BMJ Open

BMJ Open is committed to open peer review. As part of this commitment we make the peer review history of every article we publish publicly available.

When an article is published we post the peer reviewers' comments and the authors' responses online. We also post the versions of the paper that were used during peer review. These are the versions that the peer review comments apply to.

The versions of the paper that follow are the versions that were submitted during the peer review process. They are not the versions of record or the final published versions. They should not be cited or distributed as the published version of this manuscript.

BMJ Open is an open access journal and the full, final, typeset and author-corrected version of record of the manuscript is available on our site with no access controls, subscription charges or pay-per-view fees (http://bmjopen.bmj.com).

If you have any questions on BMJ Open's open peer review process please email info.bmjopen@bmj.com

BMJ Open: first published as 10.1136/bmjopen-2020-040729 on 25 September 2020. Downloaded from http://bmjopen.bmj.com/ on April 17, 2024 by guest. Protected by copyright.

BMJ Open

A clinical risk score to predict in-hospital mortality in COVID-19 patients

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2020-040729
Article Type:	Original research
Date Submitted by the Author:	20-May-2020
Complete List of Authors:	Fumagalli, Carlo; University of Florence Rozzini, Renzo; Fondazione Poliambulanza Istituto Ospedaliero, Department of Internal Medicine and Geriatrics; Fondazione Poliambulanza Istituto Ospedaliero, Department of Internal Medicine and Geriatrics Vannini, Matteo; University of Florence Coccia, Flaminia; Fondazione Poliambulanza Istituto Ospedaliero, Department of Internal Medicine and Geriatrics Cesaroni, Giulia; Fondazione Poliambulanza Istituto Ospedaliero, Department of Internal Medicine and Geriatrics Mazzeo, Francesca; Fondazione Poliambulanza Istituto Ospedaliero, Department of Internal Medicine and Geriatrics Cola, Maria; University of Florence Bartoloni, Alessandro; University of Florence Fontanari, Paolo; Careggi University Hospital Lavorini, Federico; Universityof Florence, Dept. Experimental and Clinical Medicine Marcucci, Rossella; University of Florence, Azienda Ospedaliero Universitaria Careggi Morettini, Alessandro; Careggi University Hospital Nozzoli, Carlo; Careggi University Hospital Peris, Adriano; Careggi University Hospital Pieralli, Filippo; Careggi University Hospital Pini, Riccardo; Careggi University Hospital Poggesi, Loredana; Careggi University Hospital Ungar, Andrea; Careggi University Hospital MARCHIONNI, Niccolo'; University of Florence
Keywords:	INFECTIOUS DISEASES, Public health < INFECTIOUS DISEASES, Adult intensive & critical care < INTENSIVE & CRITICAL CARE, INTERNAL MEDICINE

SCHOLARONE™
Manuscripts

BMJ Open: first published as 10.1136/bmjopen-2020-040729 on 25 September 2020. Downloaded from http://bmjopen.bmj.com/ on April 17, 2024 by guest. Protected by copyright.

I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our licence.

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which Creative Commons licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

For peer review only

A clinical risk score to predict in-hospital mortality in COVID-19 patients

Carlo Fumagalli, MD[1], Renzo Rozzini, MD[2], Matteo Vannini, MD[3], Flaminia Coccia, MD[2], Giulia Cesaroni, MD[2], Francesca Mazzeo, MD[2], Maria Cola, MD[4], Alessandro Bartoloni, MD[4], Paolo Fontanari, MD[3], Federico Lavorini, MD, PhD[1,3], Rossella Marcucci, MD, PhD[1,3], Alessandro Morettini, MD[4], Carlo Nozzoli, MD[4], Adriano Peris, MD[5], Filippo Pieralli, MD[4], Riccardo Pini, MD[4], Loredana Poggesi, MD[4], Andrea Ungar, MD, PhD[1], Niccolò Marchionni, MD[1,3]

1. Department of Experimental and Clinical Medicine, University of Florence, Italy
2. Department of Geriatrics and Internal Medicine, Poliambulanza Hospital, Brescia, Italy
3. Department of Cardiothoracovascular Medicine, Careggi Hospital, Florence, Italy
4. Department of Internal and Emergency Medicine, Careggi Hospital, Florence, Italy
5. Emergency and ECMO Unit, Careggi Hospital, Florence, Italy

Word Count: 2700 (text only, without abstract and references)

Key words: COVID-19, SARS-CoV-2, elderly, aging, mortality

Competing interests: None declared.

Funding: This research received no specific grant from any funding agency in the public,

commercial or not-for-profit sectors'

Corresponding Author:

Niccolò Marchionni, MD
Department of Experimental and Clinical Medicine, University of Florence, Italy
Largo Brambilla, 3, 50134 Florence, Italy
E-mail: niccolo.marchionni@unifi.it
Phone: +39 335210015
Fax: +39 055 2758047

For peer review only

Article Summary

Strengths and limitations of the study

- There is a lack of reliable, specific and rapidly applicable risk assessment tools readily available since the triage phase of COVID-19.
- Age, number of previous chronic diseases, respiratory rate, PaO2/FiO2, serum creatinine and platelet count – clinical variables rapidly collectable on hospital admission – were independent predictors of the risk of in-hospital death.
- All six predictors were used to build a novel COVID-19 clinical risk score that, at Kaplan-Meyer analysis, proved to be highly accurate (AUC 0.90, 95%CI 0.87-0.93 at ROC analysis) in separating patients at low-, intermediate- and high-risk of death.
- Retrospective design; novel score to be validated in other, external, COVID-19 case series.

For peer review only

ABSTRACT

Objectives

Several physiological abnormalities developing during COVID-19 are associated with increasing mortality. In the present study, we aimed at developing a clinical risk score predicting the short-term prognosis of COVID-19 patients, based on a set of variables available soon after the hospitalization triage.

Setting

Retrospective cohort study of 516 patients consecutively admitted for COVID-19 to two Italian tertiary hospitals located respectively in Northern and Central Italy were collected from February 22 (date of first admission) to April 10, 2020.

Participants

All consecutive patients ≥18 years admitted for COVID-19.

Main outcome measures

In-hospital, all-cause death was the primary outcome. Patients were compared by their survival status ('dead' vs. 'alive'), with the objective of identifying baseline variables associated with the primary outcome.

Results

Mean age was 67±13 (mean±SD) years, and 66.9% were men. At Cox analysis, tertiles of increasing age (≥75, upper vs. <62 years, lower: HR 7.92; p<0.001) and of previous chronic diseases (≥4 vs. 0-1: HR 2.09; p=0.007), respiratory rate (HR 1.04; p=0.001), PaO_2/FiO_2 (HR 0.995; p<0.001), serum creatinine (HR 1.34; p<0.001) and platelet count (HR 0.995; p=0.001), were predictors of the primary outcome. Associations persisted after adjusting for hydroxychloroquine and tocilizumab use. All six baseline predictors were used to build a novel COVID-19 clinical risk score which, at Kaplan-Meyer analysis, proved to be highly accurate (AUC 0.90, 95%CI 0.87-0.93 at receiver operating

For peer review only

characteristic analysis) in separating patients at low-, intermediate- and high-risk of in-hospital death ($p<0.001$).

Conclusions

Advanced age was the strongest predictor of unfavorable outcome in COVID-19 patients, even after adjusting for comorbidities and indicators of respiratory and renal function. Strategies aimed at protecting older people from the risk of SARS-CoV-2 infection should be promoted, irrespective of their health status. Six operator-independent clinical variables, readily available from the triage phase, produced a novel COVID-19 clinical risk score.

For peer review only

INTRODUCTION

The first human cases of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) were first reported in Wuhan, Hubei Province, China in January 2020[1]; it has then spread worldwide, officially being defined as a pandemic by the WHO on March 11, 2020. Italy was the first country outside Asia to be heavily affected by the virus, with a total of 189,973 confirmed cases as of April 23, 2020. Lumbardy is the Region with the highest burden in terms of mortality and strain on its health care system; most of other Italian Regions have benefitted from a substantial delay in both first reported cases and epidemiological peaks, with a massive reorganization of health care facilities, nonetheless.

In this complex scenario, prompt assignment to appropriate ward soon after hospital admission is of paramount importance. However, there is a lack of reliable prognostic prediction models and, at present, no tool for risk stratification yet has been identified[2]. We therefore analyzed a consecutive series of COVID-19 patients, regardless of intensity of care or patient outcome, with the aim of defining the clinical and laboratory characteristics as assessed on hospital admission, which might predict their short-term prognosis, in order to build eventually a novel risk scoring system.

For peer review only

METHODS

Study design and population

In this cohort study, we retrospectively reviewed the clinical history, and the laboratory and instrumental variables of all patients aged 18+ years with proven[3] COVID-19, admitted to two Italian tertiary hospitals located respectively in Northern and Central Italy (Poliambulanza Hospital, Brescia, and Careggi University Hospital, Florence) from February 22 (date of first admission in Brescia) to April 10, 2020.

A wide set of variables assessed on hospital admission was collected for each patient from electronic charts: these included demographics, number of drugs prescribed prior to admission, cardiovascular (CV) risk factors (history of smoke, hypertension, diabetes), as well as data on previous comorbidities, with detailed information on cancer, CV and pulmonary diseases. Functional status two weeks prior to hospitalization was also assessed with the Barthel Index, in which lower values correspond to poorer function[4]. Arterial blood gases, white blood cell (WBC), lymphocyte and platelet (PLT) count, alanine (ALT) and aspartate (AST) aminotransferase, creatinine, creatine phosphokinase (CPK), lactate dehydrogenase (LDH), high-sensitivity C-reactive protein (CRP), and D-dimer were collected in all patients. Interleukin-6 (IL-6), tumor necrosis factor alpha (TNF-α) and procalcitonin were available for a part of the patients, as in both hospitals they were collected only when deemed clinically indicated. Chest X-Ray was available in 486 (94%) patients. Information on respiratory support and drugs prescribed during hospital stay were collected as well. Six medical doctors (CF, MV, MC, FC, GC, FM) collected the data into a unique database and independently reviewed their consistency. Data were last updated on April 10, 2020. Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research.

For peer review only

In accordance with Ethics Committees indications at both hospitals, which approved data collection and granted a waiver of informed consent from study participants, patients' identity was anonymized and information protected by password. Furthermore, in keeping with statements by the Italian Regulatory Authorities (https://www.garanteprivacy.it/web/guest/home/docweb/-/docweb-display/docweb/5805552), the conditions exist to allow us to handle personal anonymized clinical data given the practical impossibility, to the best of our efforts, to obtain a retrospective informed consent from the vast majority of the patients.

Study Outcome

In-hospital, all-cause death was the primary outcome. Therefore, patients were compared by their survival status ('dead' vs. 'alive' as of April 10, 2020), with the objective of identifying since hospital admission potential determinants of the primary outcome.

Patient and public involvement

Patients or the public were not involved in the design or conduct of our research, partially because of its retrospective nature. Public Health Authorities will be involved in the upcoming, large-scale Validation of the newly presented score.

Statistical Analysis

Continuous variables, reported as mean ± standard deviation (SD) or as median with interquartile range [IQR], respectively for normal and non-normal distributions, were compared between groups ('dead' vs. 'alive' status) with t-test, analysis of variance or nonparametric tests, as appropriate. Categorical variables, reported as counts and percentages, were compared between groups with χ^2 test, or Fisher's exact test when any expected cell count was less than five.

For peer review only

In survival analyses, patients still hospitalized at study closure were considered alive, together with those who had been discharged during the study period. Cox multivariable regression analyses (with backward stepwise elimination) were calculated to identify baseline characteristics independently associated with the outcome, with inclusion of variables ($p<0.10$ at univariable analysis) which were available for all patients. A 2-sided $p<0.05$ was considered statistically significant. Analyses were performed using the SPSS v. 26.0 statistical package for Macintosh.

For peer review only

RESULTS

Regional trend and clinical characteristics on hospital admission

During the study period, 516 consecutive patients (301 in Brescia and 215 in Florence) diagnosed with COVID-19 were included in the study (Table 1). According to date of admission, Brescia hospital anticipated both the first case (February 22 vs. 25) and the peak of admissions by an average of 3 days, with a remarkably higher total and peak burden of admissions.

As of April 10, 314 (61%) patients had been discharged from hospital (273 [87%] at home and 41 [13%] to post-acute facilities), 82 (16%) were still hospitalized, while 120 (23.2%) had died.

The mean age was 67±13 years (range 21-95) and 345 (66.9%) patients were men. The demographic and clinical characteristics of non-survivors and survivors are reported in Table 1. Non-survivors were significantly older. Indeed, in-hospital fatality rate sharply increased with age and was more than 5-time higher in individuals aged ≥75 years (51.2% vs. <75 years 9.8%; p<0.001). Conversely, prognosis was similar for both genders. The median hospital stay was 9 [IQR 5-14] days, significantly longer in survivors. Non-survivors presented also a higher prevalence of CV risk factors, a greater burden of chronic comorbidities, and were more functionally impaired as shown by a lower Barthel index score (Table 1). Previous use of ACE-inhibitors or Angiotensin-receptor blockers (ACE-i/ARBs) was similar in both groups while, in accordance with their higher burden of comorbidities, non-survivors reported a greater number of drugs chronically assumed. The majority of patients presented with fever (89.1%) and cough (57.3%). Of note, non-survivors reported cough less frequently (48.5% vs. 59.8%; p=0.032), but had a significantly higher prevalence of insomnia, syncope or altered mental status. While the prevalence of dyspnea was similar in both groups (overall, 48.9%), respiratory rate (RR) on admission was higher in non-survivors ('dead' 26±7 vs. 'alive' 21±6 breaths/min; p<0.001).

For peer review only

Laboratory and imaging findings

The first nasopharyngeal swab was positive in 499 (97%) patients. Laboratory findings are presented in Table 2. In the population as a whole, the median PaO_2/FiO_2 ratio was 269 [IQR 217-319], and values <200 were significantly associated with the probability of death. Lymphocytopenia was present in 61% of the population, more frequently among non-survivors ('dead' 71% vs. 'alive' 58%; p=0.011), who also had lower PLT count and higher serum creatinine. Inflammatory markers – among which only CRP was available for all patients – were increased in both groups and to a significantly higher level in non-survivors. Conversely, albumin was lower in non-survivors. Chest X-Ray was abnormal in >95% of cases, with a trend towards a higher prevalence of interstitial or mixed (both interstitial and consolidation) patterns in deceased patients.

Medical management and clinical outcomes

Non-survivors required non-invasive (Continuous Positive Airway Pressure and Biphasic Positive Airway Pressure modes) or invasive ventilation more frequently than survivors (Table 3). While antibiotics were prescribed more frequently to non-survivors, heparin, hydroxychloroquine, antiviral agents (combination of lopinavir/ritonavir) and monoclonal antibodies (mAbs, tocilizumab) were all more frequently prescribed to survivors. In contrast, corticosteroid therapy was adopted in similar proportions in the two groups. Patients receiving mAbs were younger (65±9 vs. 68±14 years, p<0.01) and had lower levels of serum creatinine (0.9±0.3 vs. 1.2±0.9 mg/dL, p=0.024), but higher levels of IL-6, which was available in 192 cases (26 [IQR 11-85] vs. 13 [IQR 7-31] pg/mL; p<0.001).

Determinants of mortality

At Cox multivariable regression analysis (Table 4, model 1), age, number of chronic comorbidities (with inclusion of hypertension, diabetes, CV and pulmonary disease, cancer,

For peer review only

depression and dementia), RR, and creatinine were positive predictors of death, while PaO_2/FiO_2 ratio and PLT count were negative predictors. Interestingly, pre-admission functional status as assessed by Barthel Index and number of drugs previously assumed, were excluded from the model. In a further Cox analysis (Table 4, model 2) testing the association of pharmacological agents with risk of mortality while simultaneously adjusting for the same variables included in model 1, hydroxychloroquine and tocilizumab had a protective effect against mortality, while antibiotics, antiviral agents and heparin were excluded from the model. To exclude any impact of age-driven difference in treatment strategies, we conducted a further analysis dividing patients by PaO_2/FiO_2 (<200 vs. ≥200) and observed that the impact of age was maintained, with no differences between centers.

Variables included in Model 1 (Table 4) were used to calculate a clinical score intended for rapid patient's risk assessment on hospital admission. To this purpose, RR, PaO_2/FiO_2, creatinine and PLT count were re-classified into tertiles and a clinical score was then built with identification of three risk strata as reported in Table 5. Finally, a Kaplan-Meier survival analysis developed using the tertiles of clinical score provided an excellent separation of risk (Figure 1). Of note, a cutoff score of ≤8 identifies a subset of 63 (12.2%) patients with no fatalities during the study period, who therefore might be defined as 'at very low-risk'. The performance of the combined predicted probabilities measured with Receiver Operator Curve (ROC) analysis yielded an AUC of 0.90 (95%CI 0.87-0.93).

For peer review only

DISCUSSION

In this study, we developed a COVID-19 Clinical Risk Score (COVID-19CRS) that proved to be able to stratify rapidly the risk of death of COVID-19 patients since their hospital admission. Such a score includes six clinical and laboratory parameters: age, comorbidities, respiratory rate, PaO_2/FiO_2, serum creatinine, and platelet count. One-in-four patients of our cohort of Italian COVID-19 cases died and age was the strongest driver of outcome. Compared to patients younger than 62 years of age, the risk of death was almost 3 and 8 times higher in individuals 62-74 and 75+ years of age, respectively. Such an exponential risk growth persisted after adjusting for burden of comorbidities, a series of clinical characteristics and in-hospital prescribed therapy. Such a strong association between older ages and prognosis had been observed in previous studies on COVID-19 both in China and in other countries, albeit with a less brisk increase in age-specific risk[5]. This difference might be due to the lower median age reported in those studies and to the fact that we explored a wider age range (21-95 years), with one third of our population above the age of 75[5,6]. In COVID-19, age has been associated with variable degrees of increasing risk of admissions to ICU, onset of acute respiratory distress syndrome (ARDS), myocardial damage, and fatal outcome[7–11]. This observation was true also in previous epidemic or pandemic outbreaks, such as Severe Acute Respiratory Syndrome (SARS) and Middle East Respiratory Syndrome (MERS) where, as in COVID-19, the respiratory system is both the entry way and the main target of viral infection[12,13]. We might argue that lung senescence, resulting in impaired elasticity, end-expiratory lung volume and alveolar integrity[14], together with kidney senescence[15], may predispose *per se* to SARS-CoV-2-related acute respiratory and renal failure even otherwise relatively robust elderly individuals. This hypothesis is consistent with the observation that age and three indicators of target organs (RR, PaO_2/FiO_2, serum creatinine) function were independent predictors of in-hospital mortality, after adjusting for comorbidities and pharmacological therapy.

For peer review only

While a low PLT count was frequently observed in non-survivor COVID-19 patients[7,8,11,16], in our cohort lower values were directly associated with adverse outcome, suggesting a possible role of COVID-19-related coagulopathy in determining a poor outcome[17,18].

Prompt referral to the appropriate care setting (i.e. low- vs. high-intensity) is of crucial importance in improving outcomes and health care resource utilization[19–21]. Given the high in-patient flow observed during this emergency in Italy and the related shortage of hospital beds, the use of a disease-specific clinical risk score might have helped in identifying the appropriate level of care and reducing delays. In this perspective, we aimed at identifying a score readily available on hospital admission. Indeed, here we propose a score based on six objective, operator-independent variables usually available early after hospitalization, which proved able to identify three categories at increasing risk of death with a high level of statistical accuracy. The scoring process suggests that, while low-risk patients might be assigned safely to low-intensity care, higher intensity wards should be alerted during triage for the second and the third group. Moreover, the score seems to allow identification of about 10-15% of 'very low-risk' patients (score ≤ 8) with no events who, though symptomatic for proven COVID-19, might be immediately discharged home, with the sole indication to remote control and parameters monitoring.

A recent systematic review of prediction models concluded that performance of prognostic estimates for COVID-19 may be optimistic and misleading, because of high risk of bias in patient selection, inadequate population description, unclear outcome definition and length of follow-up[2]. Recently, a score to predict occurrence of critical illness during COVID-19 was developed in a cohort of Chinese patients belonging to more than 500 centers throughout the Country[22]. Interestingly, the mean age of such cohort was 49±16 years, which is 15-20 years less than observed in most European and USA studies published to date[23–25]. Although apparently similar in terms of objectives, we aimed

For peer review only

at stratifying the risk of death in a consecutive cohort of patients who shared demographics characteristics similar to other European and US studies.

Present therapeutic recommendations on COVID-19 have a limited level of evidence[26], and have evolved during progression of the pandemic wave. Therefore, we assessed whether our management strategies had varied across three tertiles of the 48-day observational period (1st 1-24 days, 2nd 25-30, 3rd >31). While types of respiratory support proved to be time-independent, we found a significant, direct association of prescription rates of heparin, hydroxychloroquine, antiviral therapy and mAbs with increasing time interval from first admitted case in both hospitals (data not shown). In a multivariable Cox regression analysis (Table 4, model 2) we observed that hydroxychloroquine and tocilizumab might have had some protective effect against mortality, at least in a real-world perspective.

The observation of the highly negative impact of age suggests that, in the absence of specifically effective drug therapy and vaccination[27], social isolation and prevention of infecting contacts are key-issues particularly relevant in individuals aged 70-75 years and over. These data may represent a call to action for health authorities, in order to update management policies in the community in general and in the nursing homes in particular, where in fact the highest mortality rates occurred in Italy and in other Countries[28].

Some limitations of our study have to be acknowledged. First, the retrospective and observational nature of our analysis does not allow to draw any firm conclusion about therapeutic strategies that, moreover, were clearly adapted over time, with some evident impact on the outcome. Second, some laboratory parameters, which proved to be of prognostic relevance in other studies[7,11], were not collected for all individuals in our sample, possibly as a consequence of variable severity of some clinical pictures (i.e. very mildly affected vs. extremely critical patients at presentation). Third, since nasopharyngeal swabs were our key criterion for SARS-CoV-2 detection,

For peer review only

we did not assess viremia, while the correlation of viral load with disease severity is still a matter of debate. Fourth, 82 out of 516 patients were still in-hospital at the time of closure of follow-up. Nevertheless, after excluding these patients from our analysis, results were fully confirmed, with a 0.91 AUC of the predictive score (data not shown). Finally, we do not have information regarding the time span between symptom onset and hospital admission, which might have had an impact on either clinical or laboratory parameters that we sampled on hospital admission.

In conclusion, we believe that, even though to be further validated in clinical series different from ours, the COVID-19CRS that we developed is a useful, easy to obtain and inexpensive clinical tool for risk stratification of COVID-19 patients.

For peer review only

REFERENCES

1. Wu F, Zhao S, Yu B, et al. A new coronavirus associated with human respiratory disease in China. *Nature*. 2020;579(7798):265-269. doi:10.1038/s41586-020-2008-3
2. Wynants L, Van Calster B, Bonten MMJ, et al. Prediction models for diagnosis and prognosis of covid-19 infection: Systematic review and critical appraisal. *BMJ*. 2020;369:m1328. doi:10.1136/bmj.m1328
3. WHO. Clinical management of severe acute respiratory infection when COVID-19 is suspected (v1.2). 2020:1-21. https://www.who.int/publications-detail/clinical-management-of-severe-acute-respiratory-infection-when-novel-coronavirus-(ncov)-infection-is-suspected.
4. MAHONEY FI, BARTHEL DW. Functional Evaluation: the Barthel Index. *Md State Med J*. 1965;14:61-65.
5. Wu Z, McGoogan JM. Characteristics of and Important Lessons from the Coronavirus Disease 2019 (COVID-19) Outbreak in China: Summary of a Report of 72314 Cases from the Chinese Center for Disease Control and Prevention. *JAMA - J Am Med Assoc*. 2020;2019. doi:10.1001/jama.2020.2648
6. The World Bank. *World Bank Staff Estimates Based on Age/Sex Distributions of United Nations Population Division's World Population Prospects: 2019 Revision.*; 2019. https://data.worldbank.org/indicator/SP.POP.65UP.TO.ZS.
7. Wu C, Chen X, Cai Y, et al. Risk Factors Associated with Acute Respiratory Distress Syndrome and Death in Patients with Coronavirus Disease 2019 Pneumonia in Wuhan, China. *JAMA Intern Med*. 2020. doi:10.1001/jamainternmed.2020.0994
8. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet*. 2020;395(10223):497-506. doi:10.1016/S0140-6736(20)30183-5
9. Guan W, Ni Z, Hu Y, et al. Clinical Characteristics of Coronavirus Disease 2019 in China. *N Engl J Med*. 2020:1-13. doi:10.1056/nejmoa2002032
10. Shi S, Qin M, Shen B, et al. Association of Cardiac Injury with Mortality in Hospitalized Patients with COVID-19 in Wuhan, China. *JAMA Cardiol*. 2020:1-8. doi:10.1001/jamacardio.2020.0950

For peer review only

11. Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet*. 2020;395(10229):1054-1062. doi:10.1016/S0140-6736(20)30566-3

12. Choi KW, Chau TN, Tsang O, et al. Outcomes and Prognostic Factors in 267 Patients with Severe Acute Respiratory Syndrome in Hong Kong. *Ann Intern Med*. 2003;139(9):715-724. doi:10.7326/0003-4819-139-9-200311040-00005

13. Hong KH, Choi JP, Hong SH, et al. Predictors of mortality in Middle East respiratory syndrome (MERS). *Thorax*. 2018;73(3):286-289. doi:10.1136/thoraxjnl-2016-209313

14. Bowdish DME. The Aging Lung: Is Lung Health Good Health for Older Adults? *Chest*. 2019;155(2):391-400. doi:10.1016/j.chest.2018.09.003

15. O'Sullivan ED, Hughes J, Ferenbach DA. Renal aging: Causes and consequences. *J Am Soc Nephrol*. 2017;28(2):407-420. doi:10.1681/ASN.2015121308

16. Chen T, Wu D, Chen H, et al. Clinical characteristics of 113 deceased patients with coronavirus disease 2019: retrospective study. *BMJ*. 2020;368:m1091. doi:10.1136/bmj.m1091

17. Bikdeli B, Madhavan M V, Jimenez D, et al. COVID-19 and Thrombotic or Thromboembolic Disease: Implications for Prevention, Antithrombotic Therapy, and Follow-up. *J Am Coll Cardiol*. April 2020:27284. doi:10.1016/j.jacc.2020.04.031

18. Lippi G, Plebani M, Henry BM. Thrombocytopenia is associated with severe coronavirus disease 2019 (COVID-19) infections: A meta-analysis. *Clin Chim Acta*. 2020;506:145-148. doi:10.1016/j.cca.2020.03.022

19. Johnson DW, Schmidt UH, Bittner EA, Christensen B, Levi R, Pino RM. Delay of transfer from the intensive care unit: A prospective observational study of incidence, causes, and financial impact. *Crit Care*. 2013;17(4):R128. doi:10.1186/cc12807

20. Churpek MM, Wendlandt B, Zadravecz FJ, Adhikari R, Winslow C, Edelson DP. Association between intensive care unit transfer delay and hospital mortality: A multicenter investigation. *J Hosp Med*. 2016. doi:10.1002/jhm.2630

21. Liu V, Kipnis P, Rizk NW, Escobar GJ. Adverse outcomes associated with delayed intensive care unit

For peer review only

transfers in an integrated healthcare system. *J Hosp Med*. 2012. doi:10.1002/jhm.964

22. Liang W, Liang H, Ou L, et al. Development and Validation of a Clinical Risk Score to Predict the Occurrence of Critical Illness in Hospitalized Patients With COVID-19. *JAMA Intern Med*. May 2020. doi:10.1001/jamainternmed.2020.2033

23. Grasselli G, Zangrillo A, Zanella A, et al. Baseline Characteristics and Outcomes of 1591 Patients Infected With SARS-CoV-2 Admitted to ICUs of the Lombardy Region, Italy. *Jama*. 2020:1-8. doi:10.1001/jama.2020.5394

24. Richardson S, Hirsch JS, Narasimhan M, et al. Presenting Characteristics, Comorbidities, and Outcomes Among 5700 Patients Hospitalized With COVID-19 in the New York City Area. *JAMA*. April 2020. doi:10.1001/jama.2020.6775

25. Helms J, Tacquard C, Severac F, et al. High risk of thrombosis in patients with severe SARS-CoV-2 infection: a multicenter prospective cohort study. *Intensive Care Med*. May 2020. doi:10.1007/s00134-020-06062-x

26. Poston JT, Patel BK, Davis AM. Management of Critically Ill Adults with COVID-19. *JAMA - J Am Med Assoc*. 2020:E1-E3. doi:10.1001/jama.2020.4914

27. Koff WC, Williams MA. Covid-19 and Immunity in Aging Populations - A New Research Agenda. *N Engl J Med*. April 2020. doi:10.1056/NEJMp2006761

28. WHO. Virtual press briefing on COVID-19: key considerations on nursing homes. In: *WHO Regional Office for Europe*. ; 2020. http://www.euro.who.int/en/media-centre/events/events/2020/04/virtual-press-briefing-on-covid-19-key-considerations-on-nursing-homes.

For peer review only

Figure Legend

Figure 1. Kaplan-Meier Analysis of Overall Survival of Patients diagnosed with COVID-19 according to three risk categories.

For peer review only

Table 1. Clinical characteristics on hospital admission

	Overall (N=516)	Dead (N=120)	Alive (N=396)	P
Demographic Characteristics				
Age, mean± SD	67 ± 13	79 ± 8	64 ± 12	<0.001
Age (tertiles)				
<62, N (%)	177 (34.3)	7 (5.8)	170 (42.9)	
62-74, N (%)	171 (33.1)	27 (22.5)	144 (36.4)	
≥75, N (%)	168 (32.6)	86 (71.7)	82 (20.7)	
Hospital stay, median [IQR]	9 [5-14]	6 [3-10]	10 [6-15]	<0.001
Gender (men), N (%)	345 (66.9)	85 (70.8)	260 (65.7)	0.321
Smoking History, N (%)	112 (21.7)	26 (21.7)	86 (21.7)	0.999
Hypertension, N (%)	182 (35.3)	65 (55.6)	117 (29.6)	<0.001
Diabetes Mellitus, N (%)	161 (31.4)	51 (43.6)	110 (27.8)	<0.001
CV Disease, N (%)	146 (28.5)	57 (47.9)	89 (22.6)	<0.001
Previous stroke/TIA, N (%)	25 (4.9)	11 (9.1)	14 (3.5)	0.011
COPD, N (%)	36 (7.0)	12 (10)	24 (6.1)	0.120
Cancer, N (%)	50 (9.7)	23 (19.2)	27 (6.8)	<0.001
Depression, N (%)	52 (20.1)	20 (17.1)	32 (8.1)	0.005
Dementia, N (%)	18 (3.4)	12 (10.0)	6 (1.5)	<0.001
Comorbidities (#), mean ± SD	2.1 ± 1.7	3.2 ± 1.9	1.8 ± 1.6	<0.001
≥3, N (%)	179 (34.7)	68 (58.1)	111 (28.2)	<0.001
Barthel Index, mean ± SD	85 ± 28	77 ± 27	94 ± 1 3	<0.001
ACE-i/ARBs, N (%)	144 (27.9)	35 (29.2)	109 (27.5)	0.725
Drugs, N (%)	3.4 ± 3.3	5.6 ± 3.5	2.7 ± 2.7	<0.001
Signs and Symptoms				
Fever, N (%)	456 (89.1)	102 (87.2)	354 (89.5)	0.457
Cough, N (%)	293 (57.3)	57 (48.5)	236 (59.8)	0.032
Dyspnea, N (%)	250 (48.9)	59 (50.4)	191 (48.5)	0.711
Respiratory Rate, mean ± SD	23 ± 7	26 ± 7	21 ± 6	<0.001
Insomnia, N (%)	68 (13.2)	18 (15)	50 (12.6)	0.004
Diarrhea, N (%)	47 (9.2)	10 (8.3)	37 (9.4)	0.782
Syncope, N (%)	27 (5.2)	11 (9.2)	16 (4.1)	0.023
Altered Mental Status, N (%)	24 (4.7)	12 (10.0)	12 (3.0)	<0.001

bmjopen-2020-040729 on 25 September 2020. Downloaded from http://bmjopen.bmj.com/ on April 17, 2024 by guest. Protected by copyright.

For peer review only

SD: Standard Deviation; ACE-i: Angiotensin Converting Enzyme Inhibitors; ARBs: Angiotensin Receptor Blockers; CV: Cardiovascular Disease; COPD: Chronic Obstructive Pulmonary Disease; TIA: Transient Ischemic Attack. (#) Comorbidities is a composite variable including from hypertension to dementia. Percentages in brackets are calculated for numbers in the columns for all dichotomous variables.

For peer review only

bmjopen-2020-040729 on 25 September 2020. Downloaded from http://bmjopen.bmj.com/ on April 17, 2024 by guest. Protected by copyright.

Table 2. Laboratory and imaging findings on admission

	Overall (N=516)	Dead (N=120)	Alive (N=396)	P
Laboratory findings				
PaO_2/FiO_2, median [IQR]	269 [217-319]	226 [169-271]	281 [232-335]	<0.001
<200, N (%)	101 (19.6)	42 (35.0)	59 (15.0)	<0.001
≥200, N (%)	415 (80.4)	78 (65.0)	337 (85.1)	
Hematocrit, % median [IQR]	41 [38-44]	39 [35-43]	42 [39-44.75]	<0.001
Hemoglobin, g/dL median [IQR]	13.0 [11.7-14.3]	12.9 [11.7-14.1]	13.3 [12.2-14.3]	0.203
WBC, ($\times 10^9$/L) median [IQR]	6.31 [5-9]	7.11 [5-10.23]	6 [4.98-8.47]	0.009
Lymphocytes, ($\times 10^9$/L) median [IQR]	0.90 [0.70-1.24]	0.77 [0.70-1.07]	0.90 [0.70-1.24]	<0.001
Lymphocytopenia, N (%)	316 (61)	85 (71)	231 (58)	0.011
Platelets, ($\times 10^9$/L) median [IQR]	182 [142-234]	156 [117-218]	187 [152-238]	0.001
ALT, U/L median [IQR]	31 [19-51]	26 [16-42]	32 [19-58]	0.004
AST, U/L median [IQR]	46 [30-69]	50 [35-71]	45 [28-69]	0.181
Serum Creatinine, mg/dL median [IQR]	0.94 [0.79-1.22]	1.23 [0.92-1.91]	0.90 [0.79-1.13]	<0.001
CPK, U/L median [IQR]	110 [64-228]	130 [60-208]	108 [64-208]	0.085
LDH, U/L median [IQR]	351 [268-480]	473 [338-610]	335 [266-437]	<0.001
CRP, mg/L median [IQR]	94 [44.3-161.8]	138 [85-188]	77 [37-152]	<0.001
Variables not Available in all patients				
Albumin (n=361), g/L median [IQR]	3.2 [2.9-3.4]	3.0 [2.8-3.2]	3.3 [3-3.5]	<0.001
BUN (n=358), mg/dL median [IQR]	40 [30-63]	63 [41-95]	37 [28-51]	<0.001
Ferritin (n=248), ng/mL median [IQR]	716 [348-1316]	1076 [481-2643]	697 [316-1192]	0.005
D-Dimer (n=247), ug/L median [IQR]	1042 [594-2006]	1870 [945-11006]	984 [578-1680]	<0.001
Procalcitonin (n=216), ng/mL median [IQR]	0.15 [0.09-0.27]	0.31 [0.14-2.25]	0.13 [0.07-0.23]	0.001
IL-6 (n=192), pg/mL median [IQR]	15.4 [7.6-39.1]	50 [23.9-70.4]	12.9 [6.5-28.6]	<0.001
TNF-α (n=128), pg/mL median [IQR]	6.7 [3.6-13.1]	9.0 [5.4-16.7]	6.3 [3.4-12.9]	0.073
Imaging	N=486	N=114	N=372	
Chest X Ray				
negative, N (%)	20 (4.1)	2 (1.8)	18 (4.8)	0.053
consolidation, N (%)	67 (13.8)	12 (10.5)	55 (14.8)	
interstitial, N (%)	346 (71.2)	81 (71.1)	265 (71.2)	
mixed, N (%)	53 (10.9)	19 (16.7)	34 (9.1)	

IQR: Interquartile Range; WBC: White Blood Cell Count; ALT: alanine aminotransferase; AST: aspartate aminotransferase ; CPK: creatine phosphokinase; LDH: lactate

bmjopen-2020-040729 on 25 September 2020. Downloaded from http://bmjopen.bmj.com/ on April 17, 2024 by guest. Protected by copyright.

For peer review only

mjopen-2020-040729 on 25 September 2020. Downloaded from http://bmjopen.bmj.com/ on April 17, 2024 by guest. Protected by copyright.

For peer review only

Table 3. Treatment strategies

	Overall (N=516)	Dead (N=120)	Alive (N=396)	p
Respiratory Support				
None, N (%)	57 (11.0)	2 (1.7)	55 (13.9)	<0.001
Oxygen, N (%)	334 (64.7)	78 (65)	256 (65)	
Non-Invasive Ventilation, N (%)	65 (12.6)	23 (19.2)	42 (10.6)	
Invasive Ventilation, N (%)	60 (11.6)	17 (14.2)	43 (10.9)	
Drugs				
Antibiotics, N (%)	407 (78.9)	106 (88.3)	301 (76.0)	0.003
Heparin, N (%)	299 (57.9)	57 (47.5)	242 (61.1)	0.008
Hydroxychloroquine, N (%)	268 (51.9)	43 (35.8)	225 (56.8)	<0.001
Lopinavir/Ritonavir, N (%)	247 (50.7)	39 (32.5)	208 (52.5)	<0.001
Corticosteroids, N (%)	176 (34.1)	45 (37.5)	131 (33.1)	0.371
Monoclonal antibodies, N (%)	57 (11.3)	3 (2.5)	54 (13.6)	<0.001

For peer review only

bmjopen-2020-040729 on 25 September 2020. Downloaded from http://bmjopen.bmj.com/ on April 17, 2024 by guest. Protected by copyright.

Table 4. Cox multivariable regression analyses of determinants of in-hospital mortality

	Model 1				Model 2			
Variables	**HR**	**95.0% CI**		**p**	**HR**	**95.0% CI**		**p**
Age (tertiles)								
62-74 vs. <62 years	2.86	1.23	6.64	0.014	2.67	1.15	6.21	0.023
≥75 vs. <62 years	7.92	3.60	17.43	<0.001	6.78	3.09	14.84	<0.001
Comorbidities (tertiles)								
2-3 vs. 0-1	1.85	1.11	3.08	0.018	1.97	1.18	3.30	0.009
≥4 vs. 0-1	2.09	1.23	3.55	0.007	3.182	1.84	5.49	<0.001
RR (breaths/min), for unit increase	1.04	1.02	1.07	0.001	1.07	1.04	1.10	<0.001
PaO_2/FiO_2, for unit increase	0.995	0.992	0.997	<0.001	0.995	0.993	0.997	<0.001
Creatinine (mg/dL), for unit increase	1.34	1.18	1.51	<0.001	1.26	1.11	1.47	<0.001
Platelets (10^9/L), for unit increase	0.995	0.992	0.998	0.001	0.995	0.992	0.998	<0.001
Hydroxychloroquine, yes vs. no	/	/	/		0.478	0.316	0.723	<0.001
Tocilizumab, yes vs. no	/	/	/		0.232	0.039	0.446	0.001

HR: hazard ratio; 95%CI: 95% confidence interval; RR: respiratory rate. History of CV disease, hypertension, diabetes, depression, dementia, cancer were included into

For peer review only

bmjopen-2020-040729 on 25 September 2020. Downloaded from http://bmjopen.bmj.com/ on April 17, 2024 by guest. Protected by copyright.

Table 5. Variables and relative scores to calculate the COVID-19 Clinical Risk Score

Age (years)	**Score**	**Comorbidities** (N)	**Score**	**RR** (breaths/min)	**Score**	**PaO_2/FiO_2**	**Score**	**Creatinine** (mg/dL)	**Score**	**Platelet Count** (10^9/L)	**Score**	**Risk Categories** (sum of individual variable scores)
< 62	1	≤1	1	≤20	1	> 300	1	<.83	1	> 212	1	Low = ≤ 10
62-74	2	2-3	2	21-24	2	236-299	2	0.83-1.12	2	156-211	2	Intermediate = 11-13
≥ 75	3	≥4	3	≥ 25	3	< 236	3	≥ 1.13	3	< 156	3	High risk = ≥ 14

Categories for each variable represent a tertile distribution

For peer review only

bmjopen-2020-040729 on 25 September 2020. Downloaded from http://bmjopen.bmj.com/ on April 17, 2024 by guest. Protected by copyright.

Contributors:

The ICMJE recommends that authorship be based on the following 4 criteria:

- Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; AND
- Drafting the work or revising it critically for important intellectual content; AND
- Final approval of the version to be published; AND
- Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

In addition to being accountable for the parts of the work he or she has done, an author should be able to identify which co-authors are responsible for specific other parts of the work. In addition, authors should have confidence in the integrity of the contributions of their co-authors.

AUTHOR LIST	**C. Fumagalli**	**R. Rozzini**	**M. Vannini**	**F. Coccia**	**G. Cesaroni**	**F. Mazzeo**	**M. Cola**	**A. Bartoloni**	**P. Fontanari**	**F. Lavorini**	**R. Marcucci**	**A. Morettini**
Conception and design of the work:	X	X								X	X	
Acquisition of the data:	X	X	X	X	X	X	X					
Analysis and interpretation of the data,	X	X								X	X	
Drafting of the manuscript	X		X							X	X	
Critical revision of the manuscript for important intellectual content,	X	X	X	X	X	X	X	X	X	X	X	X
Accountable for all aspects of the work	X	X	X							X	X	
Approval of the final manuscript:	X	X	X	X	X	X	X	X	X	X	X	X

For peer review only

bmjopen-2020-040729 on 25 September 2020. Downloaded from http://bmjopen.bmj.com/ on April 17, 2024 by guest. Protected by copyright.

CONTINUED	C. Nozzoli	A. Peris	F. Pieralli	R. Pini	L. Poggesi	A. Ungar	N. Marchionni
Conception and design of the work:							X
Acquisition of the data:							
Analysis and interpretation of the data,							X
Drafting of the manuscript							X
Critical revision of the manuscript for important intellectual content,	X	X	X	X	X	X	X
Accountable for all aspects of the work							X
Approval of the final manuscript:	X	X	X	X	X	X	X

Funding: This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests: None declared.

Patient consent: Ethics Committees at both hospitals approved data collection and granted a waiver of informed consent from study participants. patients' identity was anonymized and information protected by password.

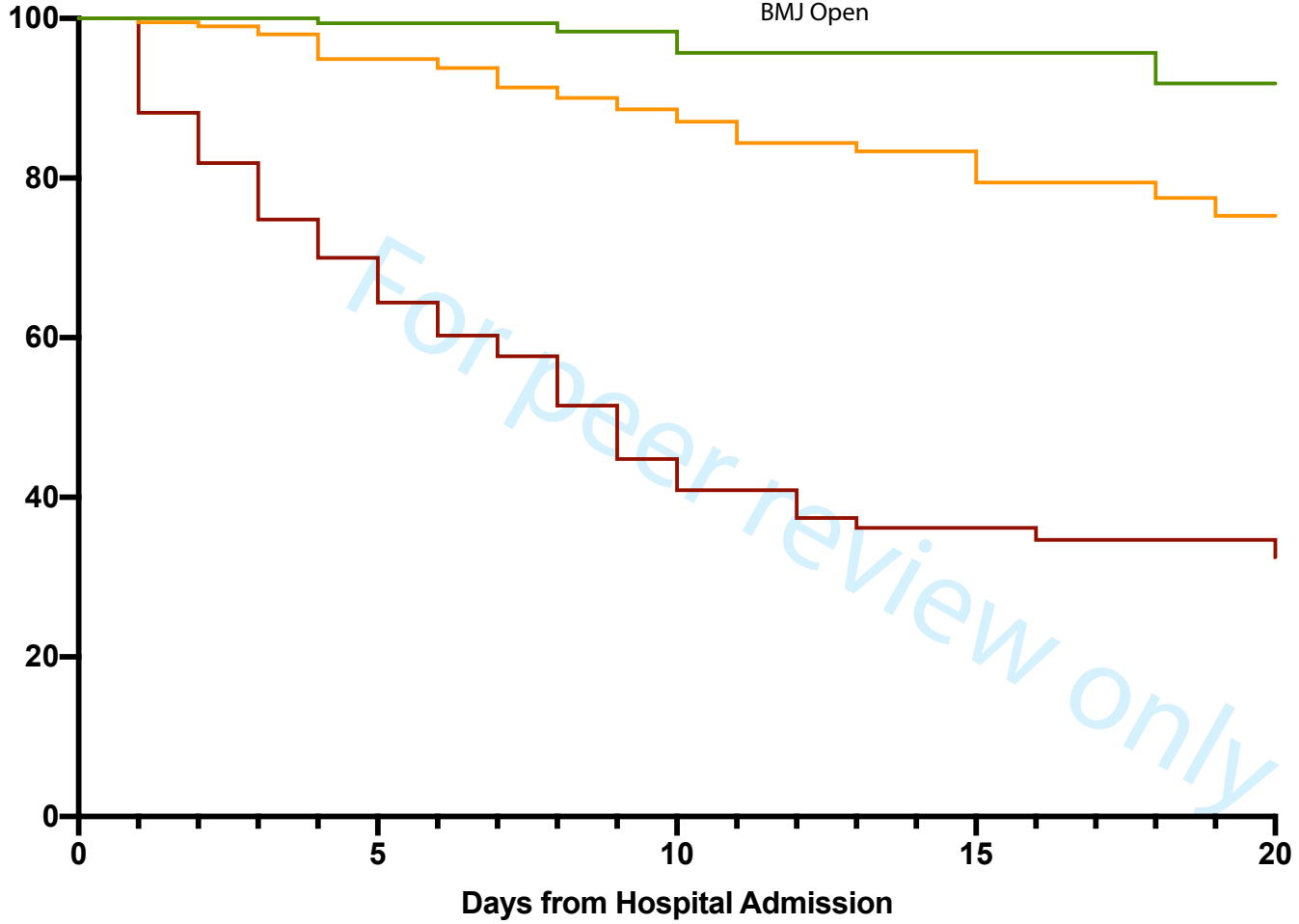
Ethics approval: The study was conducted according to the Declaration of Helsinki and approved by the local Ethics Committees.

Data sharing statement: Additional unpublished data are not publicly available.

Author note: The views expressed in this article are those of the authors alone.

For peer review only

bmjopen-2020-040729 on 25 September 2020. Downloaded from http://bmjopen.bmj.com/ on April 17, 2024 by guest. Protected by copyright.



Low	189	150	74	33	17
Intermediate	200	177	111	64	31
High	127	87	45	30	15

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

For peer review only

per 2020. Downloaded from http://bmjopen.bmj.com/ on April 17, 2024 by guest. Protected by copyright.

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	3
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	3-4
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	6-7
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6-7-8
Bias	9	Describe any efforts to address potential sources of bias	6
Study size	10	Explain how the study size was arrived at	6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7-8
		(*b*) Describe any methods used to examine subgroups and interactions	
		(*c*) Explain how missing data were addressed	
		(*d*) If applicable, explain how loss to follow-up was addressed	
		(*e*) Describe any sensitivity analyses	
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	9
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

bmjopen-2020-040729 on 24 September 2020. Downloaded from http://bmjopen.bmj.com/ on April 17, 2024 by guest. Protected by copyright.

Descriptive data		14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders (b) Indicate number of participants with missing data for each variable of interest (c) Summarise follow-up time (eg, average and total amount)	9-10
Outcome data		15*	Report numbers of outcome events or summary measures over time	10-11
Main results	16		(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included (*b*) Report category boundaries when continuous variables were categorized (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	10-11
Other analyses	17		Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	10-11
Discussion				
Key results	18		Summarise key results with reference to study objectives	12
Limitations	19		Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	14
Interpretation	20		Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	12-15
Generalisability	21		Discuss the generalisability (external validity) of the study results	13-14-15
Other information				
Funding	22		Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

bmjopen-2020-040729 on 25 September 2020. Downloaded from http://bmjopen.bmj.com/ on April 17, 2024 by guest. Protected by copyright.

For peer review only

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

BMJ Open

Clinical risk score to predict in-hospital mortality in COVID-19 patients: a retrospective cohort study

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2020-040729.R1
Article Type:	Original research
Date Submitted by the Author:	06-Aug-2020
Complete List of Authors:	Fumagalli, Carlo; University of Florence Rozzini, Renzo; Fondazione Poliambulanza Istituto Ospedaliero, Department of Internal Medicine and Geriatrics; Fondazione Poliambulanza Istituto Ospedaliero, Department of Internal Medicine and Geriatrics Vannini, Matteo; University of Florence Coccia, Flaminia; Fondazione Poliambulanza Istituto Ospedaliero, Department of Internal Medicine and Geriatrics Cesaroni, Giulia; Fondazione Poliambulanza Istituto Ospedaliero, Department of Internal Medicine and Geriatrics Mazzeo, Francesca; Fondazione Poliambulanza Istituto Ospedaliero, Department of Internal Medicine and Geriatrics Cola, Maria; University of Florence Bartoloni, Alessandro; University of Florence Fontanari, Paolo; Careggi University Hospital Lavorini, Federico; Universityof Florence, Dept. Experimental and Clinical Medicine Marcucci, Rossella; University of Florence, Azienda Ospedaliero Universitaria Careggi Morettini, Alessandro; Careggi University Hospital Nozzoli, Carlo; Careggi University Hospital Peris, Adriano; Careggi University Hospital Pieralli, Filippo; Careggi University Hospital Pini, Riccardo; Careggi University Hospital Poggesi, Loredana; Careggi University Hospital Ungar, Andrea; Careggi University Hospital Fumagalli, Stefano; University of Florence, MARCHIONNI, Niccolo'; University of Florence
Primary Subject Heading:	Medical management
Secondary Subject Heading:	Public health
Keywords:	INFECTIOUS DISEASES, Public health < INFECTIOUS DISEASES, Adult intensive & critical care < INTENSIVE & CRITICAL CARE, INTERNAL MEDICINE, COVID-19

BMJ Open: first published as 10.1136/bmjopen-2020-040729 on 25 September 2020. Downloaded from http://bmjopen.bmj.com/ on April 17, 2024 by guest. Protected by copyright.

SCHOLARONE™
Manuscripts

BMJ Open: first published as 10.1136/bmjopen-2020-040729 on 25 September 2020. Downloaded from http://bmjopen.bmj.com/ on April 17, 2024 by guest. Protected by copyright.

I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our licence.

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which Creative Commons licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

For peer review only

Clinical risk score to predict in-hospital mortality in COVID-19 patients: a retrospective cohort study

Carlo Fumagalli, MD[1], Renzo Rozzini, MD[2], Matteo Vannini, MD[3], Flaminia Coccia, MD[2], Giulia Cesaroni, MD[2], Francesca Mazzeo, MD[2], Maria Cola, MD[4], Alessandro Bartoloni, MD[4], Paolo Fontanari, MD[3], Federico Lavorini, MD, PhD[1,3], Rossella Marcucci, MD, PhD[1,3], Alessandro Morettini, MD[4], Carlo Nozzoli, MD[4], Adriano Peris, MD[5], Filippo Pieralli, MD[4], Riccardo Pini, MD[4], Loredana Poggesi, MD[4], Andrea Ungar, MD, PhD[1], Stefano Fumagalli, MD, PhD[1], and Niccolò Marchionni, MD[1,3]

1. Department of Experimental and Clinical Medicine, University of Florence, Italy
2. Department of Geriatrics and Internal Medicine, Poliambulanza Hospital, Brescia, Italy
3. Department of Cardiothoracovascular Medicine, Careggi Hospital, Florence, Italy
4. Department of Internal and Emergency Medicine, Careggi Hospital, Florence, Italy
5. Emergency and ECMO Unit, Careggi Hospital, Florence, Italy

Word Count: 2977 (text only, without abstract and references)

Key words: COVID-19, SARS-CoV-2, elderly, aging, mortality

Corresponding Author:

Niccolò Marchionni, MD
Department of Experimental and Clinical Medicine, University of Florence, Italy
Largo Brambilla, 3, 50134 Florence, Italy
E-mail: niccolo.marchionni@unifi.it
Phone: +39 335210015
Fax: +39 055 2758047

For peer review only

ABSTRACT

Objectives

Several physiological abnormalities that develop during COVID-19 are associated with increased mortality. In the present study, we aimed to develop a clinical risk score to predict the in-hospital mortality in COVID-19 patients, based on a set of variables available soon after the hospitalization triage.

Setting

Retrospective cohort study of 516 patients consecutively admitted for COVID-19 to two Italian tertiary hospitals located in Northern and Central Italy were collected from February 22 (date of first admission) to April 10, 2020.

Participants

Consecutive patients ≥18 years admitted for COVID-19.

Main outcome measures

Simple clinical and laboratory findings readily available after triage were compared by patients' survival status ('dead' vs. 'alive'), with the objective of identifying baseline variables associated with mortality. These were used to build a COVID-19 in-hospital mortality risk score (COVID-19MRS).

Results

Mean age was 67±13 years (mean±SD), and 66.9% were male. Using Cox regression analysis, tertiles of increasing age (≥75, upper vs. <62 years, lower: HR 7.92; p<0.001) and number of chronic diseases (≥4 vs. 0-1: HR 2.09; p=0.007), respiratory rate (HR 1.04 per unit increase; p=0.001), PaO_2/FiO_2 (HR 0.995 per unit increase ; p<0.001), serum creatinine (HR 1.34 per unit increase; p<0.001) and platelet count (HR 0.995 per unit increase; p=0.001), were predictors of mortality. All six predictors were used to build the COVID-19MRS (AUC 0.90, 95%CI 0.87-0.93) which proved to be highly accurate in stratifying patients at low-, intermediate- and high-risk of in-hospital death (p<0.001).

For peer review only

Conclusions

The COVID-19MRS is a rapid, operator-independent and inexpensive clinical tool that objectively predicts mortality in patients with COVID-19. The score could be helpful from triage to guide earlier assignment of COVID-19 patients to the most appropriate level of care.

For peer review only

Article Summary

Strengths and limitations of the study

- Risk assessment tools readily available since the triage phase of COVID-19 are lacking.
- Age, previous chronic diseases, respiratory rate, PaO_2/FiO_2, creatinine and platelet count were predictors of risk of in-hospital death.
- All six predictors were used to build a novel COVID-19 clinical risk score that proved to be highly accurate in stratifying patients at low, intermediate and high risk of death.
- Retrospective design; novel score to be validated in other, external, COVID-19 case series.

For peer review only

INTRODUCTION

The first human cases of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) were reported in Wuhan, Hubei Province, China in January 2020[1,2]; subsequently, it spread worldwide, officially being defined as a pandemic by the WHO on March 11, 2020[3–5]. Italy was the first country outside Asia to be heavily affected by the virus, with a total of 189,973 confirmed cases as of April 23rd, 2020. The Lombardy Region had highest burden of mortality and strain on its healthcare system[6]. However, a substantial re-organization of healthcare facilities was necessary in all Italian regions to cope with the widespread and rapid increase in COVID-19 patient flow to emergency departments.

Prompt referral to the appropriate care setting (i.e. low vs. intermediate or high intensity) is of crucial importance to improve outcomes and healthcare resource utilization[7–9]. Given the high number of patients to be triaged during this emergency and the relative shortage of hospital beds, the availability of a disease-specific mortality risk score since initial triage might have been useful in identifying the appropriate level of care and reducing delay. However, there is a lack of reliable prognostic prediction models and, at present, no tool for the early stratification of mortality risk has been fully identified[10]. A recent systematic review of prediction models concluded that the performance of prognostic estimates for COVID-19 may be over-optimistic and misleading, because of the high risk of bias in patient selection, unclear outcome definition and length of follow-up[10]. Recently, clinical scores to predict the occurrence of critical illness and/or fatal outcome during COVID-19 were developed in a cohort of Chinese patients belonging to more than 500 centers throughout the Country[11,12]. However, these were developed in a specific region which could potentially limit the generalizability of the risk score to other areas of the world.

Therefore, the aim of the present study was to develop a novel COVID-19 in-hospital mortality risk score (hereafter referred to as COVID-19MRS), based on data rapidly obtainable soon

For peer review only

after hospital admission. To this end, we analyzed a consecutive series of COVID-19 patients admitted to two tertiary care hospitals located in Northern and Central Italy.

For peer review only

METHODS

Study design

In this cohort study, we retrospectively reviewed the clinical history, laboratory and instrumental variables of all patients aged ≥18 years diagnosed with COVID-19[13], admitted to two Italian tertiary hospitals located in Northern and Central Italy (Poliambulanza Hospital, Brescia, and Careggi University Hospital, Florence) from February 22 (date of first admission in Brescia) to April 10th, 2020, in order to identify a set of early predictors of mortality and build a mortality risk stratification score. The overall capacity of the two hospitals is about 1,800 beds. The number of beds dedicated to COVID-19 patients progressively increased with the diffusion of the epidemic to a peak capacity of 655 (228/1,200 in Careggi University Hospital and 427/600 in Poliambulanza Hospital; overall, 110 high-intensity care beds at peak).

Study population data source

A wide range of variables assessed on hospital admission were collected for each patient from electronic charts: these included demographics, number of drugs prescribed prior to admission, cardiovascular (CV) risk factors (e.g. history of cigarette smoking, hypertension, diabetes), as well as data on previous chronic comorbidities (e.g. CV and pulmonary diseases, cancer, depression and dementia). Functional status two weeks prior to hospitalization was also assessed using the Barthel Index, in which lower values correspond to poorer function[14]. Arterial blood gases, white blood cell (WBC), lymphocyte and platelet (PLT) counts, alanine (ALT) and aspartate (AST) aminotransferase, creatinine, creatine phosphokinase (CPK), lactate dehydrogenase (LDH), high-sensitivity C-reactive protein (CRP), and D-dimer were collected in all patients. Chest X-Ray were also collected. Reading and interpretation of the main chest X-Ray features was performed

For peer review only

according to radiology guidelines[15]. Information on respiratory support and drugs prescribed during hospital stay were recorded. Six medical doctors (CF, MV, MC, FC, GC, FM) selectively extracted all variables from electronic charts and transferred them into a unique database and independently reviewed them for their consistency. Data were last updated on April 10, 2020.

In keeping with statements by the Italian Regulatory Authorities (https://www.garanteprivacy.it/web/guest/home/docweb/-/docweb-display/docweb/5805552), Ethical Committees of both hospitals (Comitato Etico Area Vasta Centro, Careggi University Hospital, Florence and Comitato Etico Fondazionae Poliambulanza Hospital, Brescia, Italy) approved data collection and granted a waiver of informed consent from study participants. Patients' identity was anonymized, and information protected by password.

Study outcome

Definition of an in-hospital all-cause mortality risk score based on simple, readily available clinical and laboratory findings.

Patient and public involvement

Patients or the public were not involved in the design or conduct of our research, partially due to its retrospective nature. Public Health Authorities will be involved in the upcoming, large-scale validation of the newly presented score.

Statistical analysis and mortality risk score derivation

Continuous variables were reported as mean ± standard deviation (SD) or as median with interquartile range [IQR], respectively for normal and non-normal distributions whereas categorical variables were presented as counts and percentages. All variables were compared by survival status ('dead' vs. 'alive') and patients still hospitalized at study closure were considered alive together with

For peer review only

those who had been discharged during the study period. For continuous variables, comparisons were performed using t-test, analysis of variance or nonparametric tests, as appropriate. Categorical variables were compared with χ^2 test, or Fisher's exact test when any expected cell count was less than five.

In accordance with the aim of the study, only data obtained shortly after initial triage were taken into account to build the mortality risk score. Cox multivariate regression analyses (with backward stepwise elimination) were calculated to identify baseline characteristics independently associated with the outcome, with inclusion of variables ($p<0.10$ by univariate analysis) which were available for all patients. A 2-sided $p<0.05$ was considered statistically significant.

All continuous variables which were significantly associated with mortality by multivariate analysis were divided into tertiles and each of them was then scored from 1 to 3 to quantify the increasing mortality risk. Values obtained were then summed up to produce the mortality risk score whose predictive accuracy was tested using Receiver Operating Characteristic (ROC) analysis. The mortality risk score was further divided into tertiles in order to identify low, intermediate and high-risk categories, and assessed using Cox multivariate analysis. The Kaplan–Meier estimation method was computed to assess the probability of survival in patients in the different risk groups (low, intermediate and high) and compared using the log-rank test.

Analyses were performed using the SPSS v. 26.0 statistical software package for Macintosh.

RESULTS

Regional trend and clinical characteristics on hospital admission

During the study period, 516 consecutive patients (301 in Brescia and 215 in Florence) diagnosed with COVID-19 were included in the study (Table 1). According to date of admission,

For peer review only

Brescia hospital anticipated both the first case (February 22 vs. 25) and the peak of admissions by an average of 3 days, with a remarkably higher total and peak burden of admissions.

As of April 10, 314 (61%) patients had been discharged from hospital (273 [87%] at home and 41 [13%] to post-acute facilities), 82 (16%) were still hospitalized, while 120 (23.2%) had died. Notably, no death occurred on the day of admission.

The mean age was 67±13 years (range 21-95) and 345 (66.9%) patients were men. Demographic and clinical characteristics of non-survivors and survivors are reported in Table 1. Non-survivors were significantly older (79±8 vs. 64±12, p<0.001). Indeed, in-hospital fatality rate sharply increased with age and was more than 5-times higher in individuals aged ≥75 years (51.2% vs. <75 years 9.8%; p<0.001). Conversely, prognosis was similar for both genders. The median hospital stay was 9 [IQR 5-14] days, significantly longer in survivors. Non-survivors also presented with a higher prevalence of CV risk factors, a greater burden of chronic comorbidities, and were more functionally impaired as indicated by a lower Barthel Index score (Table 1). Previous use of angiotensin converting enzyme inhibitors (ACEi) or angiotensin-receptor blockers (ARBs) was similar in both groups while, in accordance with their higher burden of comorbidities, non-survivors reported a greater number of drugs chronically assumed prior to hospitalisation. The majority of patients presented with fever (89.1%) and/or cough (57.3%). Of note, non-survivors reported cough less frequently (48.5% vs. 59.8%; p=0.032), but had a significantly higher prevalence of insomnia, syncope or altered mental status. While the prevalence of dyspnea was similar in both groups (overall, 48.9%), respiratory rate on admission was higher in non-survivors than in survivors (26±7 vs. 21±6 breaths/min; p<0.001).

Laboratory and imaging findings

For peer review only

Nasopharyngeal swab was positive in 499 (97%) patients. In the remaining patients, initially suspected diagnosis was confirmed by subsequent swabs, sputum or bronchoalveolar lavage. Laboratory findings are presented in Table 2. In the entire population, median PaO_2/FiO_2 ratio was 269 [IQR 217-319], and values <200 were significantly associated with the probability of death. Lymphocytopenia was present in 61% of the population, more frequently among non-survivors than survivors (71% vs. 58%; p=0.011), who also had lower PLT count and higher serum creatinine. CRP and LDH were increased in both groups and higher in non-survivors. Chest X-Ray was abnormal in >95% of cases, with a trend towards a higher prevalence of interstitial or mixed (both interstitial and consolidation) patterns in deceased patients.

Medical management and clinical outcomes

Non-survivors required non-invasive (continuous positive airway pressure and biphasic positive airway pressure modes) or invasive ventilation more frequently than survivors (Table 3). While antibiotics were prescribed more frequently to non-survivors, heparin, hydroxychloroquine, antiviral agents (combination of lopinavir/ritonavir) and monoclonal antibodies (mAbs, tocilizumab) were prescribed more frequently to survivors. In contrast, corticosteroid therapy was adopted in similar proportions in the two groups. Patients receiving mAbs were younger (65±9 vs. 68±14 years, p<0.01) and had lower serum creatinine (0.9±0.3 vs. 1.2±0.9 mg/dL, p=0.024).

Predictors of mortality and development of the mortality risk score

At Cox multivariate regression analysis (Table 4) age, number of chronic comorbidities, respiratory rate, and serum creatinine emerged as positive predictors, while PaO_2/FiO_2 ratio and PLT count were negative predictors of death. Supplementary Table 1 summarizes all candidate variables that were excluded by stepwise backward deletion. Interestingly, pre-admission functional

For peer review only

status as assessed by Barthel Index and the number of drugs previously assumed were excluded from the model.

Variables included in the Model (Table 4) were used to calculate the mortality risk score intended for rapid patient's risk assessment on hospital admission. In this regard, age, number of comorbidities, respiratory rate, PaO_2/FiO_2, serum creatinine and PLT count re-classified into tertiles were used to build the mortality risk score with identification of three risk strata as reported in Table 5. ROC analysis performed on the clinical risk score yielded an AUC of 0.90 (Supplementary Figure 1, 95% CI 0.87-0.93). Kaplan-Meier survival analysis developed using the tertiles of the clinical score showed an excellent stratification of risk (Figure 1; intermediate- vs. low-risk HR: 4.134 95%CI [1.725-9.905]; high- vs. low-risk HR: 22.173 95%CI [9.681-50.783], p<0.001). A cut-off score of ≤8 identified a subset of 63 (12.2%) patients without fatalities during the study period, who therefore may be defined as 'at very low-risk'.

For peer review only

DISCUSSION

In this study, we developed the COVID-19MRS that was shown to be able to stratify the risk of in-hospital death in COVID-19 patients since their admission. This score includes a composite of six objective, operator-independent variables (age, number of chronic comorbidities, respiratory rate, PaO_2/FiO_2, serum creatinine, and platelet count) usually available within a couple of hours after hospitalization. The score identified three categories at increasing risk of death with a high level of accuracy. The scoring process suggests that, while low-risk patients may be assigned safely to low-intensity care, higher intensity wards should be alerted during triage for the intermediate- and high-risk patients. Moreover, the score seems to allow for the identification of about 10-15% of 'very low-risk' patients (score ≤8) with no events who, though symptomatic for proven COVID-19, might be immediately discharged home, with the sole indication to health status monitoring.

Performance of prognostic estimates for COVID-19 are under scrutiny as thought to be over optimistic and misleading, because of the high risk of bias in patient selection[10]. As a case in point, a score based on a large cohort of COVID-19 patients in China found that age was associated with greater risk of death[11]. However, the mean age of this cohort was 49±16 years, which is 15-20 years less than observed in most European and US studies published to date. Although apparently similar in terms of objectives, we stratified the risk of death in a consecutive cohort of patients who shared demographic and clinical characteristics similar to other European and US studies[3–5]. We therefore believe that our COVID-19MRS may hold potential generalizability for other countries. The early identification of patients at risk of clinical deterioration and death is of primary importance, considering that median interval from hospital admission to the ICU is around 3 days[16]. Given that our proposed score is predictive of mortality based on six inexpensive, operator-independent and rapidly obtainable parameters, it could help clinicians to identify high-risk patients with poor prognosis since the triage phase.

For peer review only

One-in-four patients in our cohort of Italian COVID-19 cases died and age was the strongest driver of an adverse outcome. In fact, compared to patients younger than 62 years of age, the risk of death was almost 3 and 8 times higher in individuals 62-74 and 75+ years of age, respectively. Such an exponential risk growth persisted after adjusting for burden of comorbidities and a series of clinical characteristics. Such a strong association between older age and prognosis has been observed in previous studies on COVID-19 both in China and in other countries, albeit with a less rapid increase in age-specific risk[17]. This difference could be attributed to the lower median age reported in those studies and to the fact that we explored a wider age range (21-95 years), with one third of our population above the age of 75[17,18]. In COVID-19, age has been associated with variable degrees of increasing risk of admissions to ICU, onset of acute respiratory distress syndrome, myocardial damage, and fatal outcome[16,19–22]. This observation also holds true for previous epidemic or pandemic outbreaks, such as Severe Acute Respiratory Syndrome and Middle East Respiratory Syndrome where, as in COVID-19, the respiratory system is both the entry route and the main target of viral infection[23,24]. We could argue that lung senescence, resulting in decreased elasticity, increased end-expiratory lung volume and disrupted alveolar integrity[25], together with kidney senescence[26], may predispose *per se* to SARS-CoV-2-related acute respiratory and renal failure even in otherwise relatively robust elderly individuals. This hypothesis is consistent with the observation that age and three functional indicators of target organs (respiratory rate, PaO_2/FiO_2, serum creatinine) emerged as independent predictors of in-hospital mortality, after adjusting for comorbidities.

The observation of the highly negative impact of age suggests that, in the absence of specifically effective drug therapy and vaccination[27], social isolation and the prevention of infecting contacts are key-issues particularly relevant in individuals aged 70-75 years and over. These data may represent a call to action for health authorities, in order to update management policies in the

For peer review only

community in general and in nursing homes in particular, where in fact the highest mortality rates occurred in Italy and in other Countries[28].

While a low PLT count was frequently observed in non-survivor COVID-19 patients[16,19,22,29], in our cohort, lower values were directly associated with adverse outcome, suggesting a possible role of COVID-19-related coagulopathy in determining a poor outcome[30,31].

Present therapeutic recommendations on COVID-19 have a limited level of evidence[32], and have evolved during progression of the pandemic wave. Most of our patients received oxygen or mechanical ventilation support and antibiotics; conversely 1 in 2 patients were treated by antiviral and/or anti-inflammatory drugs. Given the nature of our study, we are unable to draw any firm conclusions regarding treatment efficacy, as specific analyses would be required, which were beyond the scope of the present work.

Some limitations of our study have to be acknowledged. First, the retrospective and observational nature of our analysis does not allow us to draw any firm conclusions about therapeutic strategies. Second, some laboratory parameters, which proved to be of prognostic relevance in other studies[19,22], were not collected for all individuals in our sample, possibly due to the different degrees of severity of patients (i.e. very mildly affected vs. critically-ill patients at presentation). Therefore, we cannot rule out that variables excluded from the scoring system would have had a significant impact on mortality prediction. However, consistent with our purpose, we considered variables only available soon after admission. Third, since nasopharyngeal swabs were our key criterion for SARS-CoV-2 detection, we did not assess viremia, while the correlation of viral load with disease severity is still a matter of debate. Moreover, case ascertainment methodological bias, which may impact on patient selection and outcome, cannot be excluded as partial explanation for the findings observed. Indeed, the vast majority of patients included in the present analysis had a positive RT-PCR on first testing and only in a minority of cases was sputum or bronchoalveolar

For peer review only

lavage needed to confirm the infection. Fourth, 82 out of 516 (15.9%) patients were still in-hospital at the time of closure of follow-up. Nevertheless, after excluding these patients from our analysis, results were fully confirmed, with a 0.90 AUC of the predictive score (data not shown). Finally, we do not have information regarding the time span between symptom onset and admission, which might have had an impact on either clinical or laboratory parameters that we sampled on hospital admission.

In conclusion, we developed a scoring system (COVID-19MRS) that objectively and accurately predicts in-hospital mortality COVID-19 patients. This score, simply based on age, number of chronic comorbidities, respiratory rate, PaO_2/FiO_2, serum creatinine, and platelet count is a rapid and inexpensive clinical tool which could be helpful for earlier identification of in-hospital mortality risk and, hence, assignment to the appropriate level of care and treatment of COVID-19 patients. Studies in clinical series different from ours are needed to validate the present scoring system.

Acknowledgements We thank Dr. Colin Egan for his careful revision of the manuscript. We are grateful to “Fondazione A.R. Card. ONLUS” for its unconditional support.

Contributors CF and NM conceived the study, conducted data acquisition, management and analysis, drafted and critically revised the manuscript and are accountable for all aspects of the work. RR, FL and RM contributed to conceive the study and critically revised the manuscript. MV conducted data acquisition, drafted and critically revised the manuscript, with the contribution of FC, GC, FM, and MC. AB, PF, AM, CN, AP, FP, RP, LP and AU critically revised the manuscript for important intellectual content. SF contributed substantially to data analysis and to critical revision of the manuscript. All Authors read and approved the final manuscript.

For peer review only

Funding This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient and public involvement Patients or the public were not involved in the design or conduct of our research, partially due to its retrospective nature. Public Health Authorities will be involved in the upcoming, large-scale validation of the newly presented score.

Data availability statement Deidentified participant data are stored in a University of Florence password protected in-house server

ORCID ID

Niccolò Marchionni https://orcid.org/0000-0002-8101-4695

For peer review only

REFERENCES

1. Wu F, Zhao S, Yu B, et al. A new coronavirus associated with human respiratory disease in China. *Nature*. 2020;579(7798):265-269. doi:10.1038/s41586-020-2008-3
2. Li Q, Guan X, Wu P, et al. Early Transmission Dynamics in Wuhan, China, of Novel Coronavirus–Infected Pneumonia. *N Engl J Med*. 2020;382(13):1199-1207. doi:10.1056/NEJMoa2001316
3. Grasselli G, Zangrillo A, Zanella A, et al. Baseline Characteristics and Outcomes of 1591 Patients Infected With SARS-CoV-2 Admitted to ICUs of the Lombardy Region, Italy. *Jama*. 2020:1-8. doi:10.1001/jama.2020.5394
4. Richardson S, Hirsch JS, Narasimhan M, et al. Presenting Characteristics, Comorbidities, and Outcomes Among 5700 Patients Hospitalized With COVID-19 in the New York City Area. *JAMA*. April 2020. doi:10.1001/jama.2020.6775
5. Helms J, Tacquard C, Severac F, et al. High risk of thrombosis in patients with severe SARS-CoV-2 infection: a multicenter prospective cohort study. *Intensive Care Med*. May 2020. doi:10.1007/s00134-020-06062-x
6. Buoro S, Di Marco F, Rizzi M, et al. Papa Giovanni XXIII Bergamo Hospital at the time of the COVID-19 outbreak: Letter from the warfront…. *Int J Lab Hematol*. 2020;42(S1):8-10. doi:10.1111/ijlh.13207
7. Johnson DW, Schmidt UH, Bittner EA, Christensen B, Levi R, Pino RM. Delay of transfer from the intensive care unit: A prospective observational study of incidence, causes, and financial impact. *Crit Care*. 2013;17(4):R128. doi:10.1186/cc12807
8. Churpek MM, Wendlandt B, Zadravecz FJ, Adhikari R, Winslow C, Edelson DP. Association between intensive care unit transfer delay and hospital mortality: A multicenter investigation. *J Hosp Med*. 2016. doi:10.1002/jhm.2630
9. Liu V, Kipnis P, Rizk NW, Escobar GJ. Adverse outcomes associated with delayed intensive care unit transfers in an integrated healthcare system. *J Hosp Med*. 2012. doi:10.1002/jhm.964
10. Wynants L, Van Calster B, Bonten MMJ, et al. Prediction models for diagnosis and prognosis of covid-19 infection: Systematic review and critical appraisal. *BMJ*. 2020;369:m1328.

For peer review only

doi:10.1136/bmj.m1328

11. Liang W, Liang H, Ou L, et al. Development and Validation of a Clinical Risk Score to Predict the Occurrence of Critical Illness in Hospitalized Patients With COVID-19. *JAMA Intern Med*. May 2020. doi:10.1001/jamainternmed.2020.2033

12. Chen R, Liang W, Jiang M, et al. Risk Factors of Fatal Outcome in Hospitalized Subjects With Coronavirus Disease 2019 From a Nationwide Analysis in China. *Chest*. 2020. doi:10.1016/j.chest.2020.04.010

13. WHO. Clinical management of severe acute respiratory infection when COVID-19 is suspected (v1.2). 2020:1-21. https://www.who.int/publications-detail/clinical-management-of-severe-acute-respiratory-infection-when-novel-coronavirus-(ncov)-infection-is-suspected.

14. MAHONEY FI, BARTHEL DW. Functional Evaluation: the Barthel Index. *Md State Med J*. 1965;14:61-65.

15. Hansell DM, Bankier AA, MacMahon H, McLoud TC, Müller NL, Remy J. Fleischner Society: Glossary of Terms for Thoracic Imaging. *Radiology*. 2008;246(3):697-722. doi:10.1148/radiol.2462070712

16. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet*. 2020;395(10223):497-506. doi:10.1016/S0140-6736(20)30183-5

17. Wu Z, McGoogan JM. Characteristics of and Important Lessons from the Coronavirus Disease 2019 (COVID-19) Outbreak in China: Summary of a Report of 72314 Cases from the Chinese Center for Disease Control and Prevention. *JAMA - J Am Med Assoc*. 2020;2019. doi:10.1001/jama.2020.2648

18. The World Bank. *World Bank Staff Estimates Based on Age/Sex Distributions of United Nations Population Division's World Population Prospects: 2019 Revision.*; 2019. https://data.worldbank.org/indicator/SP.POP.65UP.TO.ZS.

19. Wu C, Chen X, Cai Y, et al. Risk Factors Associated with Acute Respiratory Distress Syndrome and Death in Patients with Coronavirus Disease 2019 Pneumonia in Wuhan, China. *JAMA Intern Med*. 2020. doi:10.1001/jamainternmed.2020.0994

20. Guan W, Ni Z, Hu Y, et al. Clinical Characteristics of Coronavirus Disease 2019 in China. *N Engl J Med*. 2020:1-13. doi:10.1056/nejmoa2002032

For peer review only

21. Shi S, Qin M, Shen B, et al. Association of Cardiac Injury with Mortality in Hospitalized Patients with COVID-19 in Wuhan, China. *JAMA Cardiol*. 2020:1-8. doi:10.1001/jamacardio.2020.0950

22. Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet*. 2020;395(10229):1054-1062. doi:10.1016/S0140-6736(20)30566-3

23. Choi KW, Chau TN, Tsang O, et al. Outcomes and Prognostic Factors in 267 Patients with Severe Acute Respiratory Syndrome in Hong Kong. *Ann Intern Med*. 2003;139(9):715-724. doi:10.7326/0003-4819-139-9-200311040-00005

24. Hong KH, Choi JP, Hong SH, et al. Predictors of mortality in Middle East respiratory syndrome (MERS). *Thorax*. 2018;73(3):286-289. doi:10.1136/thoraxjnl-2016-209313

25. Bowdish DME. The Aging Lung: Is Lung Health Good Health for Older Adults? *Chest*. 2019;155(2):391-400. doi:10.1016/j.chest.2018.09.003

26. O'Sullivan ED, Hughes J, Ferenbach DA. Renal aging: Causes and consequences. *J Am Soc Nephrol*. 2017;28(2):407-420. doi:10.1681/ASN.2015121308

27. Koff WC, Williams MA. Covid-19 and Immunity in Aging Populations - A New Research Agenda. *N Engl J Med*. April 2020. doi:10.1056/NEJMp2006761

28. WHO. Virtual press briefing on COVID-19: key considerations on nursing homes. In: *WHO Regional Office for Europe*. ; 2020. http://www.euro.who.int/en/media-centre/events/events/2020/04/virtual-press-briefing-on-covid-19-key-considerations-on-nursing-homes.

29. Chen T, Wu D, Chen H, et al. Clinical characteristics of 113 deceased patients with coronavirus disease 2019: retrospective study. *BMJ*. 2020;368:m1091. doi:10.1136/bmj.m1091

30. Bikdeli B, Madhavan M V, Jimenez D, et al. COVID-19 and Thrombotic or Thromboembolic Disease: Implications for Prevention, Antithrombotic Therapy, and Follow-up. *J Am Coll Cardiol*. April 2020:27284. doi:10.1016/j.jacc.2020.04.031

31. Lippi G, Plebani M, Henry BM. Thrombocytopenia is associated with severe coronavirus disease 2019 (COVID-19) infections: A meta-analysis. *Clin Chim Acta*. 2020;506:145-148.

For peer review only

doi:10.1016/j.cca.2020.03.022

32. Poston JT, Patel BK, Davis AM. Management of Critically Ill Adults with COVID-19. *JAMA - J Am Med Assoc*. 2020:E1-E3. doi:10.1001/jama.2020.4914

Figure Legend

Figure 1. Kaplan-Meier analysis of overall survival of patients diagnosed with COVID-19 according to three risk categories. Shaded areas represent lower and upper 95% confidence intervals.

For peer review only

Table 1. Demographic and clinical characteristics on hospital admission

	Overall (N=516)	Dead (N=120)	Alive (N=396)	P
Demographic Characteristics				
Age, mean± SD	67 ± 13	79 ± 8	64 ± 12	<0.001
Age (tertiles)				
<62, N (%)	177 (34.3)	7 (5.8)	170 (42.9)	
62-74, N (%)	171 (33.1)	27 (22.5)	144 (36.4)	
≥75, N (%)	168 (32.6)	86 (71.7)	82 (20.7)	
Hospital stay, median [IQR]	9 [5-14]	6 [3-10]	10 [6-15]	<0.001
Gender (male), N (%)	345 (66.9)	85 (70.8)	260 (65.7)	0.321
Smoking history, N (%)	112 (21.7)	26 (21.7)	86 (21.7)	0.999
Hypertension, N (%)	182 (35.3)	65 (55.6)	117 (29.6)	<0.001
Diabetes Mellitus, N (%)	161 (31.4)	51 (43.6)	110 (27.8)	<0.001
CV disease, N (%)	146 (28.5)	57 (47.9)	89 (22.6)	<0.001
Previous stroke/TIA, N (%)	25 (4.9)	11 (9.1)	14 (3.5)	0.011
COPD, N (%)	36 (7.0)	12 (10)	24 (6.1)	0.120
Cancer, N (%)	50 (9.7)	23 (19.2)	27 (6.8)	<0.001
Depression, N (%)	52 (20.1)	20 (17.1)	32 (8.1)	0.005
Dementia, N (%)	18 (3.4)	12 (10.0)	6 (1.5)	<0.001
Comorbidities (#), mean ± SD	2.1 ± 1.7	3.2 ± 1.9	1.8 ± 1.6	<0.001
≥3, N (%)	179 (34.7)	68 (58.1)	111 (28.2)	<0.001
Barthel Index, mean ± SD	85 ± 28	77 ± 27	94 ± 1 3	<0.001
ACE-i/ARBs, N (%)	144 (27.9)	35 (29.2)	109 (27.5)	0.725
Drugs, N (%)	3.4 ± 3.3	5.6 ± 3.5	2.7 ± 2.7	<0.001
Signs and Symptoms				
Fever, N (%)	456 (89.1)	102 (87.2)	354 (89.5)	0.457
Cough, N (%)	293 (57.3)	57 (48.5)	236 (59.8)	0.032
Dyspnea, N (%)	250 (48.9)	59 (50.4)	191 (48.5)	0.711
Respiratory rate, mean ± SD	23 ± 7	26 ± 7	21 ± 6	<0.001
Insomnia, N (%)	68 (13.2)	18 (15)	50 (12.6)	0.004
Diarrhea, N (%)	47 (9.2)	10 (8.3)	37 (9.4)	0.782
Syncope, N (%)	27 (5.2)	11 (9.2)	16 (4.1)	0.023
Altered mental status, N (%)	24 (4.7)	12 (10.0)	12 (3.0)	<0.001

bmjopen-2020-040729 on 25 September 2020. Downloaded from http://bmjopen.bmj.com/ on April 17, 2024 by guest. Protected by copyright.

For peer review only

SD: standard deviation; ACE-i: angiotensin converting enzyme inhibitors; ARBs: angiotensin receptor blockers; CV: cardiovascular disease; COPD: chronic obstructive pulmonary disease; TIA: transient ischemic attack. (#) Comorbidities is a composite variable including from hypertension to dementia. Percentages in brackets are calculated for numbers in columns for all dichotomous variables.

For peer review only

bmjopen-2020-040729 on 25 September 2020. Downloaded from http://bmjopen.bmj.com/ on April 17, 2024 by guest. Protected by copyright.

Table 2. Laboratory and imaging findings on admission

	Overall (N=516)	Dead (N=120)	Alive (N=396)	P
Laboratory findings				
PaO_2/FiO_2, median [IQR]	269 [217-319]	226 [169-271]	281 [232-335]	<0.001
<200, N (%)	101 (19.6)	42 (35.0)	59 (15.0)	<0.001
≥200, N (%)	415 (80.4)	78 (65.0)	337 (85.1)	
Hematocrit, % median [IQR]	41 [38-44]	39 [35-43]	42 [39-44.75]	<0.001
Hemoglobin, g/dL median [IQR]	13.0 [11.7-14.3]	12.9 [11.7-14.1]	13.3 [12.2-14.3]	0.203
WBC, ($\times 10^9$/L) median [IQR]	6.31 [5-9]	7.11 [5-10.23]	6 [4.98-8.47]	0.009
Lymphocytes, ($\times 10^9$/L) median [IQR]	0.90 [0.70-1.24]	0.77 [0.70-1.07]	0.90 [0.70-1.24]	<0.001
Lymphocytopenia, N (%)	316 (61)	85 (71)	231 (58)	0.011
Platelets, ($\times 10^9$/L) median [IQR]	182 [142-234]	156 [117-218]	187 [152-238]	0.001
ALT, U/L median [IQR]	31 [19-51]	26 [16-42]	32 [19-58]	0.004
AST, U/L median [IQR]	46 [30-69]	50 [35-71]	45 [28-69]	0.181
Serum Creatinine, mg/dL median [IQR]	0.94 [0.79-1.22]	1.23 [0.92-1.91]	0.90 [0.79-1.13]	<0.001
CPK, U/L median [IQR]	110 [64-228]	130 [60-208]	108 [64-208]	0.085
LDH, U/L median [IQR]	351 [268-480]	473 [338-610]	335 [266-437]	<0.001
CRP, mg/L median [IQR]	94 [44.3-161.8]	138 [85-188]	77 [37-152]	<0.001
Imaging	N=486	N=114	N=372	
Chest X ray				
Negative, N (%)	20 (4.1)	2 (1.8)	18 (4.8	0.053
Consolidation, N (%)	67 (13.8)	12 (10.5)	55 (14.8)	
Interstitial, N (%)	346 (71.2)	81 (71.1)	265 (71.2)	
Mixed, N (%)	53 (10.9)	19 (16.7)	34 (9.1)	

IQR: interquartile range; WBC: white blood cell count; ALT: alanine aminotransferase; AST: aspartate aminotransferase ; CPK: creatine phosphokinase; LDH: lactate dehydrogenase; BUN: blood urea nitrogen ; Percentages in round brackets are calculated for numbers in columns for all dichotomous variables.

bmjopen-2020-040729 on 25 September 2020. Downloaded from http://bmjopen.bmj.com/ on April 17, 2024 by guest. Protected by copyright.

For peer review only

Table 3. Treatment strategies

	Overall (N=516)	Dead (N=120)	Alive (N=396)	p
Respiratory Support				
None, N (%)	57 (11.0)	2 (1.7)	55 (13.9)	<0.001
Oxygen, N (%)	334 (64.7)	78 (65)	256 (65)	
Non-invasive ventilation, N (%)	65 (12.6)	23 (19.2)	42 (10.6)	
Invasive ventilation, N (%)	60 (11.6)	17 (14.2)	43 (10.9)	
Drugs				
Antibiotics, N (%)	407 (78.9)	106 (88.3)	301 (76.0)	0.003
Heparin, N (%)	299 (57.9)	57 (47.5)	242 (61.1)	0.008
Hydroxychloroquine, N (%)	268 (51.9)	43 (35.8)	225 (56.8)	<0.001
Lopinavir/ritonavir, N (%)	247 (50.7)	39 (32.5)	208 (52.5)	<0.001
Corticosteroids, N (%)	176 (34.1)	45 (37.5)	131 (33.1)	0.371
Monoclonal antibodies, N (%)	57 (11.3)	3 (2.5)	54 (13.6)	<0.001

For peer review only

bmjopen-2020-040729 on 25 September 2020. Downloaded from http://bmjopen.bmj.com/ on April 17, 2024 by guest. Protected by copyright.

Table 4. Cox multivariable regression analyses of determinants of in-hospital mortality

Variables	HR	95.0% CI	p
Age (tertiles)			
62-74 vs. <62 years	2.86	1.23-6.64	0.014
≥75 vs. <62 years	7.92	3.60-17.43	<0.001
Number of comorbidities (tertiles)			
2-3 vs. 0-1	1.85	1.11-3.08	0.018
≥4 vs. 0-1	2.09	1.23-3.55	0.007
Respiratory rate (breaths/min), for unit increase	1.04	1.02-1.07	0.001
PaO_2/FiO_2, for unit increase	0.995	0.992-0.997	<0.001
Creatinine (mg/dL), for unit increase	1.34	1.18-1.51	<0.001
Platelets (10^9/L), for unit increase	0.995	0.992-0.998	0.001

HR: hazard ratio; 95 % CI: 95% confidence interval; RR: respiratory rate. History of CV disease, hypertension, diabetes, depression, dementia, cancer were included into 'comorbidities'. Variables excluded (p>0.10) from both models: N of drugs, Barthel Index, CRP.

For peer review only

bmjopen-2020-040729 on 3 September 2020. Downloaded from http://bmjopen.bmj.com/ on April 17, 2024 by guest. Protected by copyright.

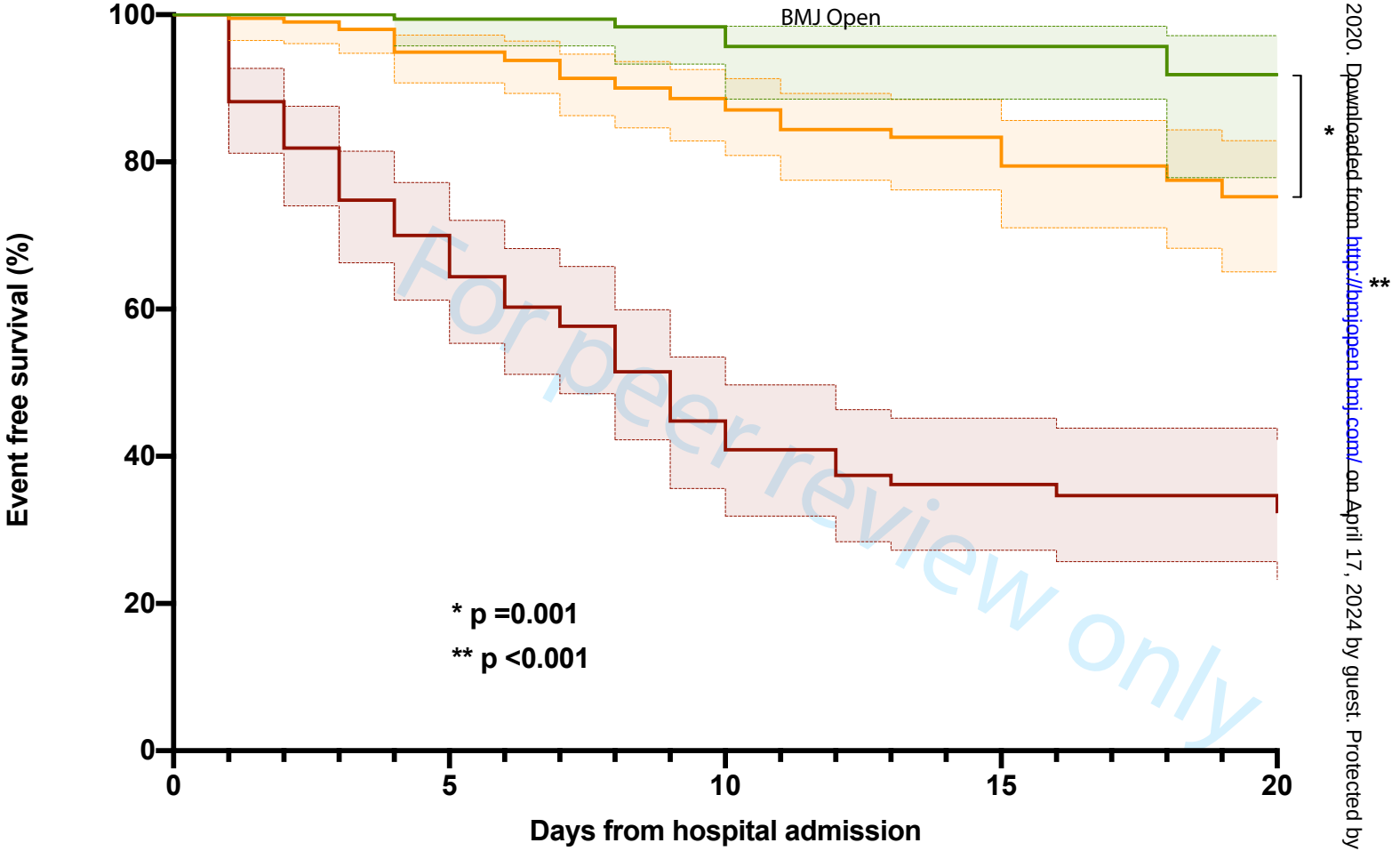
Table 5. Variables and relative scores to calculate the COVID-19 Clinical Risk Score

Age (years)	**Score**	**Comorbidities** (N)	**Score**	**RR** (breaths/min)	**Score**	**PaO_2/FiO_2**	**Score**	**Creatinine** (mg/dL)	**Score**	**Platelet Count** (10^9/L)	**Score**	**Risk Categories** (sum of individual variable scores)
< 62	1	≤1	1	≤20	1	> 300	1	< 0.83	1	> 212	1	Low = ≤ 10
62-74	2	2-3	2	21-24	2	236-299	2	0.83-1.12	2	156-211	2	Intermediate = 11-13
≥ 75	3	≥4	3	≥ 25	3	< 236	3	≥ 1.13	3	< 156	3	High risk = ≥ 14

Categories represent the tertile distribution of each variable.

For peer review only

bmjopen-2020-040729 on 25 September 2020. Downloaded from http://bmjopen.bmj.com/ on April 17, 2024 by guest. Protected by copyright.



Risk Levels

Low	189	150	74	33	17
Intermediate	200	177	111	64	31
High	127	87	45	30	15

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

er 2020. Downloaded from http://bmjopen.bmj.com/ on April 17, 2024 by guest. Protected by copyright.

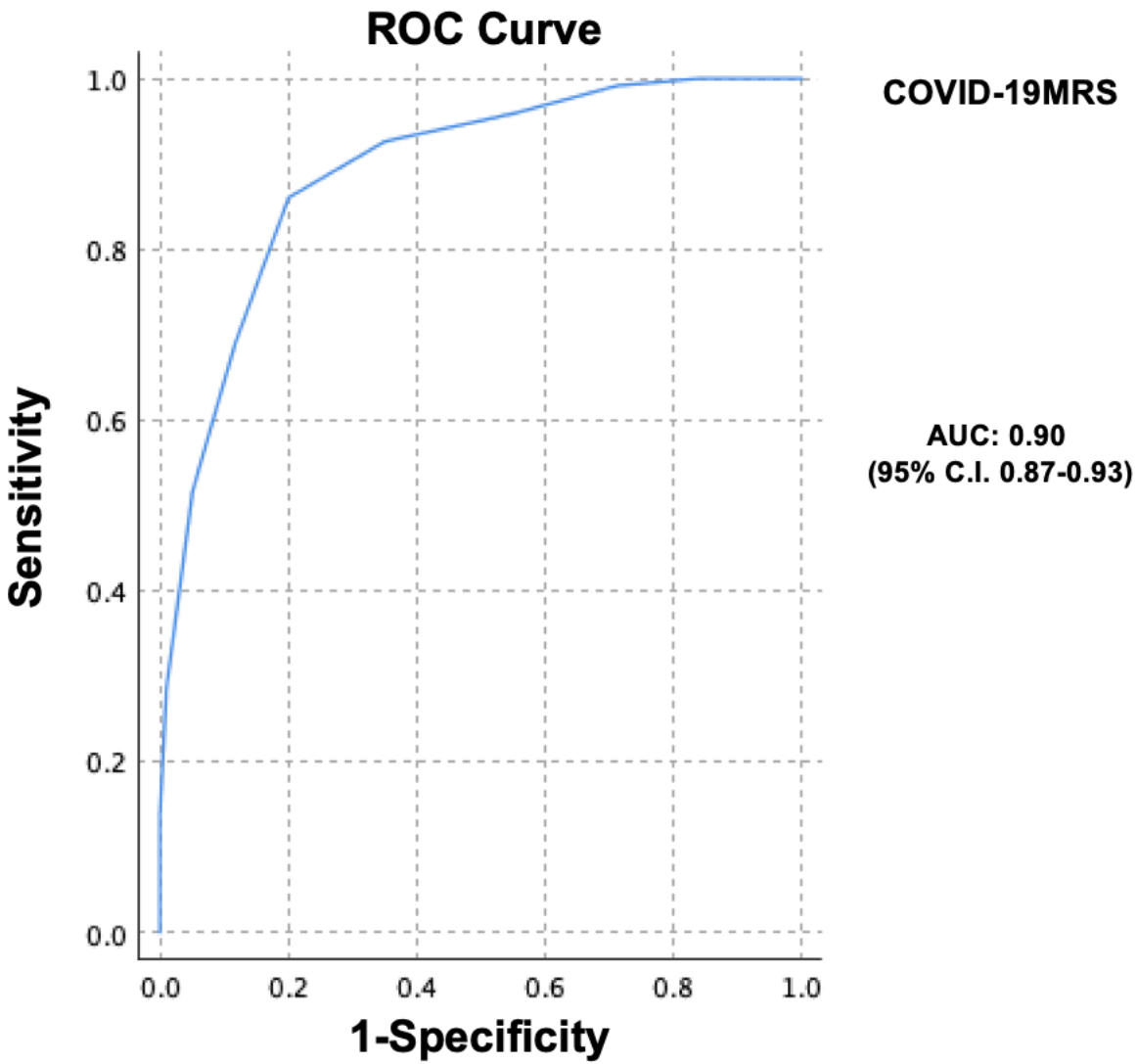
Supplementary Table 1. Cox multivariable regression analyses of variables associated with mortality at univariate analysis.

Variables	HR	95.0% CI	p
Age (tertiles)			
62-74 vs. <62 years	2.86	1.23-6.64	0.014
≥75 vs. <62 years	7.92	3.60-17.43	<0.001
Number of comorbidities (tertiles)			
2-3 vs. 0-1	1.85	1.11-3.08	0.018
≥4 vs. 0-1	2.09	1.23-3.55	0.007
Respiratory rate (breaths/min), for unit increase	1.04	1.02-1.07	0.001
PaO_2/FiO_2, for unit increase	0.995	0.992-0.997	<0.001
Creatinine (mg/dL), for unit increase	1.34	1.18-1.51	<0.001
Platelets ($\times 10^9$/L), for unit increase	0.995	0.992-0.998	0.001
Cardiovascular Disease (yes vs. no)	1.093	0.695-1.718	0.693
Pulmonary Disease (yes vs. no)	2.001	0.925-5.033	0.101
Hypertension (yes vs. no)	2.03	1.305-1.461	0.010
Diabetes (yes vs. no)	1.24	0.495-1.313	0.348
Cancer history (yes vs. no)	1.332	0.682-2.591	0.418
Cough at presentation (yes vs. no)	1.15	0.769-1.755	0.501
White blood cell count, ($\times 10^9$/L), per unit increase	1.032	0.973-1.095	0.298
Lymphocytes count ($\times 10^9$/L), per unit increase	0.966	0.972-1.021	0.661
Hemoglobin (g/dL), per unit increase	0.984	0.934-1.033	0.552
Hematocrit (%), per unit increase	0.945	0.906-0.980	0.049
Aspartate aminotransferase (UI/L), per unit increase	1.003	0.994-1.011	0.511
Alanine aminotransferase (UI/L), per unit increase	0.990	0.980-0.999	0.033
Lactate dehydrogenase (UI/L), per unit increase	1.00	1.000-1.001	0.214
Reactive C Protein (mg/L), per unit increase	1.000	0.998-1.002	0.951

HR: hazard ratio; 95 % CI: 95% confidence interval; RR: respiratory rate. History of CV disease, hypertension, diabetes, depression, dementia, cancer were included into 'comorbidities'. Variables excluded (p>0.10) from both models: N of drugs, Barthel Index, CRP. The light-grey shaded area includes all variables excluded from multivariate model predicting the risk of in-hospital mortality.

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

36/bmjopen-2020-040729 on 25 September 2020. Downloaded from http://bmjopen.bmj.com/ on April 17, 2024 by guest. Protected by copyright.



Supplementary Figure 1. ROC Curve Analysis of the COVID-19MRS performance.

36/bmjopen-2020-040729 on 25 September 2020. Downloaded from http://bmjopen.bmj.com/ on April 17, 2024 by guest. Protected by copyright.

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2-3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5
Objectives	3	State specific objectives, including any prespecified hypotheses	5-6
Methods			
Study design	4	Present key elements of study design early in the paper	7
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	7-8
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	7-8
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	8
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	8-9
Bias	9	Describe any efforts to address potential sources of bias	7
Study size	10	Explain how the study size was arrived at	7-8
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	8-9
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	8-9
		(*b*) Describe any methods used to examine subgroups and interactions	
		(*c*) Explain how missing data were addressed	
		(*d*) If applicable, explain how loss to follow-up was addressed	
		(*e*) Describe any sensitivity analyses	
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	9-10
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

bmjopen-2020-040729 on 24 September 2020. Downloaded from http://bmjopen.bmj.com/ on April 17, 2024 by guest. Protected by copyright.

Descriptive data		14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders (b) Indicate number of participants with missing data for each variable of interest (c) Summarise follow-up time (eg, average and total amount)	9-10
Outcome data		15*	Report numbers of outcome events or summary measures over time	11-12
Main results	16		(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included (*b*) Report category boundaries when continuous variables were categorized (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	11-12
Other analyses	17		Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	11-12
Discussion				
Key results	18		Summarise key results with reference to study objectives	13
Limitations	19		Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	15
Interpretation	20		Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	13-15
Generalisability	21		Discuss the generalisability (external validity) of the study results	13-14-15-16
Other information				
Funding	22		Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	20

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

bmjopen-2020-040729 on 25 September 2020. Downloaded from http://bmjopen.bmj.com/ on April 17, 2024 by guest. Protected by copyright.

For peer review only

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml