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Development and validation of a prediction model for severe respiratory failure in hospitalized patients with SARS-Cov-2 infection: a multicenter cohort study (PREDICO study)

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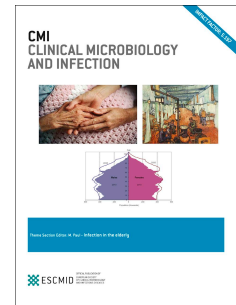
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1 **Original article:**

2 **Development and validation of a prediction model for severe respiratory failure in**
3 **hospitalized patients with SARS-Cov-2 infection: a multicenter cohort study (PREDI-CO**
4 **study)**

5

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75 **ABSTRACT**

76

77 **Objectives:** We aimed to develop and validate a risk score to predict severe respiratory failure
78 (SRF) among patients hospitalized with coronavirus disease-2019 (COVID-19).

79 **Methods:** We performed a multicentre cohort study among hospitalized (>24 hours) patients
80 diagnosed with COVID-19 from February 22 to April 3 2020, at 11 Italian hospitals. Patients were
81 divided into derivation and validation cohorts according to random sorting of hospitals. SRF was
82 assessed from admission to hospital discharge and was defined as: SpO₂<93% with 100% FiO₂,
83 respiratory rate (RR)>30bpm, or respiratory distress. Multivariable logistic regression models were
84 built to identify predictors of SRF, β -coefficients were used to develop a risk score. Trial
85 Registration NCT04316949 .

86 **Results:** We analyzed 1113 patients (644 derivation, 469 validation cohort). Mean (\pm standard
87 deviation)age was 65.7(\pm 15) years, 704 (63.3%) were male. SRF occurred in 189/644 (29%) and
88 187/469 (40%) patients in derivation and validation cohort, respectively. At multivariate analysis,
89 risk factors for SRF in the derivation cohort assessed at hospitalization were age \geq 70 years [OR
90 2.74 (95%CI 1.66-4.50)], obesity [OR 4.62 (95%CI 2.78-7.70)], body temperature \geq 38°C [OR 1.73
91 (95%CI 1.30-2.29)], RR \geq 22bpm [OR 3.75 (95%CI 2.01-7.01)], lymphocytes \leq 900/mm³ [OR 2.69
92 (95%CI 1.60-4.51)], creatinine \geq 1 mg/dl [OR 2.38 (95%CI 1.59-3.56)], C-reactive protein \geq 10mg/dl
93 [OR 5.91 (95%CI 4.88-7.17)], and lactate dehydrogenase \geq 350IU/L[OR 2.39 (95%CI 1.11-5.11)].
94 Assigning points to each variable an individual risk score (PREDI-CO score) was obtained. Area
95 under receiver-operator curve (AUROC) was 0.89 (0.86-0.92). At score of >3, sensitivity,
96 specificity, positive and negative predictive values were 71.6%(65-79%), 89.1% (86-92%), 74%(67-
97 80%), and 89%(85-91%), respectively;. PREDI-CO score showed similar prognostic ability in the
98 validation cohort: AUROC 0.85 (0.81-0.88). At score of >3, sensitivity, specificity, positive and
99 negative predictive values were 80% (73-85%), 76 (70-81%), 69%(60-74%) and 85% (80-89%),
100 respectively.

101 **Conclusion:** PREDI-CO score can be useful to allocate resources and prioritize treatments during
102 COVID-19 pandemic.

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107 INTRODUCTION

108 Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)-associated coronavirus disease
109 2019 (COVID-19) has gripped the world in a pandemic, challenging its culture, economy and
110 healthcare system. The virus was first reported in China in December 2019 and has subsequently
111 spread worldwide.

112 The clinical spectrum of COVID-19 is broad with the majority of infected individuals experiencing
113 only mild or subclinical illness, especially in the early phase of disease [1]. However, approximately
114 14 to 30% of hospitalized patients diagnosed with COVID-19 develop a severe respiratory failure
115 (SRF) requiring intensive care [2-4].

116 To date, no therapy has proven effective, thus supportive care aimed to protect multi-organ
117 function represents the main resource to reduce mortality [5]. Unfortunately, the capacity of the
118 system is limited prompting the need of rationing decisions [6]. On the other hand, a number of
119 promising innovative drugs and treatment strategies are under investigation [7]. Thus, we deemed
120 that an early identification of patients at risk of developing SRF, could support the planning of
121 resources and help to set up organizational and clinical interventions, including early
122 pharmacological treatment to prevent ICU admission.

123 The objectives of the study were therefore (a) develop a risk model to identify patients at high risk
124 of developing SRF on hospital admission using a cohort of hospitalized patient with
125 microbiologically confirmed diagnosis of COVID-19; and (b) to validate this risk model in an
126 external multicenter cohort.

127

128 METHODS

129 Design and setting

130 We performed a retrospective multicenter cohort study of prospectively collected data from patients
131 with laboratory-confirmed SARS-CoV2 virus infection, hospitalized from February 22 through April
132 3, 2020. Last follow-up date was April 23, 2020.

133 Eleven hospitals from four Italian Regions, including four tertiary teaching hospitals, five non-
134 teaching tertiary hospitals and two secondary hospitals, participated in the study (see
135 Supplementary Figure 1).

136 Diagnostic testing for COVID-19 and hospitalization were performed according to local policy and
137 clinical judgment, and were not dictated by a study protocol. The local microbiology laboratory
138 information and management systems were used to identify patients. Clinical charts and hospital
139 electronic records were used as data sources. De-identified data were collected and managed
140 using REDCap electronic data capture tools, Alma Mater University of Bologna [8, 9].

141 The study was approved by the Ethic Committee of the promoting center (Comitato Etico
142 Indipendente di Area Vasta Emilia Centro, n.283/2020/Oss/AOUBo). A waiver of informed consent
143 was granted by the Ethic Committee due to safety risk. The study protocol was registered on
144 clinicaltrials.gov with the number NCT04316949.

145

146 Participants

147 All consecutive adult patients (≥ 18 years) diagnosed with SARS-CoV-2 infection during the study
148 period were included.

149 Exclusion criteria were hospital discharge within 24 hours from admission to Emergency
150 Department and occurrence of SRF within 24 hours from hospitalization.

151 Participants were divided in two different cohorts: the derivation cohort consisted of patients
152 admitted to hospitals C, D (a., c.) and I, the validation cohort consisted of patients admitted to
153 hospitals A, B, D (b.), E, F, G, H (see Supplementary Figure 1). Hospitals were sorted randomly

154 and assigned initially to the derivation cohort. Once reached the 50% of participants with a new
155 assignment, the remaining centers were assigned to the validation cohort.

156 Variables and definitions

157 Microbiological diagnosis of SARS-CoV2 infection was defined as a positive RT-PCR test on
158 nasopharyngeal swabs.

159 The endpoint variable was occurrence of SRF. Occurrence SRF was assessed reviewing
160 collected data from admission to hospital discharge by a blinded investigator (ST). SRF was
161 defined according to World and Health Organization (WHO) criteria as: SpO₂<93% with 100%
162 FiO₂ (reservoir mask or continuous positive airway pressure ventilation or other non-invasive
163 ventilation), respiratory rate >30 bpm, or respiratory distress[10].

164 Exposure variables were assessed at hospital admission and included: age, older age (>70 years),
165 sex, body mass index, being obese (BMI >30 kg/m²). Underlying conditions were recorded
166 according to Charlson comorbidity index[11]. Hypertension was defined as history of permanent
167 increase of systolic blood pressure over 140 mmHg, and a diastolic increase to more than 90
168 mmHg. Immunosuppression included neutropenia (neutrophil count <500/mm³), solid organ
169 transplantation, hematopoietic stem cell transplantation, corticosteroid therapy at a dosage higher
170 then or equivalent to prednisone 16 mg/day ≥ 15 days, uncontrolled HIV infection (<200
171 CD4/mm³). Regarding the SARS-CoV2 infection, symptoms at onset and hospitalization, vital
172 signs and laboratory tests were collected. Severity of illness at hospitalization was recorded
173 according to sequential organ failure assessment (SOFA) score[13], quickSOFA (qSOFA)[14],
174 CURB-65 score[15] and Modified Early Warning Score (MEWS)[16].

175 Endpoint variables were assessed from hospital admission to discharge. In addition to SRF, we
176 collected in-hospital all-cause mortality and date of hospital discharge

177

178 Microbiological testing

179 The presence of SARS-Cov2 was detected by RT-PCR assay. Briefly, UTM-RT swab specimens
180 (Copan, Italy) were immediately tested or stored at 4°C until processed, no more than 48 hours.
181 Total genomic DNA/RNA was extracted from 280 µl of the clinical sample by Nuclisens EasyMag
182 (BioMerieux, Marcy l'Etoile, France) following manufacturer's instructions. Detection of SARS-CoV-
183 2 was performed by real time RT-PCR following the WHO and/or CDC protocol in a QuantStudio
184 S5 Real-time PCR system (ThermoFisher, USA). Microbiological analysis was not performed in a
185 centralized laboratory.

186

187 Study size

188 For the sample size calculation we followed recent recommendations from Riley at al. [12]. We
189 aimed to enroll at least 370 patients in the derivation cohort, with an expected number of events of
190 148 (an expected 40% rate, based on preliminary raw observations) and a maximum 8 binary
191 variables in the model, using the pmsampsize procedure in Stata 10 [12]. For the validation cohort,
192 we aimed for a similar sample size.

193

194 Statistical analysis

195 For descriptive analysis, categorical variables are presented as counts and percentages.
196 Continuous variables as mean and standard deviation if normally distributed or as median and
197 interquartile range (IQR) if non-normally distributed.

198 For group comparison, Student t test, Mann-Whitney test, and ANOVA or Kruskal-Wallis were
199 used for quantitative variables normally distributed, skewed distributed and for >2 groups,
200 respectively. Pearson's χ^2 test (Fisher exact test where appropriate) for categorical variables.
201 Shapiro Wilk's and Kolmogorov-Smirnov test, as well as visual methods, were applied to test for
202 normality.

203 To develop and validate the score, analyses were initially performed on the derivation cohort, and
204 repeated identically in the validation cohort.

205 Univariate and multivariate mixed logistic regression models were performed to investigate risk
206 factors for SRF. Variables were included in the multivariable model according the following
207 strategy: clinically relevant variables, significance at the univariable analysis ($p < 0.10$), lack of co-
208 linearity [in case of co-linearity, the model with lower Akaike Information Criterion (AIC) was
209 chosen], missing data in $< 10\%$ of cases (i.e we performed a complete case analysis). Overall
210 goodness of fit was analyzed by Akaike's Information Criteria (AIC) and Nagelkerke's R-square.
211 Discrimination of the model was assessed by receiver-operator curve (ROC) characteristics of the
212 predicted probability, Brier score and Somers' D. Calibration of the model was assessed by
213 comparing predicted versus actual probability of SRF in deciles of risk. Cluster-robust variance was
214 used, to take into account within hospital correlation.

215 To develop the risk score (PREDI-CO score), variables in the multivariate logistic regression model
216 regardless of their significance were assigned a point value corresponding to the β -coefficient
217 (fixed effects) rounded to the nearest integer; the total score was obtained by summation of
218 individual variables scores.

219 The discrimination of PREDI-CO score towards SRF was then analyzed by nonparametric analysis
220 of ROC curve under covariates, using bootstrap (1000 replications), with clustering per hospital. An
221 optimal cut-point was then assigned using the Youden's J statistic, and performance
222 characteristics at the cut-point (sensitivity, specificity, positive and negative likelihood, diagnostic
223 accuracy, positive and negative predictive values) were calculated with the corresponding 95%
224 confidence intervals.

225 In the validation cohort, the slope and intercept of the linear predictor were also assessed. The
226 results of multivariable analysis in the validation cohort was not used to change the model obtained
227 in the derivation cohort.

228 All statistical tests were two-sided. Stata computer software version 16.0 (Stata Corporation, 4905
229 Lakeway Drive, College Station, Texas 77845, USA) was used for statistical analysis.

230

231 **RESULTS**

232 The initial population consisted of 1265 patients: 739 in the derivation and 526 in the validation
233 cohort. One-hundred fifty-two patients were excluded according to eligibility criteria. Of the 1113
234 patients analyzed: 644 were in the derivation and 469 in the validation cohort (Figure 1). The
235 median number of patient included per hospital was 40 (IQR 11-84, range 4-384).

236 The mean age of included patients was 65.7 ± 15 years, and 704 (63.3%) were male. The median
237 time from onset of symptoms to hospital admission was 6 (IQR 3-9) days. The two cohorts were
238 different in several patients' characteristics (Table 1).

239 Three-hundred seventy-six patients (33%) developed SRF after ≥ 24 hours of admission. Median
240 time to SRF in this group was 4 (IQR 2-7) days from hospital admission and 10 (7-13) days from
241 onset of symptoms. The rate of SRF was 29% (189/644) and 40% (187/469) in the derivation and
242 validation cohort, respectively.

243 There were several differences between patients with and without SRF in derivation (Table 2) and
244 validation (Table 3) cohorts.

245 In the derivation cohort, multivariate analysis showed that age ≥ 70 years, obesity, fever at
246 hospitalization (body temperature $\geq 38^\circ\text{C}$), respiratory rate ≥ 22 breaths per minute, lymphocytes
247 $\leq 900/\text{mm}^3$, creatinine ≥ 1 mg/dl, C-reactive protein (CRP) ≥ 10 mg/dl, and LDH ≥ 350 UI/L were
248 independent risk factors for developing SRF (Table 4). The model was highly discriminant: Area
249 under the ROC 0.90 (Figure 2, panel A), Brier score 0.11, Somers' D 0.79 (95%CI 0.73- 0.85).
250 Calibration (Figure 2, panel B) and fitting (Figure 2, Panel C) of the model were also good. In the
251 validation cohort the model performed similarly in terms of discrimination, calibration, (Figure 2,
252 panels D and E, respectively), fitting (Figure 2, Panel F) and distribution (Supplementary Figure 2

253 panel B). Area under the ROC curve was 0.84 with Brier score 0.16 and Somers' D 0.68 (95%CI
254 0.60-0.76). Linear prediction coefficient in the validation cohort was 0.79 (95%CI 0.73-0.95).

255 Assignment of points on the basis of β coefficient for these 8 independent variables generated an
256 individual risk score for each patient ranging from 0-9 (Table 4). Median PREDI-CO score was 4
257 (IQR 2-7) (Supplementary Figure 3, panel A).

258 In derivation cohort area under the ROC curve of the PREDI-CO score was 0.89 (95%CI 0.86-
259 0.92). At a risk score of >3, the sensitivity (SE), specificity (SP), positive predictive value (PPV) and
260 negative predictive value (NPV) were 72% (65-79), 86% (89-92), 74% (67-80), and 89% (85-91),
261 respectively. The positive and negative likelihood ratios (LR) associated with a >3 score cut-off
262 were 6.73 (95%CI 5.1-8.9) and 0.31 (95%CI 0.25-0.39), respectively (Supplementary table 1).

263 In the validation cohort, the PREDi-CO score showed an area under the ROC curve of 0.85
264 (95%CI 0.81-0.88). At risk score of >3, SE, SP, PPV, NPV, positive and negative LRs were 80%
265 (73-85), 76% (70-81), 69% (62-75), 85 (80-89%), respectively (Supplementary Table 1).

266 Finally, according to the ROC curve analysis the prediction ability for SRF of our score was higher
267 than that of SOFA, qSOFA, CURB-65 and MEWS scores in both the derivation (Figure 3, Panel A)
268 and validation cohorts (Figure 3, Panel B).

269 All the models and overall score performance was reevaluated after the inclusion of covariates that
270 are supposed to change the natural history of the disease including hydroxychloroquine,
271 tocilizumab and corticosteroids without any significant change in the overall performance (data not
272 shown).

273

274 **DISCUSSION**

275 We developed and independently validated a simple individual risk score (the PREDI-CO score) to
276 identify at the time of hospitalization patients with COVID-19 at high risk of developing SRF during
277 hospitalization. We found that of the patients hospitalized with COVID-19 on the wards for at least

278 24 hours, a high percentage (33%) developed worsening of symptoms with SRF after this initial
279 period. A predictive model was built and validated, using age>70 years, obesity, fever at
280 hospitalization, respiratory rate ≥ 22 breaths per minute, lymphocytes count ≤ 900 cells per mm³,
281 creatinine ≥ 1 mg/dl, CRP ≥ 10 mg/dl, and LDH ≥ 350 IU/L. Our model and risk score performed
282 similarly even in different cohorts, as defined by different hospitals, providing independent
283 validation.

284 The rate of SRF in our cohort of hospitalized patients with COVID-19 was higher than that in initial
285 reports [4, 13], but in line with more recent findings [14, 15]. Demographic characteristics of
286 population, socio-cultural issues and local strategies for diagnostic testing have been appointed
287 among the factors contributing to the different severity of COVID-19 across countries [14]. Indeed,
288 the mean age of our patients was 65.7 years compared with 47 and 49 years in the cohorts from
289 Singapore and China, respectively [4, 13].

290 It is worth mentioning that in most of the published prognostic studies on COVID-19 demographic
291 characteristics (older age and male sex), underlying comorbidities, and altered laboratory tests
292 (e.g. CRP, LDH and lymphocytes counts) correlated with poor outcome as in our study [16, 17].
293 The strongest underlying condition influencing outcome in our analysis was obesity as observed for
294 other severe viral pneumonia, like H1N1 flu [18]. Recently, a similar score was developed and
295 validated in Chinese hospitals[19]. This score compared to ours requires online calculator so it
296 could be less applicable in emergency situations and some of the included variables like
297 hemoptysis were very rarely reported in our cohort. This may represent differences between
298 population and settings.

299 Our study has a number of limitations. First, being a retrospective study, several variables were not
300 systematically collected across all centers, especially in these times of great clinical duties and
301 stress of the healthcare system. This might introduce bias if patients in more severe clinical
302 conditions had a higher chance of missing information. For example, interleukin-6 and D-dimer
303 previously showed a significant correlation with disease progression [20], but were not available in
304 this study. However, the strict correlation between interleukin-6 and all acute phase proteins,

305 including CRP is well known [21]. Additionally, interleukin-6 is not available in most laboratory
306 chemistry panels of emergency rooms or wards of non-tertiary hospitals. The inclusion of such
307 parameters in our score could reduce the applicability of our score. Second, we included only
308 patients with SARS-CoV-2 positive nasopharyngeal swab; this could contribute to a selection bias.
309 In fact, the testing algorithm may have been affected by local policies [14]. Additionally, some
310 patients could have been excluded from the study considering the suboptimal sensitivity of
311 nasopharyngeal swabs [22]. Third, patients with SRF within the first 24 hours from admission, were
312 excluded: we made this choice because we aimed to identify patients at risk of unfavorable clinical
313 evolution, rather than discriminating between those already in severe clinical conditions at
314 admission. Fourth, our score has been developed and validated in Italian hospitals; even if
315 restricted to single Country analysis, local care practices might have strong impact on SRF rates.
316 However, the PREDI-CO score performed similarly in different cohorts, providing external
317 validation. Lastly, one risk factor for SRF (respiratory rate) may overlap with its definition. Being
318 aware that this may constitute a bias we preferred to maintain this parameter as is commonly used
319 in other clinical score (qSOFA and CURB-65) to increase the applicability of our model.

320 To conclude, we developed and validated an individual risk score including eight strong predictors
321 of SRF to identify at hospital admission patients with COVID-19 diagnosis deserving a high level of
322 care and a prompt medical treatment. In particular, in our setting with high frequency of respiratory
323 failure (as was seen in the first phases of the pandemic in Italy) the negative predictive values was
324 good, and therefore our score might be useful to identify patients which might not need ICU or high
325 intensity care. If furtherly validated in a prospective study our score might serve for both rationing
326 decisions at healthcare levels and for selecting patients to include in randomized controlled trials
327 on new treatment options.

328

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332 Study concept and design:

333 **Authors' contribution:**

334 Conceptualization: PV, MB, MG, LS, CM, ST, MT, VMR, TT

335 Methodology: MB, LS, MG, MR, MT, TT

336 Investigation: LB, GF, RP, LP, ZP, FT, LB, CC, LA, MMer, MMen, MMes, AL, SR, PG

337 Formal Analysis: MB, MG, LS

338 Writing- Original Draft: MG, MB

339 Writing- Review & Editing: LS, PV, TT, FB, VMR,

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341

342 **CONFLICT OF INTERESTS**

343 Authors state no conflict of interest related to the content of the present study.

344

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417

418 Table 1. Comparison of patients in derivation and validation cohort

	Overall cohort N=1113 (%)	Derivation N=644 (%)	Validation N=469 (%)	p
Demographics				
Age, years, mean (\pm SD)	65.7 (\pm 15.2)	63.7 (\pm 15.6)	68.5 (\pm 14.1)	<0.001
Male	704 (63.3)	376 (58.4)	328 (69.9)	<0.001
Underlying diseases				
Obesity	196 (17.6)	122 (18.9)	74 (15.8)	0.003
BMI, median (IQR)	26 (24-29)	25 (23-29)	26.1 (24-29)	0.03
Hypertension	579 (52)	321(49.8)	258 (55)	0.20
Diabetes mellitus	60 (5.4)	37 (5.7)	23 (4.9)	0.04
Coronary disease	83 (7.5)	56 (8.7)	27 (5.8)	0.08
Congestive heart failure	73 (6.6)	32 (5)	41 (8.7)	0.014
Cerebrovascular disease	93 (8.4)	44 (6.8)	49 (10.5)	0.04

Peripheral vascular disease	114 (10.2)	38 (5.9)	76 (16.2)	<0.001
Chronic kidney disease	115 (10.3)	61 (9.5)	54 (11.5)	0.3
COPD	113 (10.2)	58 (9)	55 (11.7)	0.16
ESLD	25 (2.3)	11 (1.7)	14 (3)	0.22
Immunosuppression	42 (3.8)	21 (3.3)	21 (4.5)	<0.001
Charlson index, median (IQR)	3.3 (1-5)	3.1 (1-5)	3.7 (2-5)	<0.001
Symptoms at onset				
Fever $\geq 38^{\circ}\text{C}$	597 (53.6)	332 (51.6)	265 (56.5)	0.03
Cough	635 (57.1)	380 (59)	255 (54.4)	0.06
Dyspnoea	381 (34.2)	241 (37.4)	140 (29.9)	0.007
Symptoms at hospitalization				
Fever $\geq 38^{\circ}\text{C}$	435 (39.1)	248 (38.5)	187 (39.9)	0.47
Cough	609 (54.3)	376 (58.4)	233 (49.7)	<0.001
Dyspnoea	470 (42.2)	256 (39.8)	214 (45.6)	0.03
Vital signs at hospitalization				
GCS, median (IQR)	15 (15-15)	15 (15-15)	15 (15-15)	0.54
MAP, median (IQR)	90 (83-98)	90 (83-97)	90 (83-98)	0.59
PR, median (IQR)	85 (75-95)	85 (75-95)	86 (76-95)	0.31
RR, median (IQR)	20 (16-24)	20 (16-24)	20 (18-24)	0.002
SatO ₂ on ambient air, median (IQR)	95.4 (93-97)	96.5 (94-98)	94 (92-96)	<0.001
Laboratory tests at hospitalization				
Lymphocytes ($10^9/\text{L}$)	0.97 (0.7-1.3)	1.06 (0.79-1.4)	0.89 (0.63-1.2)	<0.001

median (IQR)				
CRP (mg/dl), median (IQR)	5.2 (2.2-10.6)	5 (2.1-9.8)	5.6 (2.4-11)	0.03
LDH (IU/L), median (IQR)	287 (224-391)	271 (214-356)	316 (245-414)	<0.001
Treatments				
Hydroxychloroquine	896 (80)	477 (74)	419 (89)	<0.001
Lopinavir/ritonavir	341 (31)	154 (24)	187 (40)	<0.001
Darunavir/ ritonavir	251 (22)	9 (1)	242 (52)	<0.001
Darunavir/ cobicistat	31 (3)	14 (2)	17 (4)	0.87
LMWH	357 (32)	231 (36)	126 (27)	<0.001
Tocilizumab	129 (12)	87 (13)	42 (9)	0.23
Outcome				
ICU admission	139 (12)	71 (11)	68 (15)	<0.001
In-hospital mortality	218 (19)	102 (15)	116 (25)	<0.001

419

420 Abbreviations: BMI body mass index; COPD chronic obstructive pulmonary disease; CRP C-
421 reactive protein; ESLD end-stage liver disease; GCS Glasgow coma scale; HRCT high-resolution
422 computed tomography; LDH lactate dehydrogenase; MAP mead arterial pressure; PR pulse rate;
423 IQR interquartile range; IU international units

Table 2. Univariate analysis for severe respiratory failure among patients with SARS-CoV-2 pneumonia: derivation cohort.

	Cases with available data	Severe respiratory failure N= 189/644 (%)	No Severe respiratory failure N=455/644 (%)	Odds Ratios (95% CI)
Demographics				
Age (years), mean (\pm SD)	644	72.2 (\pm 13.9)	60.1 (\pm 14.8)	1.06 (1.045-1.073)*
Sex, Male	644	108 (57)	268 (59)	0.93 (0.66-1.31)
Underlying diseases				
Obesity	633	76 (40)	46 (10)	6.09 (3.99-9.3)
BMI, median (IQR)	393	28.3 (25-31)	25.9 (23-27)	1.14 (1.085-1.21)*
Hypertension	636	126 (67)	195 (42)	2.75 (1.92-3.93)
Diabetes mellitus	643	18 (9)	19 (4)	2.11 (1.04-4.3)
Coronary artery disease	644	25 (13)	31 (6)	2.09 (1.2-3.64)
Congestive heart failure	644	16 (8)	16 (3)	2.54 (1.2-5.2)
Cerebrovascular disease	644	30 (18)	14 (3)	5.94 (3.07-11.5)

Peripheral vascular disease	644	19 (10)	16 (3)	2.57 (1.33-4.96)
Chronic kidney disease (moderate to severe)	644	20 (11)	41 (9)	1.2 (0.68-2.1)
COPD	644	32 (16)	26 (6)	3.36 (1.94-5.8)
Immunosuppression	618	9 (5)	12 (3)	1.98 (0.82-4.79)
Charlson index (median, IQR)	588	4.4 (2-6)	2.5 (1-4)	1.32 (1.23-1.42)*
Symptoms at onset				
Fever $\geq 38^{\circ}\text{C}$	626	96 (51)	236 (51)	0.96 (0.57-1.62)
Cough	629	98 (52)	282 (62)	0.69 (0.49-0.99)
Dyspnoea	630	93 (49)	148 (32)	2.09 (1.47-2.96)
Time to hospital admission (days), median (IQR)	560	6 (3-9)	6 (3-8)	0.95 (0.93-0.97)*
Symptoms at hospitalization				
Fever $\geq 38^{\circ}\text{C}$	637	98 (52)	150 (33)	2.23 (1.58-3.17)

Cough	635	93 (49)	283 (62)	0.59 (0.42-0.83)
Dyspnoea	636	108 (57)	148 (32)	2.83 (1.99-4.02)
Vital signs at hospitalization				
GCS (median, IQR)	597	15 (15-15)	15 (15-15)	0.68 (0.53-0.87)*
MAP (median, IQR)	598	90.7 (83-96)	91.4 (83-96)	0.99 (0.98-1.01)*
PR (median, IQR)	585	85 (76-94)	85 (75-95)	1.00 (0.99-1.01)*
RR (median, IQR)	623	24 (20-27)	18 (16-21)	1.14 (1.1-1.18)*
SatO2 on ambient air (%), (median, IQR)	580	95 (93-97)	97 (95-98)	0.98 (0.96-1.00)*
Laboratory tests at hospitalization				
Lymphocytes ($10^9/L$), median (IQR)	595	0.84 (0.60-1.06)	1.17 (0.88-1.51)	0.16 (0.10-0.28)*
CRP (mg/dL), median (IQR)	601	11.0 (5.3-16.0)	3.3 (1.6-6.99)	1.2 (1.16-1.25)*
LDH (IU/L), median (IQR)	569	350 (255-491)	255 (201-313)	1.0 (1.003-1.006)*

Glucose median (IQR)	(mg/dL), 487	116 (102-137)	107 (94-123)	1.01 (1.003-1.01)*
Creatinine median (IQR)	(mg/dL), 623	1.06 (0.86-1.36)	0.86 (0.71- 1.03)	1.44 (1.15-1.81)*
Sodium median (IQR)	(mmol/L), 525	137 (135-141)	137 (135-140)	1.02 (0.98-1.06)*
Potassium median (IQR)	(mmo/L), 513	4 (3.7-4.4)	4 (3.7-4.3)	0.96 (0.82-1.14)*
Bilirubin (IQR)	(mg/dL), median 502	0.65 (0.45-0.85)	0.60 (0.46- 0.80)	1.57 (1.03-2.34)*
Aspartate aminotransferase median (IQR)	(IU/L), 531	35 (27-45)	31 (23-42)	1.00 (1.00-1.01)*
Alanine aminotransferase median (IQR)	(IU/L) 566	22 (16-32)	27 (18-40)	1.00 (0.99-1.00)*

*for each year, point or unit increase Abbreviations: BMI body mass index; COPD chronic obstructive pulmonary disease; CRP C-reactive protein; ESLD end-stage liver disease; GCS Glasgow coma scale; HRCT high-resolution computed tomography LDH lactate dehydrogenase; MAP mead arterial pressure; PR pulse rate; IQR interquartile range;

Abbreviations: BMI body mass index; COPD chronic obstructive pulmonary disease; CRP C-reactive protein; ESLD end-stage liver disease; GCS Glasgow coma scale; HRCT high-resolution computed tomography LDH lactate dehydrogenase; MAP mead arterial pressure; PR pulse rate; IQR interquartile range;

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Table 3. Univariate analysis for severe respiratory failure among patients with SARS-CoV-2 pneumonia: validation cohort.

	Cases with available data	Severe respiratory failure N= 187/469 (%)	No Severe respiratory failure N=282/469 (%)	Odds Ratios (95% CI)
Demographics				
Age (years), mean (\pm SD)	469	72.4 (\pm 12.3)	65.8 (\pm 14.6)	1.04 (1.02-1.05)*
Sex, Male	469	145 (77)	183 (64)	1.87 (1.23-2.85)
Underlying diseases				
Obesity	469	42 (22)	32 (11)	2.26 (1.37-3.74)
BMI, median (IQR)	195	28 (25-31)	25 (24-28)	1.13 (1.04-1.23)*
Hypertension	469	114 (61)	144 (51)	1.51 (1.04-2.23)
Diabetes mellitus	469	17 (9)	5 (2)	4.1 (1.27-13.3)
Coronary artery disease	469	17 (9)	10 (3)	2.72 (1.22-6.08)
Congestive heart failure	469	24 (13)	17 (6)	2.3 (1.19-4.4)

Cerebrovascular disease	469	22 (12)	27 (10)	1.26 (0.69-2.29)
Peripheral vascular disease	469	46 (25)	30 (11)	2.74 (1.66-4.54)
Chronic kidney disease (moderate to severe)	469	30 (16)	24 (9)	2.05 (1.16-3.64)
COPD	469	29 (16)	26 (9)	1.81 (1.03-3.2)
Immunosuppression	469	14 (7)	7 (2)	3.18 (1.26-8.03)
Charlson index (median, IQR)	461	5 (3-7)	3 (1-5)	1.25 (1.16-1.35)*
Symptoms at onset				
Fever $\geq 38^{\circ}\text{C}$	469	115 (61)	150 (53)	0.99 (0.5-1.95)
Cough	469	98 (52)	157 (98)	0.93 (0.64-1.35)
Dyspnoea	469	77 (41)	63 (122)	2.55 (1.7-3.8)
Time to hospital admission (days), median (IQR)	451	6 (2-9)	6 (2-9)	0.94 (0.90-1.09)*
Symptoms at hospitalization				

Fever $\geq 38^{\circ}\text{C}$	469	91 (48)	96 (34)	1.85 (1.26-2.7)
Cough	469	91 (48)	142 (59)	0.94 (0.65-1.35)
Dyspnoea	469	108 (57)	142 (50)	2.26 (1.57-3.29)
Vital signs at hospitalization				
GCS (median, IQR)	446	15 (15-15)	15 (15-15)	0.56 (0.32-0.98)*
MAP (median, IQR)	461	90.7 (83-96)	91.4 (83-96)	0.97 (0.31-3.00)*
PR (median, IQR)	468	87 (79-99)	85 (75-93)	1.02 (1.00-1.03)*
RR (median, IQR)	459	22 (16-22)	20 (16-22)	1.12 (1.07-1.16)*
SatO2 on ambient air (%), (median, IQR)	416	95 (93-97)	97 (95-98)	0.91 (0.86-0.96)*
Laboratory tests at hospitalization				
Lymphocytes ($10^9/\text{L}$), median (IQR)	468	0.72 (0.51-0.98)	0.96 (0.73-1.34)	0.25 (0.15-0.41)*
CRP (mg/dL), median (IQR)	454	11.2 (6.19-15.8)	3.5 (1.8-6.5)	1.27 (1.21-1.33)*
LDH (IU/L), median	406	398 (309-476)	278(228-355)	1.01 (1.00-1.01)*

(IQR)					
Glucose (mg/dL), median (IQR)	412	124 (110-155)	112 (101-129)	1.00 (1.00-1.01)*	
Creatinine (mg/dL), median (IQR)	460	1.12 (0.89-1.59)	0.99 (0.82- 1.15)	2.46 (1.63-3.71)*	
Sodium (mmol/L), median (IQR)	403	136 (133-139)	137 (134-139)	1.00 (0.98-1.02)*	
Potassium (mmo/L), median (IQR)	381	3.9 (3.5-4.3)	3.9 (3.7-4.2)	1.18 (0.8-1.73)*	
Bilirubin (mg/dL), median (IQR)	174	0.55 (0.38-0.80)	0.50 (0.34- 0.74)	1.88 (0.89-3.97)*	
Aspartate aminotransferase (IU/L), median (IQR)	206	44 (21-66)	28 (23-34)	1.04 (1.01-1.06)*	
Alanine aminotransferase (IU/L) median (IQR)	566	26 (16-42)	24 (17-35)	1.01 (1-1.02)*	

* for each year/day, point or unit increase Abbreviations: BMI body mass index; COPD chronic obstructive pulmonary disease; CRP C-reactive protein; ESLD end-stage liver disease; GCS Glasgow coma scale; HRCT high-resolution computed tomography LDH lactate dehydrogenase; MAP mead arterial pressure; PR pulse rate; IQR interquartile range;

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Table 4. Multivariate analysis of risk factors for respiratory failure in derivation and validation cohort, and score development

	Derivation Cohort					Validation Cohort		
	OR	95%CI	p	β - coefficient	Points	OR	95%CI	
Age \geq 70 years	2.74	1.66-4.50	<0.001	1.01	1	2.25	1.45-3.49	<0.001
Obesity	4.62	2.78-7.70	<0.001	1.53	1	1.07	0.72-1.60	0.73
Fever \geq 38°C at hospitalization	1.73	1.30-2.29	<0.001	0.55	1	1.87	0.99-3.52	0.05
RR \geq 22 bpm	3.75	2.01-7.01	<0.001	1.32	1	2.44	1.41-4.21	0.001
Lymphocytes \leq 0.9 $10^9/L$	2.69	1.60-4.51	<0.001	0.99	1	1.94	1.15-3.27	0.01
CRP \geq 10 mg/dL	5.91	4.88-7.17	<0.001	1.78	2	8.44	4.72-15.07	<0.001
LDH \geq 350 IU/L	2.39	1.11-5.11	0.025	0.87	1	3.34	2.51-4.44	<0.001
Creatinine \geq 1 mg/dL	2.38	1.59.-3.56	<0.001	0.87	1	1.35	1.16-1.57	<0.001

Abbreviations: CI confidence intervals; CRP C-reactive protein; LDH Lactate dehydrogenase OR Odds ratio; RR respiratory rate

Figure 1. Study flow-chart: derivation cohort (panel A) and validation cohort (panel B)

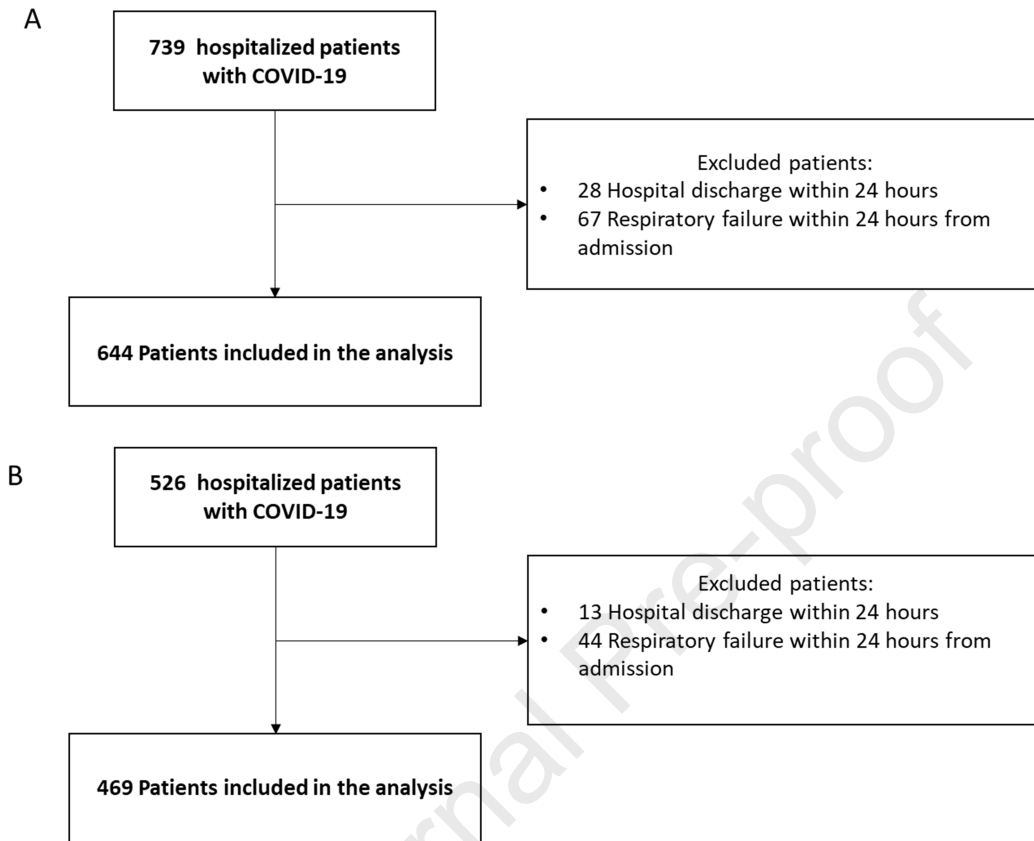
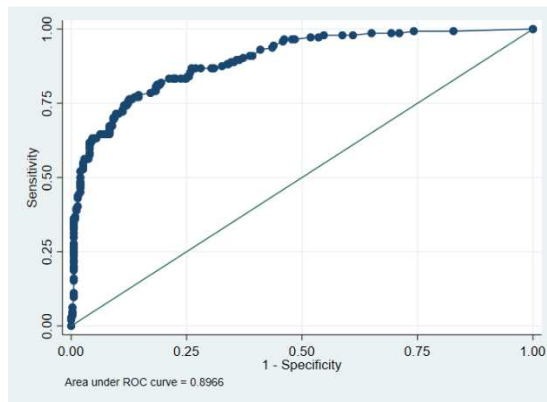
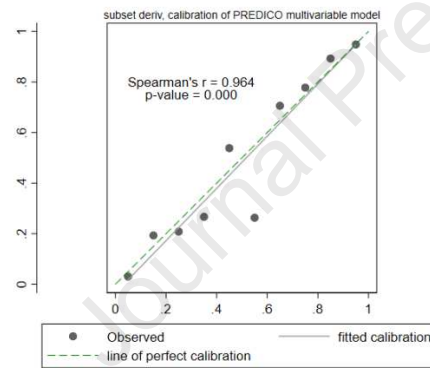


Figure 2. Discrimination (panel A) and calibration (panel B) of the multivariable model, and discrimination (panel C) of the PREDI-CO score in the derivation cohort. Discrimination (panel D), calibration (panel E), and discrimination (panel F) of the PREDICO score in the validation cohort

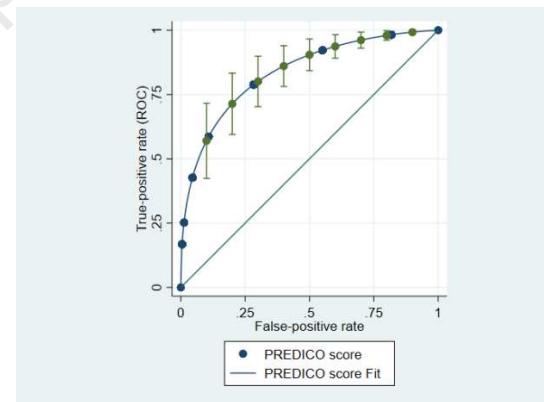
PANEL A



PANEL B



PANEL C



PANEL D

PANEL E

PANEL F

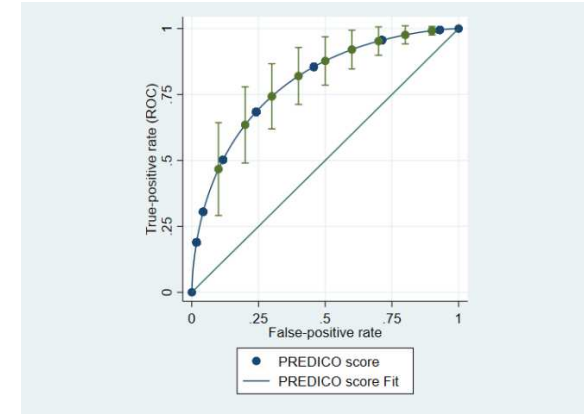
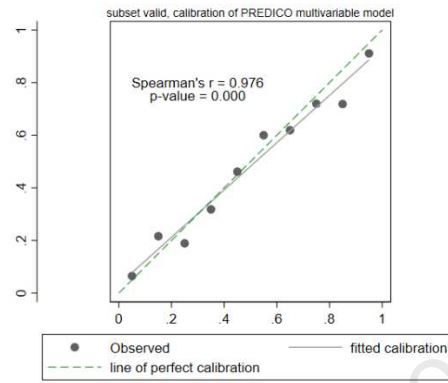
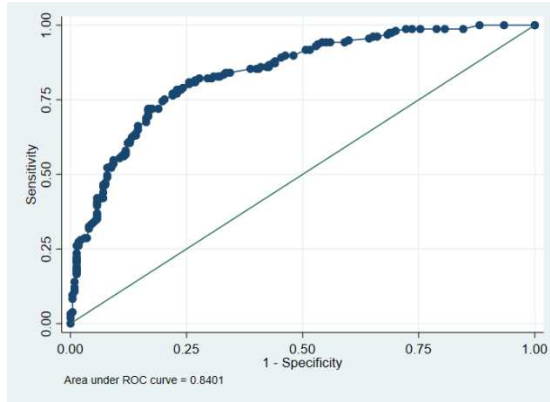
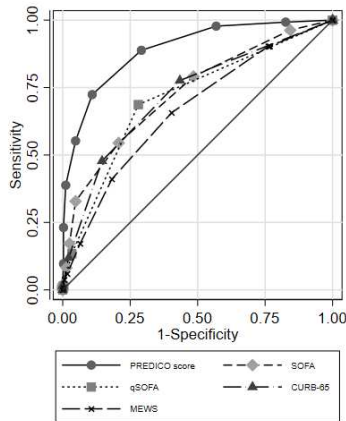


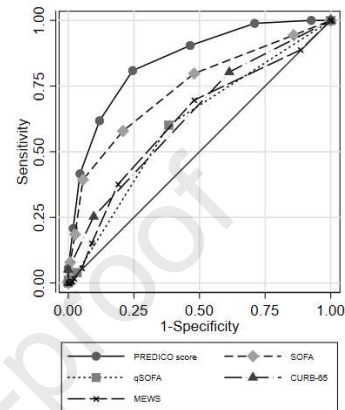
Figure 3. Comparison of prediction ability for severe respiratory failure in hospitalized patients with COVID.19 diagnosis of the PREDICO score with qSOFA, SOFA, CURB-65 and MEWS scores.

Panel A derivation cohort; Panel B validation cohort

A



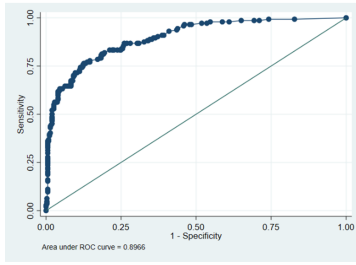
B



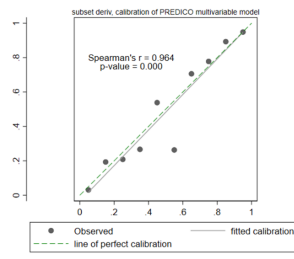
	Derivation cohort			Validation cohort		
	AUC	Lower 95% confidence interval	Upper 95% confidence interval	AUC	Lower 95% confidence interval	Upper 95% confidence interval
PREDI-CO score	0.89	0.86	0.92	0.85	0.81	0.88
SOFA	0.73	0.68	0.78	0.74	0.69	0.79
qSOFA	0.71	0.66	0.76	0.61	0.56	0.65
CURB-65	0.72	0.67	0.77	0.64	0.59	0.68
MEWS	0.66	0.61	0.72	0.62	0.56	0.67

Abbreviations: AUC area under the curve MEWS Modified Early Warning Score, SOFA Sequential Organ Failure Assessment

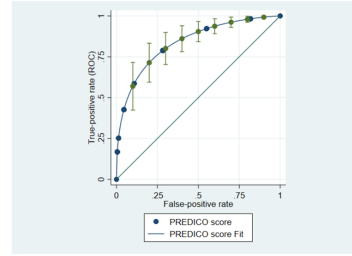
A



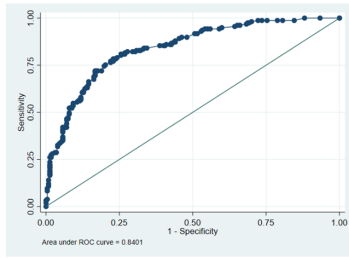
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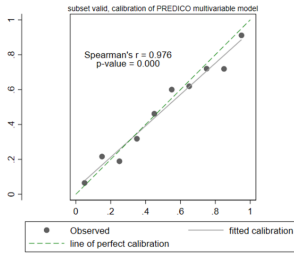
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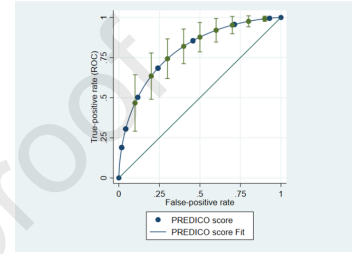
D



E

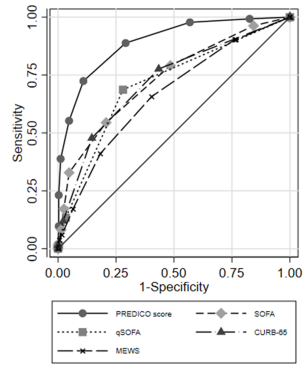


F



Journal Pre-proof

A



B

