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Original Research

Clinical prediction models in hospitalized patients with COVID-19: A multicenter cohort study

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ARTICLE INFO

Keywords:
Clinical decision rules
Mortality
SARS-CoV-2

ABSTRACT

Background: Clinical spectrum of novel coronavirus disease (COVID-19) ranges from asymptomatic infection to severe respiratory failure that may result in death. We aimed at validating and potentially improve existing clinical models to predict prognosis in hospitalized patients with acute COVID-19.

Methods: Consecutive patients with acute confirmed COVID-19 pneumonia hospitalized at 5 Italian non-intensive care unit centers during the 2020 outbreak were included in the study. Twelve validated prognostic scores for pneumonia and/or sepsis and specific COVID-19 scores were calculated for each study patient and their accuracy was compared in predicting in-hospital death at 30 days and the composite of death and orotracheal intubation.

Results: During hospital stay, 302 of 1044 included patients presented critical illness (28.9%), and 226 died (21.6%). Nine out of 34 items included in different prognostic scores were independent predictors of all-cause-death. The discrimination was acceptable for the majority of scores (APACHE II, COVID-GRAM, REMS, CURB-65, NEWS II, ROX-index, 4C, SOFA) to predict in-hospital death at 30 days and poor for the rest. A high negative predictive value was observed for REMS (100.0%) and 4C (98.7%) scores; the positive predictive value was poor overall, ROX-index having the best value (75.0%).

Conclusions: Despite the growing interest in prognostic models, their performance in patients with COVID-19 is modest. The 4C, REMS and ROX-index may have a role to select high and low risk patients at admission. However, simple predictors as age and PaO2/FiO2 ratio can also be useful as standalone predictors to inform decision making.

1. Introduction

The spectrum of disease in patients affected by SARS-CoV-2 infection ranges from asymptomatic infection to critical illness. Patients with coronavirus disease 19 (COVID-19) admitted to the hospital require assessment for short-term prognosis to optimize clinical management and resources allocation. During the first wave, in-hospital mortality ranged from 21% to 29%, and admission to intensive care units (ICUs) from 14% to 16% \cite{1–4}. It should be noted that the efficacy of immunomodulatory and antiviral agents in reducing death or adverse outcome is still debated in COVID-19 patients, mainly when used in advanced phases of the disease \cite{5–7}. Despite vaccination and spreading of several new variants may have impacted on severity of the disease, caution is required in inferring a reduced severity of COVID-19 infection \cite{8,9}. In this view, the opportunity of early identification of patients that will progress to severe disease would allow tailored treatment strategies.

Clinical prediction models have been specifically developed to predict prognosis in patients with COVID-19; in addition, several scores

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https://doi.org/10.1016/j.rmed.2022.106954
Received 26 April 2022; Received in revised form 9 August 2022; Accepted 11 August 2022
Available online 21 August 2022
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validated in patients with no-COVID-19-related lung failure have been applied to patients with COVID-19 [10,11]. Unfortunately, currently available evidence showed poor performance for all these models to predict prognosis in patients with COVID-19 and no incremental value was observed for scores in comparison to simple univariable predictors [3,10]. Among univariable predictors, oxygen saturation on room air and patient age have been found to be strong predictors of deterioration and of mortality, respectively [10]. In addition, many of the existing COVID-19 clinical prediction models have a high risk of bias due to poor reporting, over-estimation of predictive performance, and lack of external validation [4,12].

For these reasons, further external validation is required before moving these scores to the clinical use.

We performed a multicenter cohort study to identify predictors of 30-day in-hospital death or critical illness in patients admitted to hospital for COVID-19 pneumoniae and to evaluate the accuracy of available clinical prediction models in this setting.

2. Materials and methods

2.1. Patients and study design

Data from retrospectively collected cohorts of patients enrolled at 5 Italian non-ICU centers (Perugia, Pisa, Cesena, Empoli and Terni) were merged in a collaborative database. Consecutive patients to the study centers (3 Emergency Departments, 2 Internal Medicine wards, 1 Infectious Disease unit) with confirmed COVID-19 pneumoniae from March 3rd 2020 to March 16th 2021 were evaluated for inclusion in the study.

Table 1

| Parameters included in the prognostic scores. | Score |
|-----------------------------------------------|-------|
| APACHE-II | COVID-Gram | CSS | CURB-65 | 4C | HACOR | MEWS | NEWS-II | qSOFA | REMS | ROX index | SOFA |
| Age | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| Gender | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| Body temperature | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| History of severe organ failure or immunocompromise | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| Coronary heart disease | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| Cancer | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| Number of comorbidities | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| Clinical presentation | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| Shortness of breath | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| Hemoptysis | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| Systolic blood pressure | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| Mean blood pressure | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| Heart rate | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| Respiratory rate | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| SpO2 | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| Need for oxygen | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| Mechanical ventilation | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| FiO2 | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| GCS | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| AVPU score | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| Unconsciousness | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| Confusion | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| Laboratory findings | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| Platelet, mmc | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| White blood cells, mmc | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| Lymphocyte count | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| N/L ratio | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| Hematocrit | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| Urea | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| Creatinine | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| Lactate dehydrogenase | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| Bilirubin | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| pH | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| PaO2 | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| PaO2/FiO2 | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| AaDO2 | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| Hypercapnia | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| Sodium | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| Potassium | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| C-RP | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| Procalcitonin | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| D-dimer | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| Chest X ray abnormalities | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |

AaDO2 = alveolar-arterial oxygen gradient; AVPU = Alert, Verbal, Pain, Unresponsive scale; C-RP = C reactive protein; FiO2 = fraction of inspired oxygen; GCS = Glasgow Coma Scale; N/L = neutrophil to lymphocyte ratio; PaO2 = arterial partial pressure of oxygen; SpO2 = oxygen saturation.

§ Heart failure class IV, cirrhosis, chronic lung disease, or dialysis-dependent.
+ AaDO2 or PaO2 (for FiO2≥0.5 or <0.5, respectively).
* chronic obstructive pulmonary disease (COPD), hypertension, diabetes, coronary heart disease, chronic kidney disease, cancer, cerebral vascular disease, hepatitis B, and immunodeficiency.
* Chronic cardiac disease, chronic respiratory disease -excluding asthma-, chronic renal disease, mild to severe liver disease, dementia, chronic neurological conditions, connective tissue disease, diabetes mellitus, HIV or AIDS, and malignancy.
* Mean arterial pressure OR administration of vasoactive agents required.
study.

Inclusion criteria were:
- age 18 years or older;
- need for oxygen support or COVID-19 pneumonia (clinical or imaging diagnosed);
- SARS-CoV2 infection confirmed by RT-PCR throat/nasal swab.

Exclusion criteria were:
- patients intubated before hospital arrival or intubated in the Emergency Department;
- insufficient data to calculate at least one risk stratification score.

The study was approved by the Ethical Committee and/or Institutional Review Boards of the participating centers.

Informed consent was obtained in accordance with current regulations for observational studies.

2.1. Study outcome

The study primary outcome was all-cause-death occurring within 30 days from hospital admission. Secondary outcome was critical illness defined as the composite of all-cause-death or orotracheal intubation. Study outcomes were considered occurring within hospital stay or at a maximum of 30 days whichever comes first.

2.2. Measurements

The following risk stratification scores were calculated for each patient at admission: APACHE II, COVID-GRAM, CSS, CURB-65, 4C, HACOR, MEWS, NEWS II, qSOFA, REMS, ROX-index, SOFA (Table 1) [13–22].

2.3. Data collection

For included patients the following data were collected: age, gender, comorbidities (cardiovascular disease [coronary or peripheral artery disease], type 2 diabetes, chronic obstructive pulmonary disease [COPD], cancer, kidney disease), number of comorbidities, clinical presentation at admission (hemoptysis, shortness of breath, body temperature, systolic and diastolic blood pressure [mmHg], heart rate [beats per minute], respiratory rate [breaths per minute], oxygen saturation, fraction of inspired oxygen [FiO2], respiratory index [oxygen saturation to respiratory rate ratio] [23], Glasgow coma scale [GCS], confusion), chest x-ray abnormalities, laboratory findings (platelet count, white blood cells count, neutrophils and lymphocytes count, haematocrit, urea, creatinine, bilirubin, lactate dehydrogenase, electrolytes, d-dimer, C-reactive protein, and arterial partial pressure of oxygen [PaO2] values), date of hospital admission, date of discharge, date of death, date of endotracheal intubation.

2.4. Statistical analysis

Main baseline characteristics of patients were reported as frequencies for categorical data and as mean ± standard deviation (SD) for continuous data. The predictive value for in-hospital death at 30 days and for critical illness of the individual items included in prognostic scores and models was assessed by Cox proportional hazard model. Separate multivariable analyses were performed - to verify the independent prognostic value of the included items; results were reported as hazard ratio (HR) at 95% confidence interval (CI).

Information on candidate predictors was collected at admission; however, where information on physiological or laboratory measures was not available on the day of admission, measures recorded up to 24 h after admission were used. Patients were excluded from analyses when candidate predictors were missing.

Irrespective of these results, the performance of each risk stratification score (APACHE II, COVID-GRAM, CSS, CURB-65, 4C, HACOR, MEWS, NEWS II, qSOFA, REMS, ROX-index, and SOFA) at the established cut-off value was assessed.

In addition to validating existing scores, independent predictors of in-hospital death at 30 days at multivariate analysis were combined to derive a new prognostic model. According to the presence of a significant association with study outcomes and to the magnitude of the effect (β-coefficient), candidate variables were arranged in new candidate models. The final model was chosen according to the best performance.

The most discriminant cut-off was determined by calculating the Youden’s index. Bootstrapping analysis (2000 samples, bias corrected and accelerated 95% CIs) of the new models was performed.

The following parameters were evaluated to assess performance of clinical models and scores: discrimination by calculating the area under the receiver operating characteristic curve (AUC) at 95% CI, calibration by applying the Hosmer-Lemeshow test (p > 0.05 showed no significant differences between observed and predicted values), sensitivity, specificity, positive and negative predictive value. The risk for in-hospital death at 30 days and for critical illness by risk categories according to individual models/score was calculated using Cox proportional hazard model. Survival was reported by Kaplan-Meier curves and log-rank test.

All tests were 2-sided and statistical significance was accepted if p value < 0.05.

We followed the TRIPOD statement for reporting [24]. Statistical analysis was performed with SPSS software (version 25).

3. Results

Overall, 1047 patients were evaluated and 3 excluded for lack of baseline information. Thus, 1044 patients were included in the study: mean age 68.3 ± 15.6 years, 62.1% were males. Characteristics of the included population at admission are reported in Table 2.

During a mean hospital stay of 15.5 days, in-hospital death at 30 days

| Table 2 |
| --- |
| Baseline characteristics of included patients. |
| --- |
| Baseline characteristics | Population (n = 1044) |
| Age, years, mean, SD | 68.3 ± 15.6 |
| Male, n/N, % | 648/1044 62.1 |
| Main comorbidities | |
| Cardiovascular disease, n/N, % | 331/1044 31.7 |
| Type 2 diabetes, n/N, % | 187/1044 17.9 |
| COPD, n/N, % | 123/1044 11.8 |
| Cancer, n/N, % | 140/1043 13.4 |
| Clinical presentation | |
| Shortness of breath, n/N, % | 472/839 56.3 |
| Hemoptysis, n/N, % | 10/839 1.2 |
| Fever, n/N, % | 274/751 36.5 |
| Systolic blood pressure, mmHg mean, SD | 131 ± 19.6 |
| Diastolic blood pressure, mmHg mean, SD | 76 ± 12.0 |
| Heart rate, beats per minute mean, SD | 86 ± 16.9 |
| Respiratory rate, breaths per minute mean, SD | 22 ± 6.0 |
| PaO2/FiO2, mmHg mean, SD | 272 ± 103 |
| SaO2, % mean, SD | 92.3 ± 6.4 |
| PaO2, mmHg mean, SD | 73.9 ± 31.0 |
| Respiratory index, mean, SD | 4.7 ± 1.3 |
| Laboratory findings | |
| Platelet, mmc mean, SD | 212689 ± 96818 |
| White blood cells, mmc mean, SD | 7917 ± 4477 |
| N/L ratio, mean, SD | 8.6 ± 10.8 |
| Hematocrit, % mean, SD | 38.6 ± 5.4 |
| Urea, mg/dl mean, SD | 45.9 ± 36.1 |
| Creatinine, mg/dl mean, SD | 1.17 ± 0.91 |
| D-dimer, mg/ml mean, SD | 2091 ± 4827 |
| Lactate dehydrogenase, U/l mean, SD | 377 ± 242 |

COPD = chronic obstructive pulmonary disease; PaO2/FiO2 = ratio of the arterial partial pressure of oxygen to the fraction of inspired oxygen; PaO2 = arterial partial pressure of oxygen; SpO2 = oxygen saturation; respiratory index = ratio of the oxygen saturation to the respiratory rate.
occurred in 226 patients (21.6%) (Fig. 1 A) and critical illness in 302 (28.9%).

Predictors of in-hospital death at 30 days at univariate analysis are reported in e-Table 1. Association of age or respiratory rate at increasing cutoffs and of PaO2, PaO2 to FiO2 ratio, and oxygen saturation at decreasing cutoffs with death are reported in Fig. 1 B–F.

Out of 34 items included in the 12 assessed scores, age ≥60 years (HR 4.13, 95% CI 1.49 to 11.43), the presence of at least 2 comorbidities (HR 2.43, 95% CI 1.57 to 3.76), GCS lower than 15 (HR 1.94, 95% CI 1.07 to 3.54), mean blood pressure lower than 70 mmHg (HR 4.19, 95% CI 1.50 to 11.71), respiratory rate higher than 20 Bpm (1.58, 95% CI 1.00 to 2.50), PaO2 to FiO2 ratio lower than 200 mmHg (HR 1.88, 95% CI 1.22 to 2.89), PaO2 lower than 60 mmHg (HR 1.60, 95% CI 1.05 to 2.45), oxygen saturation lower than 90% (HR 1.73, 95% CI 1.12 to 2.69), and respiratory index lower or equal to 3.8 (HR 1.82, 95% CI 1.19 to 2.80) were identified as independent predictors of in-hospital death at 30 days (Table 3, e-Table 2).

Age ≥60 years (HR 2.57, 95% CI 1.27 to 5.21), the presence of at least 2 comorbidities (HR 1.93, 95% CI 1.32 to 2.83), respiratory rate higher than 20 Bpm (HR 1.63, 95% CI 1.07–2.46), PaO2 lower than 60 mmHg (HR 1.67, 95% CI 1.15 to 2.43), oxygen saturation lower than 92% (HR 1.83, 95% CI 1.26 to 2.67), and respiratory index lower or equal to 3.8 (HR 1.72, 95% CI 1.19 to 2.50) were independent predictors of 30-day critical illness (e-Table 3 and e-Table 4).

3.1. Performance of existing risk stratification scores

The ability to discriminate categories of patients with different risk of in-hospital death at 30 days (discrimination) was acceptable for nine out of the 12 assessed scores (Table 4 and Fig. 2). The APACHE-II, 4C and REMS scores showed the highest AUC values, while the HACOR, MEWS and qSOFA the lowest. The established cut-offs of the individual scores showed a high sensitivity for REMS (100.0%) and 4C (98.9%) scores, and a high specificity for ROX-index (98.3%) and SOFA (96.6%) scores. The negative predictive value was high for REMS (100.0%) and 4C (98.7%), the positive predicted value overall was poor with the highest value for the ROX-index (75.0%).

No significant differences between observed and predicted events were found for CSS, 4C, HACOR, NEWS-II, q-SOFA, REMS, ROX-index and SOFA scores, while calibration was poor for the APACHE-II, COVID-GRAM, CURB-65 and MEWS scores.

The 4C score was confirmed to have the highest discrimination in predicting critical illness: AUC 0.770, 95% CI 0.720 to 0.820 (e-Table 5). Similarly, the 4C and the REMS showed a high negative predictive value: 96.2% and 97.4%, respectively. ROX-index showed the best specificity and positive predictive value: 99.1% and 87.5%, respectively. Calibration was good for ROX-index, CSS, NEWS-II, SOFA, qSOFA, CURB-65, REMS, HACOR, and 4C scores.

3.2. Optimization of existing risk stratification scores

The performance of the 4C and REMS scores was re-evaluated by recalculating SpO2 and respiratory rate at a different cut-off point. No advantage was found for the 4C score with SpO2 lower than 90% (AUC 0.802, 95% CI 0.755 to 0.849), however, discrimination improved after REMS score recalculation for respiratory rate higher than 20 Bpm (AUC 0.800, 95% CI 0.755 to 0.845).

3.3. Derivation of new predicting models

Variables identified as independent predictors for in-hospital death at 30 days were combined in new candidate models. All the examined new models showed a good discrimination and high negative predicted values (e-Table 6, Table 4). All the new models showed a good
Among the 34 items included in the 12 models, age respectively, and negative predictive values of 99% and 100%, respectively. For risk stratification of acutely ill patients, the 4C and REMS scores had calibration.

Among the candidate models, a good performance in predicting in-hospital death at 30 days for New Model 5 (age ≥60 years, mean blood pressure <70 mmHg, mean blood pressure <70 mmHg, respiratory rate over 20 Bpm, PaO2/FiO2 <200 mmHg; AUC 0.809, 95% CI, 0.765 to 0.853) was observed (e-Fig. 2). The results of the bootstrapping analysis on the predictive value of the New Model 5 were consistent with those of the main analysis.

### 4. Discussion

Our multicenter cohort study shows that, among 12 existing models for risk stratification of acutely ill patients, the 4C and REMS scores had good accuracy to predict in-hospital death at 30 days in patients hospitalized with COVID-19, with a sensitivity of 99% and 100%, respectively, and negative predictive values of 99% and 100%, respectively. Among the 34 items included in the 12 models, age ≥60 years, having at least two comorbidities, GCS lower than 15, mean blood pressure lower than 70 mmHg, respiratory rate higher than 20 Bpm, PaO2/FiO2 <200 mmHg (e-Fig. 2).

Similar findings were observed for the prediction of critical illness. COVID-19 continues to be a major health problem still causing high number of deaths worldwide [25,26], despite the understanding of its pathophysiology continues to grow exponentially [27].

The experience from the initial phase of the pandemic along with the overwhelming amount of scientific evidence on mortality risk factors, respiratory support measures and treatments, allowed greater expertise in facing upcoming pandemic waves. Notwithstanding, the mortality among critical COVID-19 patients remains unacceptably high [28], and it is unclear if improvements in patients’ care have truly improved clinical outcomes [29]. In this view, a better understanding of
Determinants of prognosis could improve clinical management and also resources allocation for current COVID-19 patients and for potential new COVID-19 waves. These data can certainly serve to implement the management of non-COVID related acute respiratory distress syndromes.

Our study shows that currently available prognostic models recommended for risk stratification in different setting of critically ill patients (sepsis, pneumonia, …) have modest performance in assessing mortality and risk of critical illness in hospitalized patients with COVID-19. The 4C model that has been specifically derived and validated to risk stratify patients with COVID-19 and the REMS score, derived and validated to predict mortality and length of stay in nonsurgical patients attending the emergency department, showed good sensitivity and negative predictive values. These results have biological plausibility as COVID-19 infection rarely causes hemodynamic impairment rather severe respiratory failure potentially leading to acute respiratory distress syndrome as the final cause of death. Thus, clinical models with high performance in patients with sepsis or bacterial pneumonia can have limited value in patients with COVID-19. The ROX-index, derived to assess the risk of mechanical ventilation in pneumonia patients with hypoxemic acute respiratory failure treated with high-flow nasal cannula, revealed to be useful to identify COVID-19 at increased risk for mortality and for critical illness. In particular, age ≥ 60 years showed high sensitivity (95%) and negative predictive value (97%). According to these results, age itself has similar accuracy to 4C and REMS for prognostic stratification. These results are in line with data from a recent study in 411 patients with COVID-19 [10]. In this study, none of the evaluated prognostic models offered incremental value for patient stratification with respect to univariable predictors such as oxygen saturation on room air at admission (AUC 0.76, 95% CI 0.71 to 0.81 for in-hospital deterioration) and patient age (AUC 0.76, 95% CI 0.71 to 0.81 for in-hospital mortality). However, in our study the combination of age to other predictors in the 4C and REMS scores allowed to improve negative predictive value up to 99 and 100%.

In addition to offer external validation of existing models, we built new models from the combination of independent predictors. The performance of model 5 including age ≥ 60 years, having two or more comorbidities, GCS < 15, mean blood pressure < 70 mmHg, respiratory rate > 20 Bpm and PaO2/FiO2 < 200 mmHg was similar to that of 4C and REMS scores with the advantage of being simpler. Bootstrapping analysis on the predictive value of the new model 5 showed consistent results with those of the main analysis. However, as for all new scores, this model requires external validation.

Study limitations include the observational study design, thus, owing to the limitations of routinely collected data, predictor variables were
Appendix A. Supplementary data

Appendix A: Supplementary data can be found online at https://doi.org/10.1016/j.rmed.2022.106954.

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[6] No fundings.

[7] All the authors have read and approved the final manuscript.

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Declaration of competing interest

None of the authors have conflict of interest to declare for this study.

Acknowledgment

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