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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 multicentre 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 22 February to 3 April 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_2 <93% with 100% Fio_2, respiratory rate >30 breaths/min or respiratory distress. Multivariable logistic regression models were built to identify predictors of SRF, β-coefficients were used to develop a risk score. Trial Registration NCT04316949.
Results: We analysed 1113 patients (644 derivation, 469 validation cohort). Mean (±SD) age was 65.7 (±15) years, 704 (63.3%) were male. SRF occurred in 189/644 (29%) and 187/469 (40%) patients in the derivation and validation cohorts, respectively. At multivariate analysis, risk factors for SRF in the derivation cohort assessed at hospitalization were age ≥70 years (OR 2.74; 95% CI 1.66–4.50), obesity (OR 4.62; 95% CI 2.78–7.70), body temperature ≥38°C (OR 1.73; 95% CI 1.30–2.29), respiratory rate ≥22 breaths/min (OR 3.75; 95% CI 2.01–7.01), lymphocytes ≤900 cells/mm^3 (OR 2.69; 95% CI 1.60–4.51), creatinine ≥1 mg/dL (OR 2.38; 95% CI 1.59–3.56), C-reactive protein ≥10 mg/dL (OR 5.91; 95% CI 4.88

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Severe acute respiratory syndrome coronavirus 2
Severe respiratory failure

−7.17) and lactate dehydrogenase ≥350 IU/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 the receiver-operator curve was 0.89 (0.86−0.92). At a score of >3, sensitivity, specificity, and 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: area under the receiver-operator curve 0.85 (0.81−0.88). At a score of >3, sensitivity, specificity, and positive and negative predictive values were 80% (73%−85%), 76% (70%−81%), 69% (60%−74%) and 85% (80%−89%), respectively.
Conclusion: PREDI-CO score can be useful to allocate resources and prioritize treatments during the COVID-19 pandemic. **Michele Bartoletti, Clin Microbiol Infect 2020;▪:1**

Introduction

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

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

To date, no therapy has proven effective, so supportive care aimed to protect multi-organ function represents the main resource to reduce mortality [5]. The capacity of the system is limited, prompting the need of rationing decisions [6], but a number of promising innovative drugs and treatment strategies are under investigation [7]. We deemed that an early identification of patients at risk of developing SRF could support the planning of resources and help to set up organizational and clinical interventions, including early pharmacological treatment to prevent admission to the intensive care unit.

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

Methods

Design and setting

We performed a retrospective multicentre cohort study of prospectively collected data from patients with laboratory-confirmed SARS-CoV-2 infection, hospitalized from 22 February through 3 April, 2020. Last follow-up date was 23 April 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 material, Fig. S1).

Diagnostic testing for COVID-19 and hospitalization were performed according to local policy and clinical judgement, 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 Ethics Committee of the promoting centre (Comitato Etico Indipendente di Area Vasta Emilia Centro, n.283/2020/Oss/AOUBo). A waiver of informed consent was granted by the Ethics Committee due to safety risk. The study protocol was registered on clinicaltrials.gov with the number NCT04316949.

Participants

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

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

Participants were divided into two 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 and H (see Supplementary material, Fig. S1). Hospitals were sorted randomly and assigned initially to the derivation cohort. Once 50% of participants with a new assignation was reached, the remaining centres were assigned to the validation cohort.

Variables and definitions

Microbiological diagnosis of SARS-CoV-2 infection was defined as a positive RT-PCR test on nasopharyngeal swabs.

The end-point variable was occurrence of SRF. Occurrence SRF was assessed through review of the collected data from admission to hospital discharge by a blinded investigator (ST). SRF was defined according to WHO criteria as: Spo_2 <93% with 100% Fio_2 (reservoir mask or continuous positive airway pressure ventilation or other non-invasive ventilation), respiratory rate >30 breaths/minute, or respiratory distress [10].

Exposure variables were assessed at hospital admission and included: age, older age (>70 years), sex, body mass index, being obese (body mass index >30 kg/m^2). Underlying conditions were recorded according to the Charlson co-morbidity 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^3), solid organ transplantation, haematopoietic stem cell transplantation, corticosteroid therapy at a dosage higher then or equivalent to prednisone 16 mg/day ≥15 days, uncontrolled human immunodeficiency virus infection (<200 CD4/mm^3). Regarding the SARS-CoV-2 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, quickSOFA (qSOFA), CURB-65 score and Modified Early Warning Score (MEWS).

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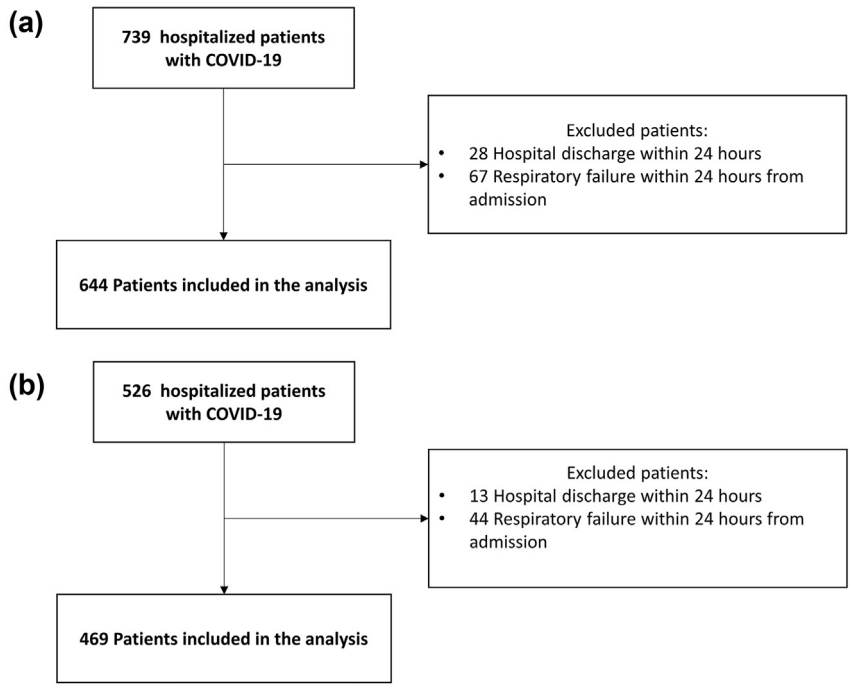

Fig. 1. Study flow-chart: derivation cohort (a) and validation cohort (b).

End-point 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-CoV-2 was detected by RT-PCR assay. Briefly, UTM-RT swab specimens (Copan, Brescia, 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 (BioMérieux, Marcy l'Étoile, France) following the 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, Waltham, MA, 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 eight 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's *t* test, Mann–Whitney *U* test and analysis of variance, or Kruskal–Wallis test were used for normally distributed quantitative variables, skewed distributed quantitative variables and more than two groups, respectively. Pearson's χ^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.

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

Univariate and multivariate mixed logistic regression models were performed to investigate risk factors for SRF. Variables were included in the multivariable model according the following strategy: clinically relevant variables, significance at the univariable analysis ($p < 0.10$), lack of co-linearity (in case of co-linearity, the model with lower Akaike Information Criterion was chosen), missing data in <10% of cases (i.e. we performed a complete case analysis). Overall goodness of fit was analysed by Akaike's Information Criteria and Nagelkerke's R^2. Discrimination of the model was assessed by receiver-operator characteristics (ROC) curve of the predicted probability, Brier score and Somers' D. Calibration of the model was assessed by comparing predicted probability with actual probability of SRF in deciles of risk. Cluster-robust variance was used, to take into account within-hospital correlation.

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

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

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

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Table 1
Comparison of patients in derivation and validation cohort

	Overall cohort ($n = 1113$)	Derivation cohort ($n = 644$)	Validation ($n = 469$)	p
Demographics				
Age (years), mean (±SD)	65.7 (±15.2)	63.7 (±15.6)	68.5 (±14.1)	<0.001
Sex, 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 (kg/m^2), 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 ≥38°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 ≥38°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/L) median (IQR)	0.97 (0.7–1.3)	1.06 (0.79–1.4)	0.89 (0.63–1.2)	<0.001
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
Tociluzumab	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

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; IQR, interquartile range; IU, international units; LDH, lactate dehydrogenase; MAP, mean arterial pressure; PR, pulse rate.
All values given are *n* (%) unless otherwise stated.

All statistical tests were two-sided. Stata computer software version 16.0 (Stata Corp., College Station, TX, USA) was used for statistical analysis.

Results

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

The mean age of participants was 65.7 ± 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 patient characteristics (Table 1).

Three-hundred and seventy-six individuals (33%) developed SRF after ≥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 rates of SRF were 29% (189/644) and 40% (187/469) in the derivation and validation cohorts, respectively.

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

In the derivation cohort, multivariate analysis showed that age ≥70 years, obesity, fever at hospitalization (body temperature ≥38°C), respiratory rate ≥22 breaths/minute, lymphocytes ≤900 cells/mm^3, creatinine ≥1 mg/dL, C-reactive protein ≥10 mg/dL and lactate dehydrogenase ≥350 UI/L were independent risk factors for developing SRF (Table 4). The model was highly discriminant: area under the ROC 0.90 (Fig. 2a), Brier score 0.11, Somers' D 0.79 (95% CI 0.73–0.85). Calibration (Fig. 2b) and fitting (Fig. 2c) of the model were also good. In the validation cohort the model performed similarly in terms of discrimination, calibration (Fig. 2d,e, respectively), fitting (Fig. 2f) and distribution (see Supplementary material, Fig. S2b). Area under the ROC curve was 0.84 with Brier score 0.16 and Somers' D 0.68 (95% CI 0.60–0.76).

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Linear prediction coefficient in the validation cohort was 0.79 (95% CI 0.73–0.95).

Assignment of points on the basis of the β coefficient for these eight independent variables generated an individual risk score for each patient ranging from 0 to 9 (Table 4). Median PREDI-CO score was 4 (IQR 2–7) (see Supplementary material, Fig. S3a).

In the derivation cohort, the area under the ROC curve of the PREDI-CO score was 0.89 (95% CI 0.86–0.92). At a risk score of >3, the sensitivity, specificity, positive predictive value and negative predictive value were 72% (65%–79%), 86% (89%–92%), 74% (67%–80%) and 89% (85%–91%), respectively. The positive and negative likelihood ratios associated with a >3 score cut-off were 6.73 (95% CI 5.1–8.9) and 0.31 (95% CI 0.25–0.39), respectively (see Supplementary material, Table S1).

In the validation cohort, the PREDI-CO score showed an area under the ROC curve of 0.85 (95% CI 0.81–0.88). At risk score of >3, the sensitivity, specificity, positive predictive value and negative predictive value, and postive likelihood ratio 3.30 (2.65–4.11), negative likelihood ratio 0.27 (0.20–0.36) (Supplementary material, Table S1).

Finally, according to the ROC curve analysis the prediction ability for SRF of our score was higher than that of SOFA, qSOFA, CURB-65 and MEWS scores in both the derivation (Fig. 3a) and validation (Fig. 3b) cohorts.

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

Discussion

We developed and independently validated a simple individual risk score (the PREDI-CO score) to identify at the time of hospitalization individuals with COVID-19 who were at high risk of developing SRF during hospitalization. We found that of the individuals hospitalized with COVID-19 on the wards for at least 24 hours, a high percentage (33%) developed worsening of symptoms with SRF after this initial period. A predictive model was built and validated, using age >70 years, obesity, fever at hospitalization, respiratory rate ≥22 breaths/minute, lymphocyte count ≤900 cells/mm^3, creatinine ≥1 mg/dL, C-reactive protein ≥10 mg/dL and lactate dehydrogenase ≥350 IU/L. Our model and risk score performed similarly even in different cohorts, as defined by different hospitals, providing independent validation.

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

	Derivation cohort			Validation cohort		
	AUC	Lower 95% CI	Upper 95% CI	AUC	Lower 95% CI	Upper 95% CI
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.

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)	No severe respiratory failure (n = 455)	OR (95% CI)
Demographics				
Age (years), mean (±SD)	644	72.2 (±13.9)	60.1 (±14.8)	1.06 (1.045–1.073)[a]
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 (kg/m^2), median (IQR)	393	28.3 (25–31)	25.9 (23–27)	1.14 (1.085–1.21)[a]
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)[a]
Symptoms at onset				
Fever ≥38°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)

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Table 2 (*continued*)

	Cases with available data	Severe respiratory failure ($n = 189$)	No severe respiratory failure ($n = 455$)	OR (95% CI)
Time to hospital admission (days), median (IQR)	560	6 (3–9)	6 (3–8)	0.95 (0.93–0.97)[a]
Symptoms at hospitalization				
Fever ≥38°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)[a]
MAP (median, IQR)	598	90.7 (83–96)	91.4 (83–96)	0.99 (0.98–1.01)[a]
PR (median, IQR)	585	85 (76–94)	85 (75–95)	1.00 (0.99–1.01)[a]
RR (median, IQR)	623	24 (20–27)	18 (16–21)	1.14 (1.1–1.18)[a]
$Sato_2$ on ambient air (%), (median, IQR)	580	95 (93–97)	97 (95–98)	0.98 (0.96–1.00)[a]
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)[a]
CRP (mg/dL), median (IQR)	601	11.0 (5.3–16.0)	3.3 (1.6–6.99)	1.2 (1.16–1.25)[a]
LDH (IU/L), median (IQR)	569	350 (255–491)	255 (201–313)	1.0 (1.003–1.006)[a]
Glucose (mg/dL), median (IQR)	487	116 (102–137)	107 (94–123)	1.01 (1.003–1.01)[a]
Creatinine (mg/dL), median (IQR)	623	1.06 (0.86–1.36)	0.86 (0.71–1.03)	1.44 (1.15–1.81)[a]
Sodium (mmol/L), median (IQR)	525	137 (135–141)	137 (135–140)	1.02 (0.98–1.06)[a]
Potassium (mmo/L), median (IQR)	513	4 (3.7–4.4)	4 (3.7–4.3)	0.96 (0.82–1.14)[a]
Bilirubin (mg/dL), median (IQR)	502	0.65 (0.45–0.85)	0.60 (0.46–0.80)	1.57 (1.03–2.34)[a]
Aspartate aminotransferase (IU/L), median (IQR)	531	35 (27–45)	31 (23–42)	1.00 (1.00–1.01)[a]
Alanine aminotransferase (IU/L) median (IQR)	566	22 (16–32)	27 (18–40)	1.00 (0.99–1.00)[a]

All values given are *n* (%) unless otherwise stated.
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; IQR interquartile range; LDH, lactate dehydrogenase; MAP, mean arterial pressure; PR, pulse rate.
[a] For each year, point or unit increase.

It is worth mentioning that in most of the published prognostic studies on COVID-19, demographic characteristics (older age and male sex), underlying co-morbidities and altered laboratory tests (e.g. C-reactive protein, lactate dehydrogenase and lymphocyte counts) correlated with poor outcome, as in our study [16,17]. The strongest underlying condition influencing outcome in our analysis was obesity, as observed for other severe viral pneumonia, like H1N1 flu [18]. Recently, a similar score was developed and validated in Chinese hospitals [19]. This score compared with ours requires an online calculator so it could be less applicable in emergency situations and some of the included variables like haemoptysis were rarely reported in our cohort. This may represent differences between populations and settings.

Our study has a number of limitations. First, being a retrospective study, several variables were not systematically collected across all centres, especially in these times of increased clinical duties and stresses of the health-care system. This might introduce bias if patients with more severe clinical conditions had a higher chance of missed information. For example, interleukin-6 and D-dimer previously showed a significant correlation with disease progression [20], but were not available in this study. However, the strict correlation between interleukin-6

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

	Cases with available data	Severe respiratory failure ($n = 187$)	No severe respiratory failure ($n = 282$)	OR (95% CI)
Demographics				
Age (years), mean (±SD)	469	72.4 (±12.3)	65.8 (±14.6)	1.04 (1.02–1.05)[a]
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 (kg/m^2), median (IQR)	195	28 (25–31)	25 (24–28)	1.13 (1.04–1.23)[a]
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)[a]
Symptoms at onset				
Fever ≥38°C	469	115 (61)	150 (53)	0.99 (0.5–1.95)

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Table 3 (*continued*)

	Cases with available data	Severe respiratory failure ($n = 187$)	No severe respiratory failure ($n = 282$)	OR (95% CI)
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)[a]
Symptoms at hospitalization				
Fever ≥38°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)[a]
MAP (median, IQR)	461	90.7 (83–96)	91.4 (83–96)	0.97 (0.31–3.00)[a]
PR (median, IQR)	468	87 (79–99)	85 (75–93)	1.02 (1.00–1.03)[a]
RR (median, IQR)	459	22 (16–22)	20 (16–22)	1.12 (1.07–1.16)[a]
$Sato_2$ on ambient air (%), (median, IQR)	416	95 (93–97)	97 (95–98)	0.91 (0.86–0.96)[a]
Laboratory tests at hospitalization				
Lymphocytes ($10^3$9/L), median (IQR)	468	0.72 (0.51–0.98)	0.96 (0.73–1.34)	0.25 (0.15–0.41)[a]
CRP (mg/dL), median (IQR)	454	11.2 (6.19–15.8)	3.5 (1.8–6.5)	1.27 (1.21–1.33)[a]
LDH (IU/L), median (IQR)	406	398 (309–476)	278(228–355)	1.01 (1.00–1.01)[a]
Glucose (mg/dL), median (IQR)	412	124 (110–155)	112 (101–129)	1.00 (1.00–1.01)[a]
Creatinine (mg/dL), median (IQR)	460	1.12 (0.89–1.59)	0.99 (0.82–1.15)	2.46 (1.63–3.71)[a]
Sodium (mmol/L), median (IQR)	403	136 (133–139)	137 (134–139)	1.00 (0.98–1.02)[a]
Potassium (mmo/L), median (IQR)	381	3.9 (3.5–4.3)	3.9 (3.7–4.2)	1.18 (0.8–1.73)[a]
Bilirubin (mg/dL), median (IQR)	174	0.55 (0.38–0.80)	0.50 (0.34–0.74)	1.88 (0.89–3.97)[a]
Aspartate aminotransferase (IU/L), median (IQR)	206	44 (21–66)	28 (23–34)	1.04 (1.01–1.06)[a]
Alanine aminotransferase (IU/L) median (IQR)	566	26 (16–42)	24 (17–35)	1.01 (1–1.02)[a]

All values given are *n* (%) unless otherwise stated.
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; IQR interquartile range; LDH, lactate dehydrogenase; MAP, mean arterial pressure; PR, pulse rate.
[a] For each year/day, point or unit increase.

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	p
Age ≥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 ≥38°C at hospitalization	1.73	1.30–2.29	<0.001	0.55	1	1.87	0.99–3.52	0.05
RR ≥ 22 breaths/min	3.75	2.01–7.01	<0.001	1.32	1	2.44	1.41–4.21	0.001
Lymphocytes $\leq 0.9 \times 10^9$/L	2.69	1.60–4.51	<0.001	0.99	1	1.94	1.15–3.27	0.01
CRP ≥10 mg/dL	5.91	4.88–7.17	<0.001	1.78	2	8.44	4.72–15.07	<0.001
LDH ≥350 IU/L	2.39	1.11–5.11	0.025	0.87	1	3.34	2.51–4.44	<0.001
Creatinine ≥1 mg/dL	2.38	1.59.–3.56	<0.001	0.87	1	1.35	1.16–1.57	<0.001

Abbreviations: CRP, C-reactive protein; LDH, lactate dehydrogenase; OR, odds ratio; RR, respiratory rate.

and all acute-phase proteins, including C-reactive protein 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 its applicability. Second, we included only individuals with SARS-CoV-2-positive nasopharyngeal swabs; 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, individuals with SRF within the first 24 hours after admission were excluded; we made this choice because we aimed to identify patients at risk of unfavourable clinical evolution, rather than discriminating between those already in severe clinical condition 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 a 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 scores (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 those individuals with a COVID-19 diagnosis deserving a high level of care and prompt medical treatment. In particular, in our setting with a high frequency of respiratory failure (as was seen in the first phases of the pandemic in Italy) the negative predictive values were good, so our score might be useful to identify those patients who might not need intensive or high intensity care. If further validated in a prospective study our score might serve for both rationing decisions at health-care levels and selecting patients to include in randomized controlled trials on new treatment options.

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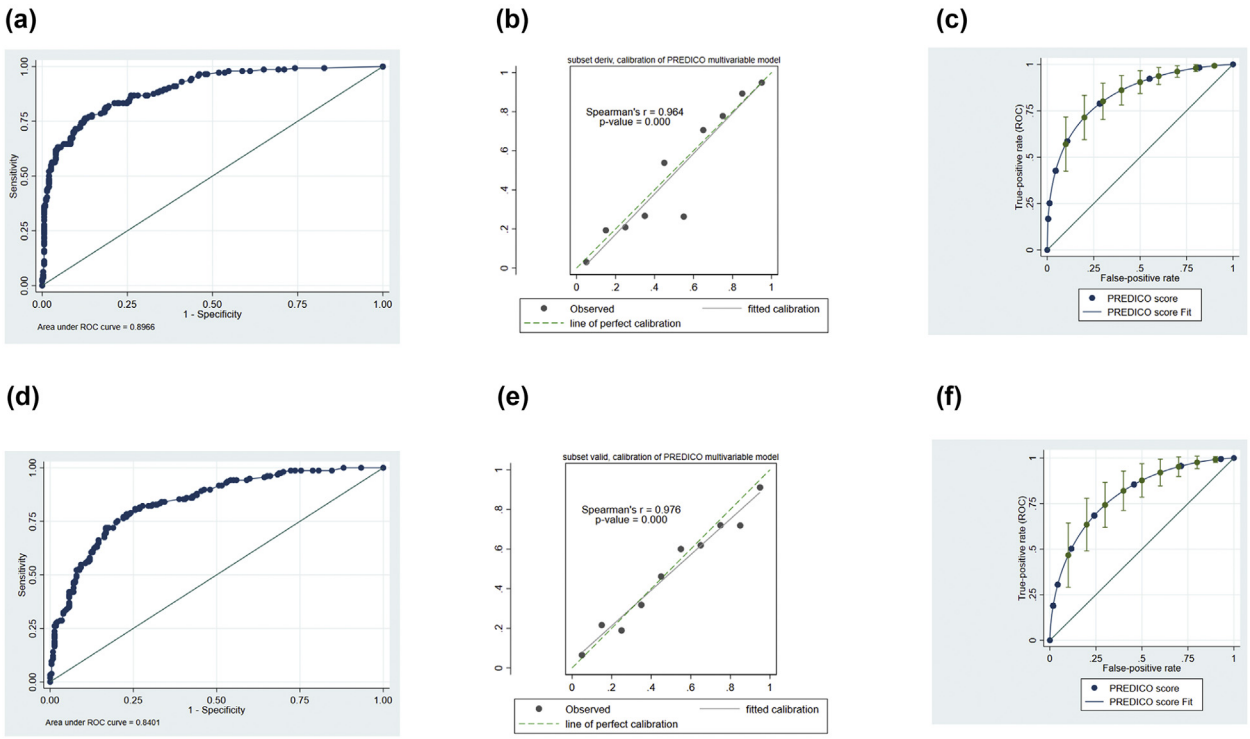

Fig. 2. Discrimination (a) and calibration (b) of the multivariable model and discrimination (c) of the PREDI-CO score in the derivation cohort. Discrimination (d), calibration (e) and discrimination (f) of the PREDICO score in the validation cohort.

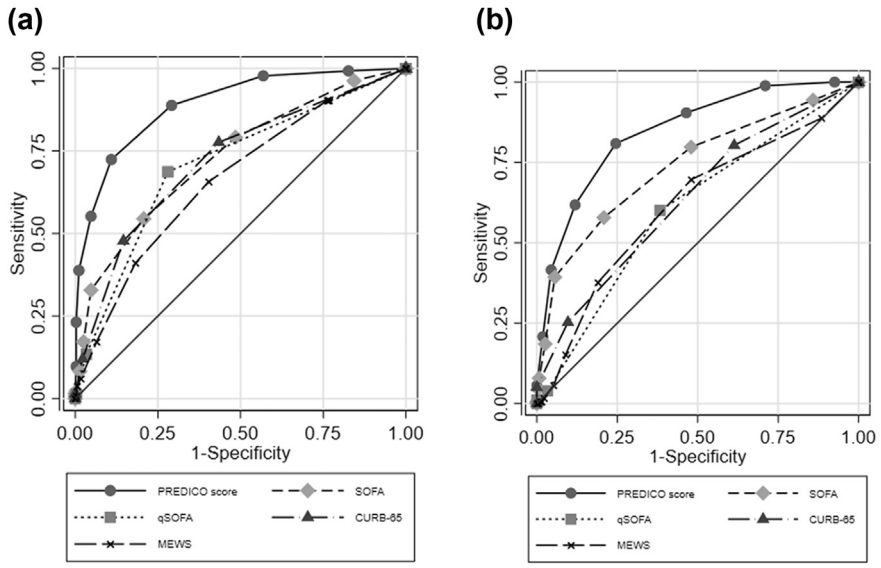

Fig. 3. Comparison of prediction ability for severe respiratory failure in hospitalized individuals with a diagnosis of COVID-19 of the PREDICO score with qSOFA, SOFA, CURB-65 and MEWS scores. (a) Derivation cohort; (b) validation cohort.

Authors' contribution

PV, MB, MG, LS, CM, ST, MT, VMR and TT contributed to conceptualization; MB, LS, MG, MR, MT and TT to methodology; LB, GF, RP, LP, ZP, FT, LB, CC, LA, MMer, MMen, MMes, AL, SR and PG to investigations; and MB, MG and LS to the formal analysis. MG and MB wrote the original draft and LS, PV, TT, FB and VMR contributed to reviewing and editing. FB, MC, MP; CM, FC and PV supervised the work.

Transparency declaration

The authors declare that they have no conflicts of interest. No external funding was received for the present study.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.cmi.2020.08.003.

Appendix

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