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# Journal Pre-proof

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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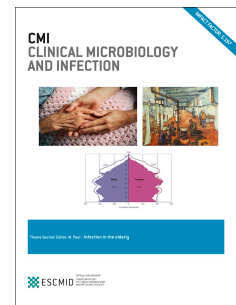
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**Original article:**

**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)**

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## ABSTRACT

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

**Methods:** We performed a multicentre cohort study among hospitalized (>24 hours) patients diagnosed with COVID-19 from February 22 to April 3 2020, at 11 Italian hospitals. Patients were divided into derivation and validation cohorts according to random sorting of hospitals. SRF was assessed from admission to hospital discharge and was defined as: SpO<sub>2</sub><93% with 100% FiO<sub>2</sub>, respiratory rate (RR)>30bpm, or respiratory distress. Multivariable logistic regression models were built to identify predictors of SRF,  $\beta$ -coefficients were used to develop a risk score. Trial Registration NCT04316949 .

**Results:** We analyzed 1113 patients (644 derivation, 469 validation cohort). Mean ( $\pm$  standard deviation) age was 65.7( $\pm$ 15) years, 704 (63.3%) were male. SRF occurred in 189/644 (29%) and 187/469 (40%) patients in derivation and validation cohort, respectively. At multivariate analysis, risk factors for SRF in the derivation cohort assessed at hospitalization were age  $\geq$ 70 years [OR 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 (95%CI 1.30-2.29)], RR  $\geq$ 22bpm [OR 3.75 (95%CI 2.01-7.01)], lymphocytes  $\leq$ 900/mm<sup>3</sup> [OR 2.69 (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 [OR 5.91 (95%CI 4.88-7.17)], and lactate dehydrogenase  $\geq$ 350IU/L [OR 2.39 (95%CI 1.11-5.11)]. Assigning points to each variable an individual risk score (PREDI-CO score) was obtained. Area under receiver-operator curve (AUROC) was 0.89 (0.86-0.92). At score of >3, sensitivity, specificity, positive and negative predictive values were 71.6%(65-79%), 89.1% (86-92%), 74%(67-80%), and 89%(85-91%), respectively;. PREDI-CO score showed similar prognostic ability in the validation cohort: AUROC 0.85 (0.81-0.88). At score of >3, sensitivity, specificity, positive and negative predictive values were 80% (73-85%), 76 (70-81%), 69%(60-74%) and 85% (80-89%), 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

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

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

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

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

#### Participants

All consecutive adult patients ( $\geq 18$  years) diagnosed with SARS-CoV-2 infection during the study period were included.

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

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

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

#### Variables and definitions

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

The endpoint variable was occurrence of SRF. Occurrence SRF was assessed reviewing collected data from admission to hospital discharge by a blinded investigator (ST). SRF was defined according to World and Health Organization (WHO) criteria as: SpO<sub>2</sub><93% with 100% FiO<sub>2</sub> (reservoir mask or continuous positive airway pressure ventilation or other non-invasive ventilation), respiratory rate >30 bpm, or respiratory distress[10].

Exposure variables were assessed at hospital admission and included: age, older age (>70 years), sex, body mass index, being obese (BMI >30 kg/m<sup>2</sup>). Underlying conditions were recorded according to Charlson comorbidity index[11]. Hypertension was defined as history of permanent increase of systolic blood pressure over 140 mmHg, and a diastolic increase to more than 90 mmHg. Immunosuppression included neutropenia (neutrophil count <500/mm<sup>3</sup>), solid organ transplantation, hematopoietic stem cell transplantation, corticosteroid therapy at a dosage higher than or equivalent to prednisone 16 mg/day ≥ 15 days, uncontrolled HIV infection (<200 CD4/mm<sup>3</sup>). Regarding the SARS-CoV2 infection, symptoms at onset and hospitalization, vital signs and laboratory tests were collected. Severity of illness at hospitalization was recorded according to sequential organ failure assessment (SOFA) score[13], quickSOFA (qSOFA)[14], CURB-65 score[15] and Modified Early Warning Score (MEWS)[16].

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

#### Microbiological testing

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

### Study size

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

### Statistical analysis

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

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



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

## RESULTS

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

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

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

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

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

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

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

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**AUTHORS CONTRIBUTION:**

Study concept and design:

**Authors' contribution:**

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

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

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

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

Supervision: FB, MC, MP; CM, FC, PV

**CONFLICT OF INTERESTS**

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

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Table 1. Comparison of patients in derivation and validation cohort

	Overall cohort N=1113 (%)	Derivation N=644 (%)	Validation N=469 (%)	p
<b>Demographics</b>				
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
<b>Underlying diseases</b>				
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
<b>Symptoms at onset</b>				
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
<b>Symptoms at hospitalization</b>				
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
<b>Vital signs at hospitalization</b>				
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
SatO2 on ambient air, median (IQR)	95.4 (93-97)	96.5 (94-98)	94 (92-96)	<0.001
<b>Laboratory tests at hospitalization</b>				
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
<b>Treatments</b>				
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
<b>Outcome</b>				
<b>ICU admission</b>	139 (12)	71 (11)	68 (15)	<0.001
<b>In-hospital mortality</b>	218 (19)	102 (15)	116 (25)	<0.001

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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)
<b>Demographics</b>				
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)
<b>Underlying diseases</b>				
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)*
<b>Symptoms at onset</b>				
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)*
<b>Symptoms at hospitalization</b>				
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)
<b>Vital signs at hospitalization</b>				
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)*
<b>Laboratory tests at hospitalization</b>				
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 (mg/dL), median (IQR)	487	116 (102-137)	107 (94-123)	1.01 (1.003-1.01)*
Creatinine (mg/dL), median (IQR)	623	1.06 (0.86-1.36)	0.86 (0.71-1.03)	1.44 (1.15-1.81)*
Sodium (mmol/L), median (IQR)	525	137 (135-141)	137 (135-140)	1.02 (0.98-1.06)*
Potassium (mmo/L), median (IQR)	513	4 (3.7-4.4)	4 (3.7-4.3)	0.96 (0.82-1.14)*
Bilirubin (mg/dL), median (IQR)	502	0.65 (0.45-0.85)	0.60 (0.46-0.80)	1.57 (1.03-2.34)*
Aspartate aminotransferase (IU/L), median (IQR)	531	35 (27-45)	31 (23-42)	1.00 (1.00-1.01)*
Alanine aminotransferase (IU/L) median (IQR)	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)
<b>Demographics</b>				
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)
<b>Underlying diseases</b>				
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)*
<b>Symptoms at onset</b>				
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)*
<b>Symptoms at hospitalization</b>				



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)
<b>Vital signs at hospitalization</b>				
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)*
<b>Laboratory tests at hospitalization</b>				
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 mean 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	$\beta$ - 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)

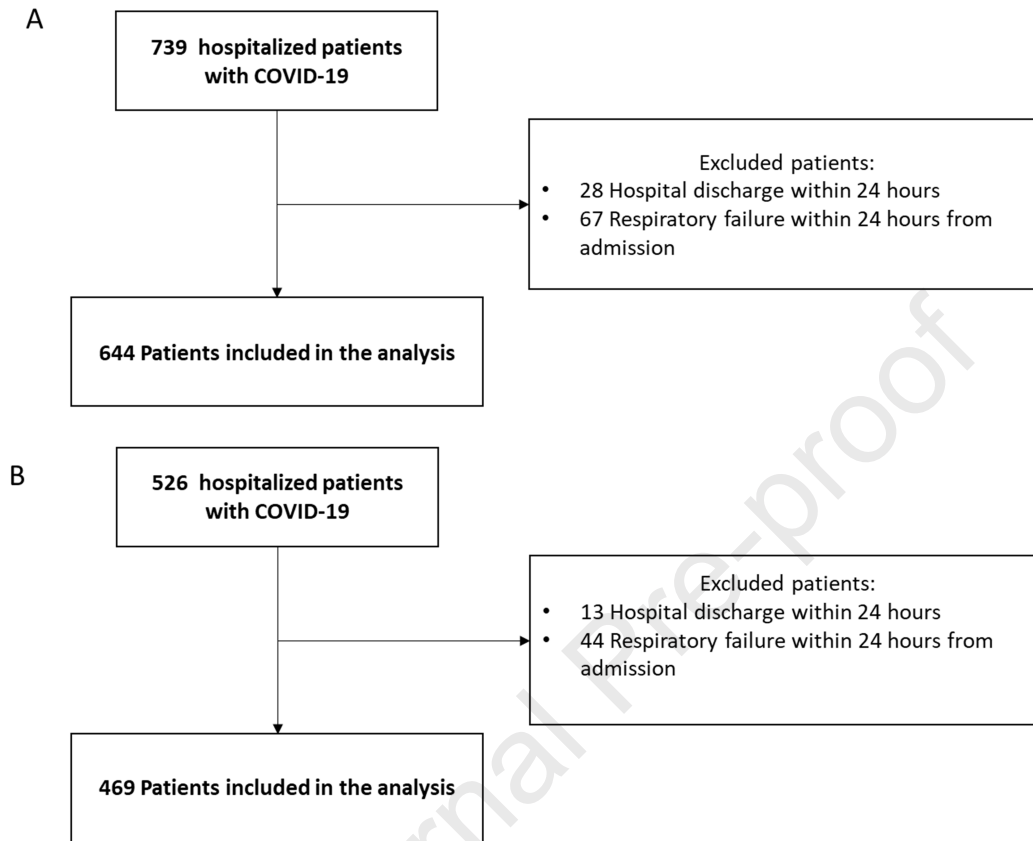
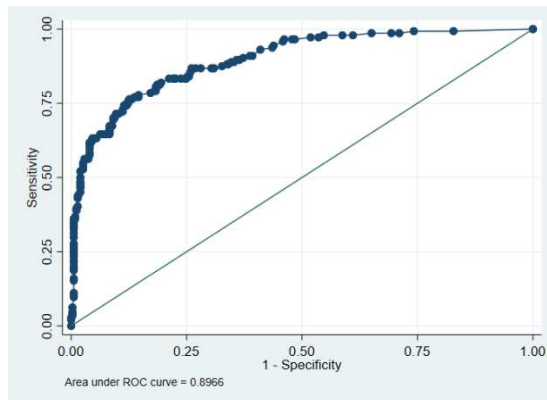
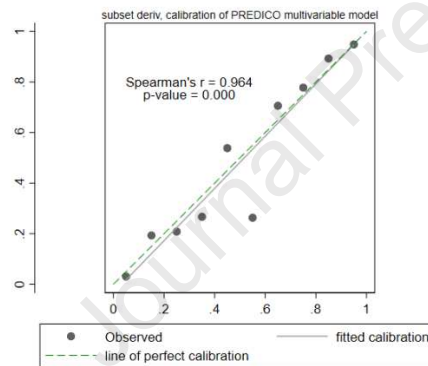


Figure 2. Discrimination (panel A) and calibration (panel B) of the multivariable model, and discrimination (panel C) of the PREDI-CO score in the derivation cohort. Discrimination (panel D), calibration (panel E), and discrimination (panel F) of the PREDICO score in the validation cohort

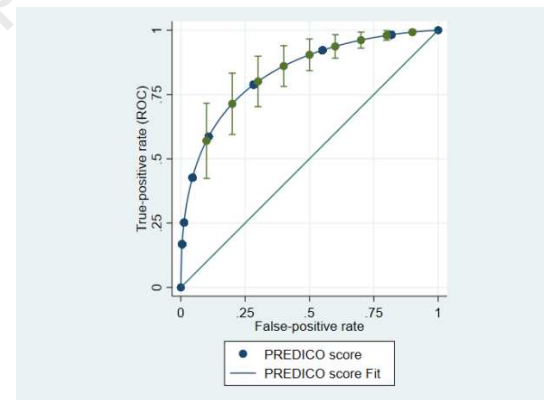
PANEL A



PANEL B



PANEL C



PANEL D

PANEL E

PANEL F

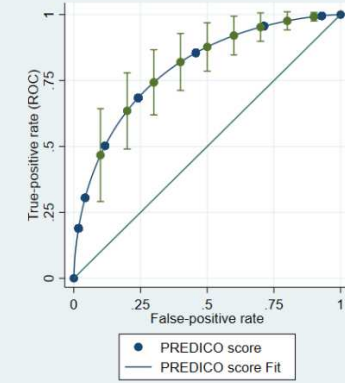
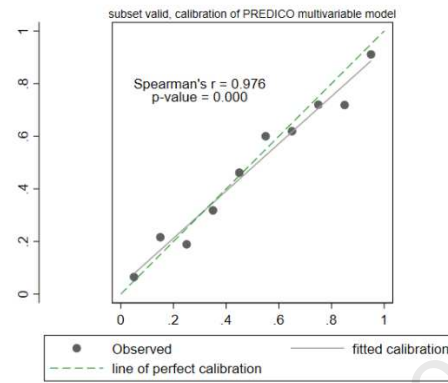
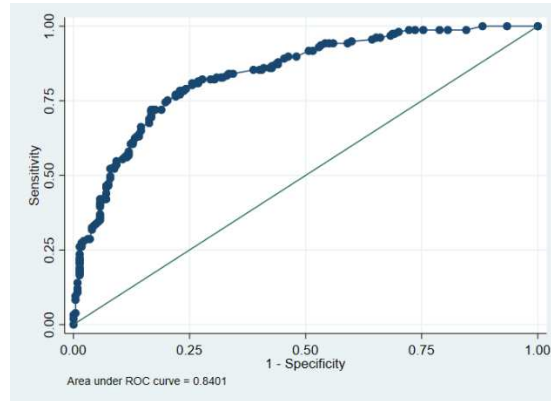
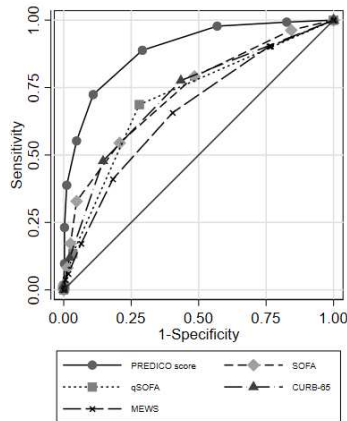


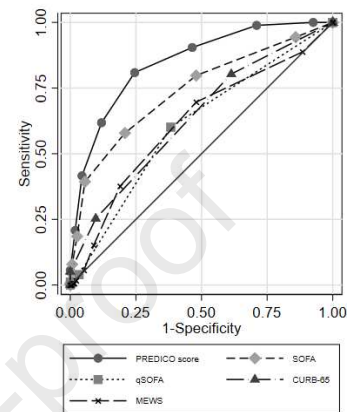
Figure 3. Comparison of prediction ability for severe respiratory failure in hospitalized patients with COVID.19 diagnosis of the PREDICO score with qSOFA, SOFA, CURB-65 and MEWS scores.

Panel A derivation cohort; Panel B validation cohort

A



B

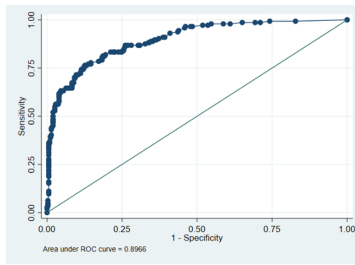


	Derivation cohort			Validation cohort		
	AUC	Lower 95% confidence interval	Upper 95% confidence interval	AUC	Lower 95% confidence interval	Upper 95% confidence interval
PREDI-CO score	0.89	0.86	0.92	0.85	0.81	0.88
SOFA	0.73	0.68	0.78	0.74	0.69	0.79
qSOFA	0.71	0.66	0.76	0.61	0.56	0.65
CURB-65	0.72	0.67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

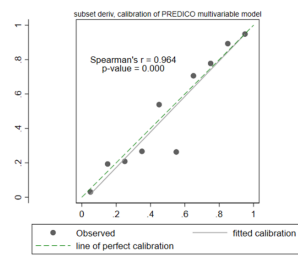
Abbreviations: AUC area under the curve MEWS Modified Early Warning Score, SOFA Sequential Organ Failure Assessment



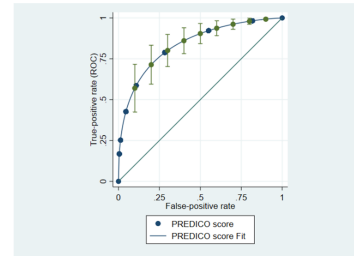
A



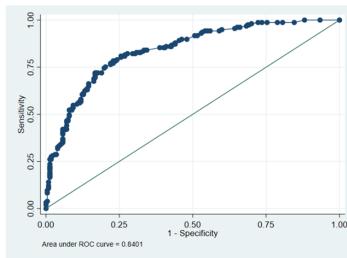
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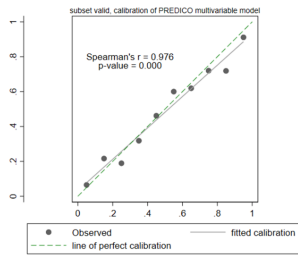
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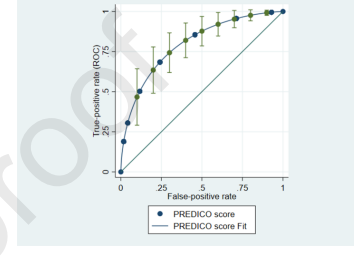
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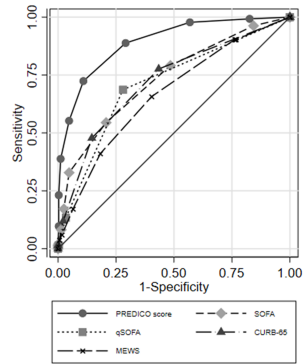
E



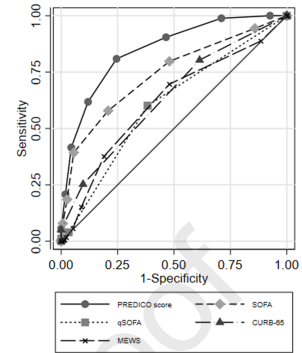
F



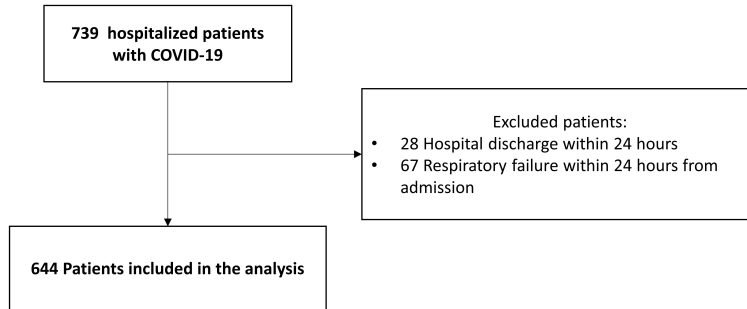
A



B



A



B

