Multivariable prediction model of intensive care unit transfer and death: a French prospective cohort study of COVID-19 patients.

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Abstract

Background: Prognostic factors of coronavirus disease 2019 (COVID-19) patients among European population are lacking. Our objective was to identify early prognostic factors upon admission to optimize the management of COVID-19 patients hospitalized in a medical ward.

Methods: French single-center prospective cohort study of 152 patients with positive Severe acute respiratory syndrome coronavirus 2 (SARS-Cov2) real-time reverse transcriptase–polymerase chain reaction (RT-PCR) assay, hospitalized in a medical ward. Multivariable models and a simplified scoring system assessed predictive factors of intensive care unit (ICU) transfer or death at day 14 (D14), of being discharge alive and severe status at D14 (remaining with ventilation, or death). A validation was performed on an external sample of 132 patients.

Findings: At D14, the probability of ICU transfer or death was 32% (95% CI 25-40). Older age (OR 2.61, 95% CI 0.96-7.10), poorer respiratory presentation (OR 4.04 per 1-point increment on World Health Organization (WHO) clinical scale, 95% CI 1.76-9.25), higher CRP-level (OR 1.63 per 100mg/L increment, 95% CI 0.98-2.71) and lower lymphocytes count (OR 0.36 per 1000/mm$^3$ increment, 95% CI 0.13-0.99) were associated with an increased risk of ICU requirement or death. A 8-point ordinal scale scoring system defined low (score 0-2), moderate (score 3-5), and high (score 6-8) risk patients, with predicted respectively 2%, 25% and 81% risk of ICU transfer or death at D14.

Interpretation: In this prospective cohort study of laboratory-confirmed COVID-19 patients hospitalized in a medical ward in France, 32% were transferred to ICU or died. A simplified scoring system at admission predicted the outcome at D14.

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Research in context

Evidence before this study: The natural history and outcome of the coronavirus disease 2019 (COVID-19) patients initially hospitalized in a medical ward remain unpredictable. Currently, the main existing medical information stem from China and prognostic factors of COVID-19 among European population are lacking.

Added value of this study: We defined high-risk group of ICU transfer or death using a simplified scoring system from the multivariable models including age, World Health Organization (WHO) scale, C-reactive protein level, and lymphocytes count.

Implication of all the available evidence: We provided a simplified score stratifying upon hospital admission low, moderate, and high risk patients in order to optimize the management of COVID-19 patients hospitalized in a medical ward.
Introduction

In January 2020, the World Health Organization (WHO) declared the outbreak of coronavirus disease 2019 (COVID-19) to be a Public Health Emergency of International Concern. This outbreak started in China (Wuhan), from where most of the data is available to now. Clinical presentation varies widely among individuals. Although population-based data are lacking, up to one third of patients might be asymptomatic. Among the symptomatic ones, more than 80% develop a mild disease, while only a minority presents the severe form of severe acute respiratory syndrome coronavirus 2 (SARS-CoV2) infection. Intensive care unit (ICU) admissions range from 5% to 16%, depending on characteristics of the studied population. Also, Chinese retrospective studies reported an inpatient mortality rate of 17·6-28·2%, with median time to death between 15 and 18·5 days. Different prognostic factors emerge in this context, such as age and comorbidities. After Asia, Europe was quickly and severely affected by the epidemic. First in Italy then in France, the outbreak rapidly overwhelmed the public health system and ICUs were filled. As of April 15th 2020, France had already confirmed 131.362 cases with 15.750 deaths.

Currently, there are no validated treatments for COVID-19 and huge efforts have allowed designing and implementing very rapidly randomized controlled trials. Also, predictive prognostic factors are critical to improve management of high-risk COVID-19 patients. It is crucial to early identify those at risk of worsening for (i) an optimized management of patients' flow and to (ii) to define the population to treat, ensuring healthcare quality. At this time, very limited prospective data is available on outcome and prognostic factors of COVID-19 patients among European population. Our objective through this French single-center prospective cohort study of 152 COVID-19 patients was to develop and validate
multivariable predictive models for the patient status at day 14, i.e. (i) major clinical worsening (death or ICU transfer by day 14), (ii) severe status at day 14 (remaining with non-invasive or mechanical ventilation, or death, at day 14), and (iii) favorable hospital outcome (discharge alive by day 14), in adult patients requiring initial hospitalization in a medical ward.
Methods

Study Population

This is a prospective single-center observational cohort study of 152 COVID-19 adult patients admitted from March 16th 2020 in the Internal Medicine and Clinical Immunology Department, at Pitié-Salpêtrière’s Hospital, in Paris, France, a tertiary care university hospital. Included patients were those older than 18 years with initial requirement for hospitalization in medical ward, and diagnosed with COVID-19, defined as positive SARS-CoV-2 real-time reverse transcriptase–polymerase chain reaction (RT-PCR) assay from nasal swabs. All patients benefitted from current standard COVID-19 care at the time. The study followed the Strengthening Reporting of Observational Studies in Epidemiology (STROBE) and the TRIPOD reporting guideline for cohort studies.12 We received local ethical committee approval, and our study is registered as (NCT04320017).

All data were prospectively collected in a standardized form. At baseline (i.e., hospital admission), we assessed demography and epidemiology features, comorbidity profile, previous treatments, clinical presentation along with the laboratory, chest computed tomography (CT) scan and echocardiogram data. Routine blood examinations included full blood count, glycaemia, renal and liver function tests, creatine kinase, lactate dehydrogenase, C-reactive protein (CRP), procalcitonin, fibrinogen, D-dimer, troponin, ferritin and interleukin-6 (IL-6). CT scan imaging results were reported according to the predominant pattern of lesions and the extent of the lesions. The first administered treatments and clinical course during hospitalization were recorded.

Patients were categorized using the WHO clinical improvement Scale13 on day 1 (D1) and day 14 (D14). This 8-point ordinal scale measures illness severity over time as follows: 0,
uninfected; 1, ambulatory, no limitation of activities; 2, ambulatory, limitation of activities; 3, hospitalized, no oxygen therapy; 4, hospitalized, oxygen by mask or nasal prongs; 5, hospitalized, oxygen by non-invasive ventilation or high-flow; 6, intubation and mechanical ventilation; 7, ventilation with additional organ support (i.e., vasopressors, dialysis, extracorporeal membrane oxygenation); 8, death. All data were collected and reviewed by three physicians (AH, GM and MV). Patients discharged from hospital before D14 were contacted by phone to assess their status at that time point.

Definitions of study endpoints

The study endpoints were defined as the occurrence of ICU transfer or death within 14 days of admission, the need for non invasive or mechanical ventilation, or death, at day 14 after hospital admission, and being discharged alive within 14 days of admission.

Statistical Analysis

The sample size (n=152) consisted in all consecutive eligible patients hospitalized at the study center, during the first weeks of the 2020 SARS-CoV2 outbreak in Paris, France. For descriptive analyses, categorical variables are reported with counts (percent) and quantitative variables with median [interquartile range]. Categorical variables were compared using Fisher’s exact test and quantitative variable with Wilcoxon’s rank sum test. We considered predictors that would be available in most medical wards. Quantitative predictors were considered as continuous variables (except for age) and qualitative as binary or dummy variables, for model development. A set of predictors was defined after checking for
redundancy among candidate predictors based on clinical expertise, and accounting for an acceptable number of degrees of freedom given the limiting number of events. No statistical-based variable selection was performed. The multivariable models of the endpoints of interest were evaluated using logistic regression models, with maximum likelihood. Validation was performed in two stages. Internal validation of the models was first performed using 1000 bootstrap resamples;\textsuperscript{14} we estimated models performances, corrected for over-optimism (see Supplementary material). The models were further evaluated on an external validation sample from another French hospital close to Paris (see Supplementary Table 1). We defined a tentative simplified scoring system, from the multivariable models; to that aim, continuous variables were to be dichotomized (for simplified field risk-assessment) and a unit coefficient was allocated to each of the model variables (see Supplementary material). The simplified score was validated internally using a resampling approach by bootstrap (N=1000 samples), and on the external cohort. For each variable, missing data was described with count. For model development, we used routinely obtained predictors (no missing data). All statistical tests were two-sided at a 5%-significance level. Analyses were performed on R statistical platform, version 3.5.3.
Results

A total of 152 consecutive eligible patients were hospitalized in the ward and included in the study. The main baseline features are presented in Table 1. Median age was 77 years [60-83], male sex and Caucasian origin were predominant, and 80.9% of the patients had comorbidities. By the time of arrival, 28 (18.4%) patients reported angiotensin-converting-enzyme inhibitors as continuous-use medication, while 16 (10.5%) had taken nonsteroidal anti-inflammatory drugs. Dyspnea was the most frequently symptom, followed by fever and dry cough. On admission, 44 patients (28.9%) had a WHO score of 3, 89 patients (58.6%) had a WHO score of 4, and 19 patients (12.5%) had a score of 5. Most patients presented with lymphopenia, with more than a half showing values below 800 cells/mm³. Chest CT scan showed that ground glass opacities were the most frequent lesions with an extent greater than 50% of the parenchyma evidenced in 24.7% of patients. IL-6 level was 31.8 pg/mL [14.8-56.0] and higher levels (161.1 pg/mL [32.7-237.8]) were observed in patients with extensive lung opacities (> 50%) as compared to those with a non-extensive lung involvement (31.7 pg/mL [15.4-51.6], p=0.022). At admission, 129 (84.9%) patients received antibiotics, 68 (45%) hydroxychloroquine and 6 (3.9%) tocilizumab.

The study's flow-chart represents all patients’ outcomes (Figure 1). Complete 14-day follow-up was available for 146 patients. During their clinical course, 56 (38.3%) patients experienced respiratory worsening, with 49 of them requiring an oxygen flow over 6 L/min at some point. As of day 14 (D14), 17 (11.6%) had been transferred to ICU, 5 to the semi-intensive unit, and, eventually, 32 (21.9%) patients had died, and 84 (57.5%) had been discharged alive from the hospital. For those who died, median time to death from symptom onset or hospital admission were 11 (6.75-14.5) and 6 (4-9) days, respectively. The estimated
probability of ICU transfer or death by D14 was 32% (95% CI 25-40), the estimated probability of still needing non-invasive ventilation (NIV) or mechanical ventilation (MV), or being dead, at D14 was 27% (95% CI 20-35), while the estimated probability of being discharged alive by D14 was 58% (95% CI 49-66).

In univariable analysis, age at admission, chronic respiratory failure, respiratory rate ≥ 24 breaths per minute, peripheral capillary oxygen saturation (SpO2) on room air, oxygen therapy on admission, SpO2 on oxygen, dyspnea, myalgia, WHO clinical scale, neutrophilia, eosinopenia, lymphopenia, CRP level, IL-6 level, procalcitonin, fibrinogen, serum ferritin, high-sensitivity cardiac troponin T, lactate dehydrogenase (LDH), D-dimer, and chest CT scan were associated with ICU transfer and/or death within 14 days (Table 1). For adjusted model development, the limiting number of events was 47 patients with ICU transfer or death within 14 days in the original sample. The multivariable model included age (≤ or > 60 years), respiratory baseline presentation (assessed by WHO scale levels from 3 to 5), CRP level and lymphocytes count. Older age (OR 2·61, 95% CI 0·96-7·10), poorer respiratory presentation (OR 4·04 per 1-point increment on WHO scale, 95% CI 1·76-9·25) and higher CRP level (OR 1·63 per 100mg/L increment, 95% CI 0·98-2·71) were associated with an increased risk of ICU requirement or death, while lymphocytes count were associated with better outcome (OR 0·36 per 1000/mm³ increment, 95% CI 0·13-0·99) (Figure 2, Supplementary Table 2). Internal and external validation of the model was performed: the C-index (equivalent to AUC) was 0·80, 0·78 after correction for over-optimism by resampling, and 0·78 on the external cohort (see Supplementary material for further details and Supplementary Table 1 for description of the external cohort).
A tentative simplified scoring system was defined, for routine clinical field practice. To that aim, based on the linear predictor and the coefficients of the multivariable model, in an additive manner, 1 point was allocated for age above 60 years old; 1 point for oxygen therapy by nasal prongs or mask (WHO scale level 4); 3 points for high flow oxygen or NIV (WHO scale level 5); 1 point if $10 \leq \text{CRP plasma level} \leq 75 \text{ mg/L}$, 2 points if $75 \leq \text{CRP} \leq 150 \text{ mg/L}$, 3 points if $\text{CRP} \geq 150 \text{ mg/L}$; 1 point if lymphocytes count below $800/\text{mm}^3$ (See supplementary material). We illustrated the score in Figure 2 and defined 3 risk groups: low (score 0-2), moderate (score 3-5), and high (score 6-8) (Figure 3).

At day 14, a total of 40 patients were still treated with NIV ($n=1$) or MV ($n=7$) ventilation, or had died ($n=32$), out of 146 evaluable patients. In univariable analysis, age at admission, weight, chronic respiratory failure, respiratory rate $\geq 24$, SpO2 on room air, Oxygen therapy on admission, SpO2 on oxygen, dyspnea, myalgia, WHO clinical scale, neutrophils, eosinophils, lymphocytes, platelets, CRP level, IL-6 level, procalcitonin, serum ferritin, high-sensitivity cardiac troponin T, D-dimer, and chest CT-scan were associated with WHO scale $\geq 5$ within day 14. Multivariable analysis is represented in Figure 2.

Eighty-four patients had been discharged by day 14, out of 146 evaluable patients. In univariable analysis, age at admission, respiratory rate $< 24$, SpO2 on room air, Oxygen therapy on admission, ageusia, dyspnea, WHO clinical scale, neutrophils, eosinophils, lymphocytes, platelets, CRP level, IL-6 level, procalcitonin, fibrinogen, serum ferritin, high-sensitivity cardiac troponin T, LDH, D-dimer, and chest CT scan were associated with discharge alive within 14 days. Multivariable analysis is represented in Figure 2.
Discussion

The natural history and outcome of the COVID-19 patients initially hospitalized in a medical ward remain unpredictable. Currently, the main existing medical information stem from China and prognostic factors of COVID-19 among European population are lacking. The most striking conclusions drawn by this study are (i) up to 35% of the COVID-19 patients hospitalized in a medical ward were transferred to ICU or died at day 14, (ii) we defined high-risk group of ICU transfer or death using a simplified scoring system from the multivariable models including age, CRP level, lymphocytes count and WHO scale and (iii) we highlighted correlation between IL-6 level and extensive lesions in CT scan.

A clear and strong age gradient in death risk has been identified, increasing dramatically after 60 years.15 Besides older age, comorbidities are also highlighted as key factors associated with death.7,8,16 Compared to presente study, retrospective Chinese cohorts population were younger (from 51 to 56 years) and had less comorbidities (up to 48%).7,16 Even with a median age of 77 years and more than 80% of comorbidity our reported 21·9% mortality rate lies within the 17·6-28·2% range extracted from other cohorts.7,8 In contrast, the median time from symptoms onset to death in our population (11 days) is shorter than the 18·5 days previously reported,7 which can be ultimately the consequence of the higher risk profile of patients in the presente study. Additionally, our ICU transfer rate (11·6%) was lower than the 26% described in Chinese cohorts.7,16 In this regard, we must underline that our patients presented with less severe infection at baseline.7,16 In addition, they were less eligible to ICU admission, due to age and comorbidities. Beyond demographic and clinical characteristics, several laboratory features have been linked to a higher mortality. Studies identified a positive correlation with mortality for neutrophilia, lymphopenia, troponin, LDH and D-dimer.
levels.\textsuperscript{7,16} Additionally, high levels of serum CRP, procalcitonin, and ferritin have also occasionally been associated with mortality.\textsuperscript{16,17} In our cohort, two simple biomarkers from routine practice, lymphocytes count and CRP level, are independently associated with a worse prognosis. CRP level higher than 75 mg/L and lymphopenia below 800/mm\textsuperscript{3} increased by two fold the odds of being transfer in ICU or death.

Herein, we provided for the first time a simplified scoring system which allows stratifying COVID-19 patients initially hospitalized in a medical ward, at low, intermediate, or high risk of ICU transfer or death. The score was validated with calibration evaluated both with an internal resampling approach and by external validation on a cohort sample from a different hospital. Based on the linear predictor of the multivariate model, age above 60 years, WHO scale, CRP level (10-75, 75-150, or > 150 mg/L), and lymphocytes count below 800/mm3 were included in the scoring system. A COVID-19 patient with a score of 6 or more at admission in a medical ward had more than 60% predicted probability of ICU transfer or death within day 14. In a systematic review of the prediction models for diagnosis and prognosis of COVID 19 patients, Wynants et al identified ten prognostic models proposed by different Chinese teams.\textsuperscript{12} All these models are still in pre-print and are not yet published. They are exclusively based on retrospectives studies of small cohorts in China. Most of them lacked an external validation cohort, or presented a small validation cohort not comparable to their initial samples.

Apart from CRP level and lymphocyte count, other significant findings from our study could be further used to refine the score. Chest CT scan is a useful diagnostic tool, specially for RT-PCR negative patients, but its role as a prognostic instrument is still unclear.\textsuperscript{18} Herein, we pointed out that parenchymal involvement greater than 50% on chest CT scan at admission
was associated with ICU transfer or death in 41% of cases. In parallel, high levels of serum IL-6 have been reported in moderate to severe cases of COVID-19 pneumonia.\textsuperscript{7,17} IL-6 may result in increased alveolar-capillary blood-gas exchange dysfunction, especially impaired oxygen diffusion, and lead to pulmonary fibrosis and organ failure.\textsuperscript{19} We were able to establish for the first time the correlation between IL-6 level and extensive parenchymal involvement on chest CT scan for ICU transfer or death.

Our study has several limitations. We present models, with both internal and external validation. Discrimination of the model and of the simplified score was consistent in the external cohort. Calibration assessment showed that the model and score slightly overestimated the risk of event in the external cohort, in patients with higher scores. The external sample was one of patients from a regional non-university hospital (Aulnay-sous-Bois, Île-de-France) which could explain differences on catchment area and patient recruitment. Further external validation on large prospective cohorts will be useful.

To our knowledge, this is the first prospective European cohort of COVID-19 non-critical inpatients and one of the largest standardized studies describing short term patients outcome. We provided a very simple and easily accessible score to estimate the risk of ICU transfer or death by day 14. In the context of the pandemic, this tool can help the management of patient flow, and also clinical trial design and therapeutic management.
Contributors

YA, DS, OB and PC developed the concept and designed the study. YA, DS, OB, PC, GM, MV, AH, JB, HG, JES, and DIMICOVID provided study material or participants. LB and MRR did the data analyses. YA, DS, GM and MV, wrote the initial draft of the manuscript, and PC, OB, LB, MRR, and JB provided critical comments and editing.

All authors contributed to the data interpretation, reviewed the analyses of this manuscript, and approved its final version.

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Data sharing

Individual participant data set will be made available via an online request to corresponding authors.

Declaration of interests

YA, DS, OB, PC, GM, MV, AH, JB, HG, JES, MRR, LB and DIMICOVID have nothing to disclose.
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Table 1. Demographic, clinical, laboratory findings of patients and treatments on admission

|                                | All          | ICU-free and alive | ICU or death | P value |
|--------------------------------|--------------|--------------------|--------------|---------|
| **Total sample‡**              | 152          | 100 (68%)          | 47 (32%)     |         |
| **Demographics**               |              |                    |              |         |
| Male patients                  | 91 (59·9%)   | 59 (59%)           | 31 (66%)     | 0·47    |
| Age at admission (years)       |              |                    |              | 0·014*  |
| ≤ 60                           | 41 (27%)     | 34 (34%)           | 7 (15%)      |         |
| 61-74                          | 28 (18%)     | 14 (14%)           | 14 (30%)     |         |
| ≥ 75                           | 83 (55%)     | 52 (52%)           | 26 (55%)     |         |
| Caucasian                      | 90/140 (64·3%) | 57/90 (63%)     | 28/45 (62%) |         |
| **Comorbidities**              |              |                    |              |         |
| Smoking                        | 10 (6·6%)    | 9 (9%)             | 0 (0%)       | 0·058   |
| Hypertension                   | 82 (53·9%)   | 52 (52%)           | 25 (53%)     | 1       |
| Diabetes                       | 37 (24·3%)   | 25 (25%)           | 12 (26%)     | 1       |
| Dyslipidemia                   | 50 (32·9%)   | 31 (31%)           | 17 (36%)     | 0·57    |
| Ischemic heart disease         | 35 (23%)     | 21 (21%)           | 13 (28%)     | 0·41    |
| Cancer                         | 30 (19·7%)   | 20 (20%)           | 9 (19%)      | 1       |
| Chronic obstructive pulmonary disease | 12/151 (7·9%) | 7/99 (7%)     | 4 (9%)       | 0·75    |
| Ambulatory oxygen therapy      | 3 (2%)       | 0 (0%)             | 3 (6%)       | 0·031   |
| **Baseline on-going medications** |            |                    |              |         |
| ACE inhibitor                  | 28 (18·4%)   | 19 (19%)           | 6 (12·8%)    | 0·48    |
| NSAIDs                         | 16 (10·5%)   | 12 (12%)           | 4 (8·5%)     | 0·78    |
| Corticosteroids                | 16 (10·5%)   | 11 (11%)           | 5 (10·6%)    | 1       |
| **Signs and symptoms on admission** |        |                    |              |         |
| Days from first symptoms to admission | 5 (2;8)    | 5 (2;9)            | 5 (2;8)      | 0·95    |
| Fever ≥ 38.8 °C                | 38 (25%)     | 23 (23%)           | 13 (28%)     | 0·54    |
| Respiratory rate ≥ 24 breaths per minute | 85/151 (56%) | 49 (49%)        | 32/46 (70%)  | 0·031   |
| SpO2 on room air, %            | 93 (90-96)   | 94 (91-96)         | 91 (89-93)   | 0·0001  |
| Oxygen therapy on admission    | 110 (72·4%)  | 65 (65%)           | 42 (89%)     | 0·003   |
| SpO2 on oxygen therapy, % | 96 (95-98) | 98 (95-99) | 95 (94-97) | 0.0009 |
|--------------------------|-----------|-----------|-----------|--------|
| Oxygen flow, L/min       | 2 (2-4)   | 2 (2-3)   | 3 (2-9)   | 0.0008 |
| Anosmia                  | 17/150 (11·3%) | 13/99 (13%) | 3/46 (7%) | 0·39 |
| Dry cough                | 68/151 (45%) | 43 (43%) | 23/46 (50%) | 0·48 |
| Dyspnea                  | 102/150 (67·5%) | 58 (58%) | 41/46 (89%) | 0·0001 |
| Myalgia                  | 32/150 (21·3%) | 27/99 (27%) | 5/46 (11%) | 0·031 |
| Fatigue                  | 70/150 (46·7%) | 50/99 (51%) | 20/46 (43%) | 0·48 |
| WHO clinical scale       | 4 (3;4)   | 4 (3;4)   | 4 (4;5)   | <0·0001 |

**Laboratory findings**

| Neutrophils, /mm³        | 4350 (2948-6962) | 4155 (2722-6145) | 5240 (3465-9120) | 0·020 |
|--------------------------|------------------|------------------|------------------|-------|
| Eosinophils, /mm³        | 0 (0-22)         | 10 (0-30)        | 0 (0-10)         | 0·014 |
| Lymphocytes, < 800/mm³   | 73 (48%)         | 39 (39%)         | 30 (64%)         | 0·008 |
| C-Reactive protein, mg/L | 74·5 (30·9-135·1) | 56·6 (24·0-110·6) | 112·0 (66·2-212·9) | <0·0001 |
| Interleukine-6            |                  |                  |                 | 0.002 |
| ≥ 30 pg/mL               | 31/55 (56·4%)    | 17/38 (45%)      | 13/14 (93%)     |       |
| Procalcitonin, ng/mL     | 0·2 (0·1-0·5)    | 0·1 (0·1-0·3)    | 0·4 (0·1-0·9)   | 0·0001 |
| Ferritin, µg/L           | 913 (341-1612)   | 786 (318-1348)   | 1482 (758-2682) | 0·004 |
| Troponin, ng/mL          | 18·6 (9·4-39·7)  | 16·5 (7·9-31·1)  | 24·4 (14·2-47·7) | 0·020 |
| Lactate dehydrogenase, U/L | 364 (284-444) | 349 (272-418) | 404 (311-498) | 0·044 |
| D-Dimer, µg/L            | 890 (570-1775)   | 830 (510-1270)   | 1550 (825-2305) | 0·022 |

**Imaging Studies**

| No. | 105 | 70 | 32 |
|-----|-----|----|----|
| Signs of SARS-CoV2 pneumonia | 101/103 (98%) | 66/68 (97%) | 32 (100%) | 1 |
| Stage |       |     | 0·009* |
| No lesions | 2/103 (2%) | 2/68 (3%) | 0 (0%) |
| Ground-glass opacity | 48/103 (47%) | 36/68 (53%) | 10 (31%) |
| Consolidation | 36 /103(35%) | 24/68 (35%) | 11 (34%) |
| Bilateral pulmonary infiltration | 17/103 (17%) | 6/68 (9%) | 11 (34%) |
|---------------------------------|--------------|-----------|---------|
| More than 50%                   | 25/103 (24%) | 10/61 (15%) | 13 (41%) | 0.009 |

**Echocardiography**

|                  | 63        | 46        | 15        |
|------------------|-----------|-----------|-----------|
| Left ventricle ejection fraction, % | 65 (60-65) | 65 (65-65) | 65 (52-65) | 0.065 |

**Medications received during hospitalization**

|                  | 68 (45%) | 48 (48%) | 20 (43.5%) | 0.72 |
|------------------|----------|----------|------------|------|
| Plaquenil        | 6 (4.1%) | 2 (2.1%) | 4 (8.7%)   | 0.087 |
| Tocilizumab      | 46       | 46       | 46         | 0.087 |

Data are median (IQR), n (%) or n/N (%). P values were calculated by Mann-Whitney U test, Fisher's exact test, as appropriate. ACE=angiotension-converting enzyme. NSAIDs=Nonsteroidal anti-inflammatory drugs. SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2. WHO=World Health organization. SpO2: peripheral capillary oxygen saturation.

‡5 of the 152 patients has incomplete follow-up for ICU transfer or death within 14 days; *Fisher's exact test comparing all subcategories.
Figure 1. Flow chart of COVID-19 patients’ outcome (maximum follow-up = 14 days)

Hospitalized in medical ward
n=152

Discharge alive
n=82

Still hospitalized
n=23*

Transfer to ICU
n=17

Death in medical ward
n=30

Discharge alive
n=2

Still hospitalized
n=13*

Death in ICU
n=2

*at the time of analysis, 6 patients were still followed up for the study endpoint, 5 hospitalized in the medical ward and 1 in the ICU
Figure 2. Forest plot of multivariable analysis of COVID-19 patients’ outcome.

| Variable                                           | Odds ratio (95% CI)                  |
|----------------------------------------------------|-------------------------------------|
| **Age at admission above 60 y.o.**                  |                                     |
| ICU transfer or death within 14 days               | 2.61 (0.96–7.10)                   |
| Still hospitalized at day 14                        | 5.08 (1.90–13.58)                  |
| NIV, ICU or death at day 14                        | 12.35 (2.47–61.75)                 |
| **WHO scale at admission (per 1 point increment)** |                                     |
| ICU transfer or death within 14 days               | 4.04 (1.76–9.25)                   |
| Still hospitalized at day 14                        | 3.34 (1.51–7.39)                   |
| NIV, ICU or death at day 14                        | 4.18 (1.69–10.32)                  |
| **CRP level (per 100mg/L increment)**              |                                     |
| ICU transfer or death within 14 days               | 1.63 (0.98–2.71)                   |
| Still hospitalized at day 14                        | 2.03 (1.16–3.57)                   |
| NIV, ICU or death at day 14                        | 1.91 (1.07–3.39)                   |
| **Lymphocytes count (per 1000/mm3 increment)**     |                                     |
| ICU transfer or death within 14 days               | 0.36 (0.13–0.99)                   |
| Still hospitalized at day 14                        | 0.42 (0.17–1.00)                   |
| NIV, ICU or death at day 14                        | 0.44 (0.15–1.31)                   |
Figure 3. Proportions of ICU transfer or death within 14 days after admission by risk score

Left panel A: development cohort. Right panel B: external validation cohort.
Figure 4. Cumulative incidence of ICU transfer or death by risk score.

| Score 0–2 | Score 3–5 | Score 6–8 |
|-----------|-----------|-----------|
| Number at risk* | | |
| Score 0–2 | 17 | 16 | 13 | 11 | 9 | 8 | 6 | 2 |
| Score 3–5 | 105 | 104 | 95 | 80 | 63 | 43 | 27 | 19 |
| Score 6–8 | 25 | 21 | 17 | 13 | 10 | 7 | 5 | 4 |
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