolidation	0.0269	1.0273
Radiological RALE Score (0–8):Image findings	poly(, 2)1:No specific signs	−0.3580	0.6991
	poly(, 2)2:No specific signs	1.8706	6.4925

(continued on next page)

Table 1 (*continued*)

Variables	Categories	Coefficients	OR
	poly(, 2)1:Frosted glass opacity	3.4435	31.2963
	poly(, 2)2:Frosted glass opacity	0.9309	2.5367
	poly(, 2)1: Consolidation	−0.1509	0.8600
	poly(, 2)2: Consolidation	−4.9564	0.0070

OR = Odds Ratio; poly = polynomial transformation (for example poly(, 2)3 is the second-degree coefficient of a three-degree polynomial transformation); Predictors or categories without estimated effect had the coefficient shrunk to zero in the penalization. Initial vaccination means at least one vaccine dose of any manufacturer (Pfizer, AstraZeneca, CoronaVac, Janssen).

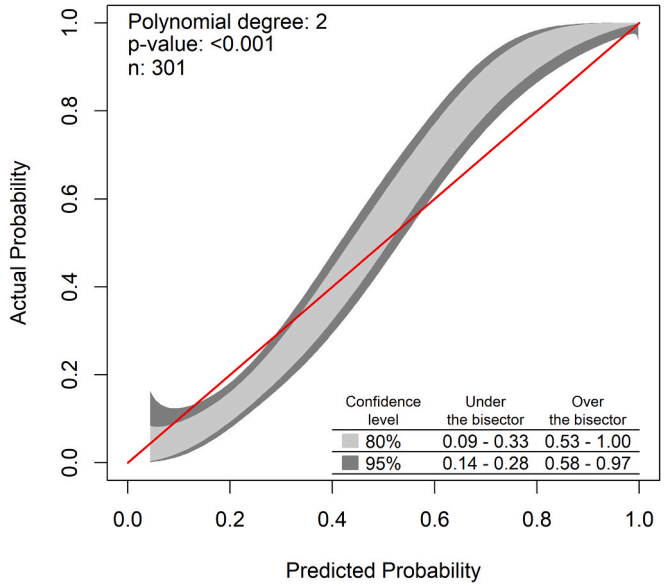

Fig. 1. Final penalized and cross-validated logistic model taking death or intensive care as outcome calibration belt.

Discussion

The main results to be discussed are: (a) it was possible to develop and internally validate a final model able to make reasonable risk predictions to identify progression to critical condition in patients with COVID-19; (b) it was possible to estimate reasonable thresholds to recommend decision making.

Many prediction models for COVID-19 progression to critically ill were published even after the pandemic was considered no longer a global threat [12–16,31–35]. This is likely due to the changes over time since the beginning of the pandemic, such as different waves of SARS-CoV-2 strains, different transmissibility, prognosis, and likely different clinical manifestations [35], not mentioning that the disease was still present and likely to behave as a seasonal condition. Vaccines [6,36] and antiviral treatments [37] became available quickly and there was a reduction in the frequency of severe disease, ICU admission, and mortality - estimated from a non-hospitalized population [31]. The setting differences and these circumstances raise the suspicion that the disease's natural history changed over time and possibly the performance or applicability of all prognostic instruments. However, these issues are of concern only if the mortality or critical illness incidence relationship with the presence or absence of predictors also changes [6,7,37]. This makes it desirable for prognostic instruments to be validated, where they would be used to increase certainty that performance travels [16].

A systematic review of diagnostic and prognostic COVID-19 instruments shows that only four studies were conducted in Brazil. From these, only one developed/validated a prognostic model with clinical data. The remaining used either CT or X-ray images only [12]. They questioned the quality of existing studies and concluded that data storage is needed to validate existing models across different populations.

The enrollment period included wave periods of Alpha, Gama, Delta, and Omicron variants. At first, it seems the applicability of predictions may work for different variants that may express different prevalences of clinical findings and different severities. CoronaVac vaccine was the first available to the public [38], and participants who received it were the most frequent in the sample, but this vaccine was not common worldwide. These vaccinated participants were also the elders (as public vaccination effort schedules at Niteroi city started with the elders and progressively advanced to the younger population), and the elders were also most frequently with severe disease. As mentioned in the first manuscript of this project, [25] 56.6 % of the sample was vaccinated with at least one dose, and a complete vaccination scheme was observed in 80.82 % of the vaccinated. Although there is evidence that vaccination reduces the number of hospitalizations, it appears that vaccination does not contribute to severe disease prediction in hospitalized patients.

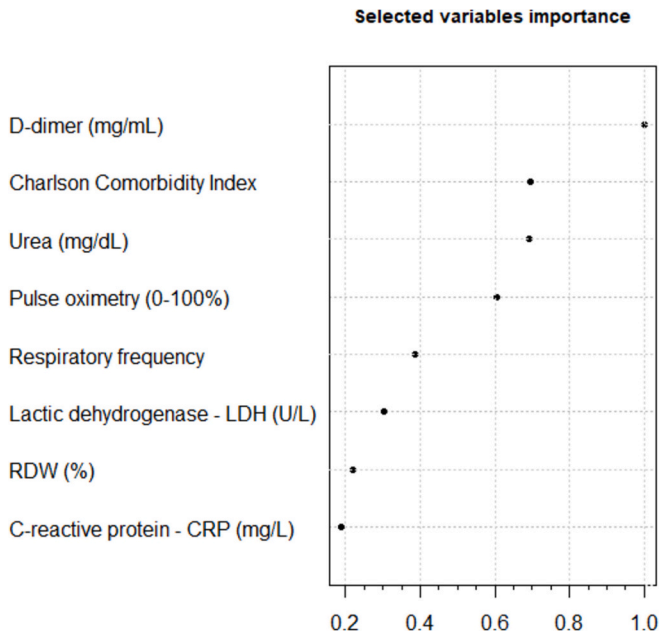

Fig. 2. Random Forest classification taking death or ICU admission as outcome final selected variables importance.

Table 2
Diagnostic accuracy (and its 95 % confidence interval) from the out-of-bag confusion matrix for the random forest classification taking death or ICU admission as outcome.

Statistics	Estimate	lower.cl	upper.cl
Sample size:	301		
Prevalence:	0.419	0.364	0.475
Sensitivity:	0.651	0.564	0.728
Specificity:	0.766	0.698	0.822
Positive predictive value:	0.667	0.579	0.744
Negative predictive value:	0.753	0.685	0.810
Positive likelihood ratio:	2.778	2.073	3.722
Negative likelihood ratio:	0.456	0.354	0.587
Diagnostic Odds Ratio:	6.049	3.561	10.441
Error rate:	0.282	0.235	0.336
Accuracy:	0.718	0.664	0.765
Youden J index:	0.417	0.312	0.521
The area under ROC curve:	0.708		

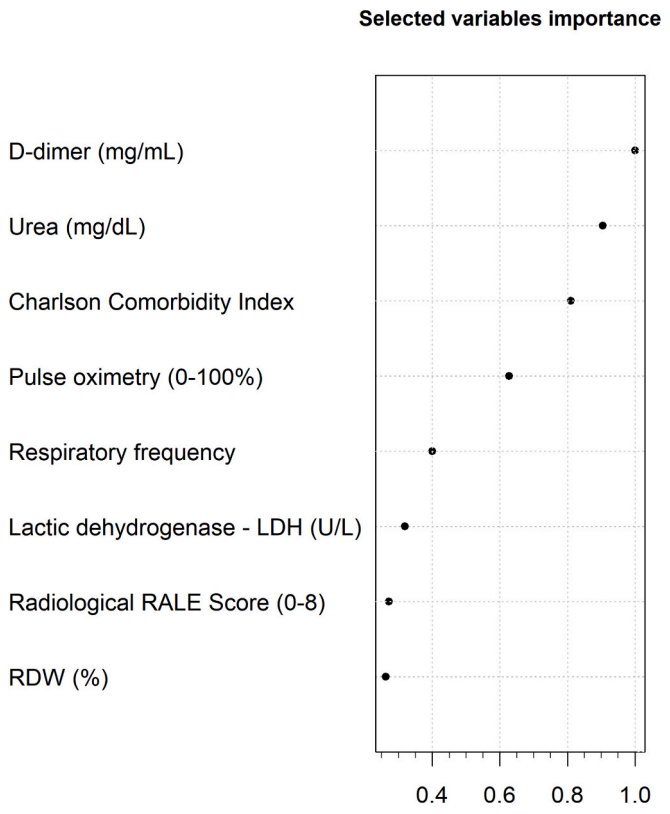

Fig. 3. Random Forest regression importance of the predictors retained in the final model.

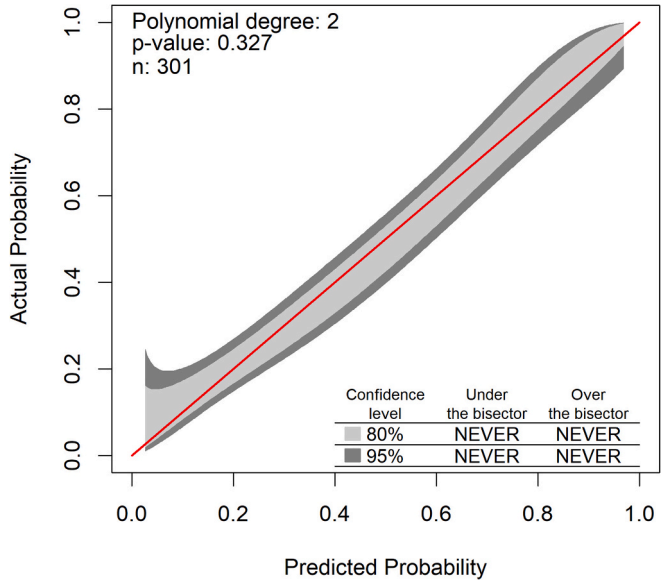

Fig. 4. Random Forest regression calibration belt shows the correspondence of the observed and the predicted risks.

Therefore, once one is infected and hospitalized the vaccination status has little or no effect on prognosis.

Thromboembolic events are major prognostic events in COVID-19, and the coagulation pathways are involved in the disease's immune response and inflammation intensity [39–42]. D-dimer and other hematological changes are important features and significantly deviate from normal values with disease severity [43]. Nevertheless, coagulation parameters are seldom explored and retained in COVID-19

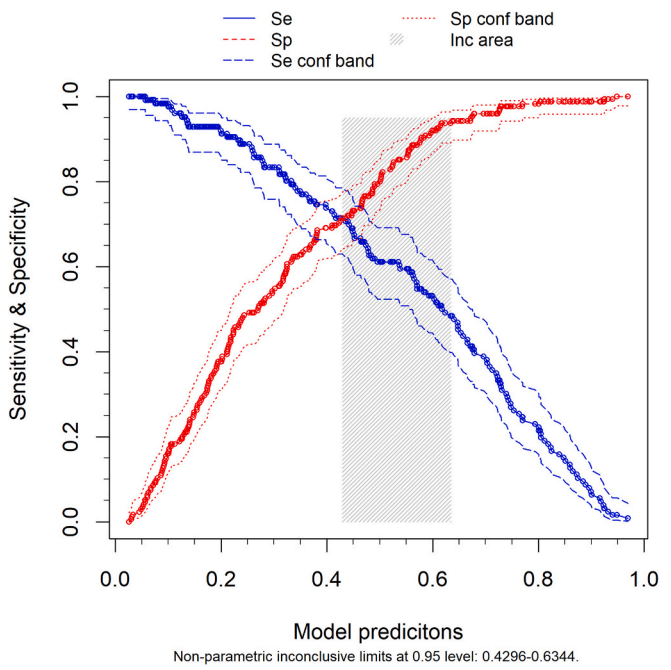

Fig. 5. Random Forest Regression Two-Graphic ROC analysis showing the Sensitivity and Specificity trade-off for all possible thresholds and the uncertain range of risks.

prognostic models [12,14]. Elevated D-dimer and RDW are likely to represent these phenomena.

Multiple previous comorbidities have been associated with severe COVID-19, higher prevalence of hospitalization, ICU admission and mechanical ventilation, or death [44]. The Charlson Comorbidity Index was previously associated with severity [45,46]. The score may represent how intensely health status is impaired, in this case at hospital admission. Although there is a balance in exploring comorbidities as a score and as individual predictors, this is a well-known and familiar tool for practitioners experienced with severe conditions.

Acute respiratory distress syndrome incidence was estimated in 20 % of COVID-19 patients, and mechanical ventilation was implemented in 12.3 % [47]. In the United States, 12 % to 24 % of hospitalized patients with altered respiratory symptoms progressed to mechanical ventilation [44]. Several imaging patterns of pulmonary involvement are possible [48]. Here, the pulmonary consolidation alone would indicate a risk of outcome of 65 %. Additionally, it seems that the amount of respiratory involvement and function is more important than the type of image. Respiratory involvement is a fundamental element in predicting disease severity, however, critical illness is frequent in the group with "0" RALE index score, independently of respiratory findings.

The renal impairment is likely to be multifactorial in COVID-19 natural history. Besides the SARS-CoV-2 direct injury, hypoxia and hypercoagulability may play a role. Renal failure is less frequent than respiratory failure. It was estimated to be 4.5 % overall, and 52.9 % in the non-survivors [49]. Serum creatinine, BUN, and urine analysis are frequently abnormal when a patient is admitted to the hospital, and there is evidence that these abnormalities raise the likelihood of a poor outcome. [49]. Here, urea may represent a hydration status, shock, or renal damage, but probably a combination.

Among the three alternative approaches, the Random Forest regression has the most attractive balance of calibration and discrimination and fewer predictors facilitating applicability. A web calculator was developed to allow its use. The most appropriate moment to make this prediction is during emergency room admittance, or during ward admittance, when COVID-19 is suspected or a patient already with COVID-19 confirmed is hospitalized. The calculator will use the

underlying model to return the outcome probability and a recommended risk group after the user enters or clicks on the patient characteristics on the calculator website.

There were limitations such as the large number of missing data for some predictors, mainly from some laboratory biomarkers. Although the imputed data is a workaround, the unavailability of predictors also raises an applicability and inference discussion, as some predictors explored previously and detected to have prediction contributions were not explored here. In the early periods of the pandemic the criteria used to recommend patients to seek medical aid, and the criteria adopted to keep patients hospitalized may have changed, when compared to nowadays. Therefore, as the pandemic changed, the population to which the instrument would apply may have changed accordingly. That does not mean the instruments are useless. This means they need additional assessments to check that their performance remains the same as circumstances change.

The different protocols for COVID-19 case management in the two target hospitals of this study possibly influenced the outcome incidence in different directions, as they had different clinical, structural, or administrative criteria for directing patients to critical sectors and different availability of ICU beds. It is possible that patients indicated for admission to a critical unit remained in non-critical beds due to the lower availability of ICU beds. On the other hand, this could make the results inference to a more general population, although it makes it more complex to define this population.

Another issue is the lack of specificity of the mode of death or organ failure. This instrument may be accurate in predicting disease progression to critically ill condition but does not reveal which organ system will fail, such as acute renal failure, thromboembolic events, etc. One may intuitively understand that, depending on organ involvement, different support and treatment measures may be preferential. Nevertheless, experienced health professionals may have a good hunch based on clinical presentation or rely on the predictors that most deviate from normal values.

Conclusions

The developed and validated prognostic model to predict the composite outcome of critical illness and death has good performance and could be recommended for clinical use on non-critical patients. The prediction instrument is intended to be applied to patients with flu-like symptoms, or suspected lung image, COVID-19 (suspected and later) confirmed by a laboratory test in the first ER or ward admission day. The decision thresholds are just recommendations based on the observed data and could be ignored by an experienced caregiver who may choose alternative limits. Attention must be paid to whether the future scenarios will continue to change, as the clinical benefit and the performance in different settings are yet to be known. This is also true regarding the limits of the recommended decision thresholds as the in-hospital severity reduces or increases, the mixed distribution of predictions of those with and without the outcome may also move accordingly and new thresholds may be required.

Ethics and patient consent statement

The study was developed in accordance with the Regulatory Guidelines and Standards for Research involving Human Beings (Resolution CNS/MS No. 466/2012). All participants signed a written consent. The Ethics Committee of the INI-Fiocruz registry and approval can be accessed at https://plataformabrasil.saude.gov.br/login.jsf with number CAAE 39520820.7.0000.5262.

CRediT authorship contribution statement

Vinicius Lins Costa Ok Melo: Writing – original draft, Project administration, Investigation, Formal analysis, Data curation, Conceptualization. **Pedro Emmanuel Alvarenga Americano do Brasil:** Writing – review & editing, Writing – original draft, Supervision, Methodology, Investigation, Formal analysis, Data curation, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.gloepi.2024.100181.

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