Panminerva Medica
EDIZIONI MINERVA MEDICA

At the peak of Covid-19 age and disease severity but not comorbidities are predictors of mortality. Covid-19 burden in Bergamo, Italy.

Luca NOVELLI, Federico RAIMONDI, Arianna GHIRARDI, Dario PELLEGRINI, Davide CAPODANNO, Giovanni SOTGIU, Giulio GUAGLIUMI, Michele SENNI, Filippo Maria RUSSO, Ferdinando Luca LORINI, Marco RIZZI, Tiziano BARBUI, Alessandro RAMBALDI, Roberto COSENTINI , Lorenzo GRAZIOLI, Gianmariano MARCHESI, Giuseppe Francesco SFERRAZZA PAPA, Simonetta CESA, Michele COLLEDAN, Roberta CIVILETTI, Caterina CONTI, Monica CASATI, Francesco FERRI, Stefania CAMAGNI, Maria SESSA, Arianna MASCIULLI, Antonello GAVAZZI, Anna FALANGA, Luigi Filippo DA POZZO, Sabrina BUORO, Giuseppe REMUZZI, Piero RUGGENENTI, Annapaola CALLEGARO, Lorenzo D`ANTIGA, Luisa PASULO, Fabio PEZZOLI, Andrea GIANATTI, Piercarlo PARIGI, Claudio FARINA, Antonio BELLASI, Paolo SOLIDORO, Sandro SIRONI, fabiano DI MARCO, Stefano FAGIUOLI

Panminerva Medica 2020 Nov 27
DOI: 10.23736/S0031-0808.20.04063-X

Article type: Original Article

Supplementary material available online at http://www.minervamedica.it
Article first published online: November 27, 2020
Manuscript accepted: November 26, 2020
Manuscript revised: October 19, 2020
Manuscript received: July 23, 2020

At the peak of Covid-19 age and disease severity but not comorbidities are predictors of mortality.

Covid-19 burden in Bergamo, Italy.

Luca NOVELLI, M.D.[1], Federico RAIMONDI, M.D. [1,27], Arianna GHIRARDI, Ph.D.[2], Dario PELLEGRINI, M.D.[3], , Ph.D., Davide CAPODANNO, M.D.[4], Ph.D., Giovanni SOTGIU, M.D.[5], Ph.D., Giulio GUAGLIUMI, M.D. [3], Michele SENNI, M.D. [3], Filippo M. RUSSO, M.D.[6,27], Ferdinando L. LORINI, M.D. [6], Marco RIZZI, M.D.[7], Tiziano BARBUI, M.D. [2], Alessandro RAMBALDI, M.D., Ph.D.[8,27], Roberto COSENTINI, M.D.[9], Lorenzo S.C. GRAZIOLI, M.D. [6], Gianmariano MARCHESI, M.D. [6], Giuseppe F. SFERRAZZA PAPA, M.D., Ph.D.[10,27], Simonetta CESA, RN MSN[11], Michele COLLEDAN, M.D.[12], Roberta CIVILETTI, M.D. [1,28], Caterina CONTI, M.D. [1], Monica CASATI, RN MSN[11], Francesco FERRI, M.D.[6], Stefania CAMAGNI, M.D.[12], Maria SESSA, M.D.[13], Arianna MASCIULLI, Ph.D. [2], Antonello GAVAZZI, M.D. [2], Anna FALANGA, M.D.[14,29], Luigi F. DA POZZO, M.D.[15,29], Sabrina BUORO, Ph.D.[16], Giuseppe REMUZZI, M.D.[17], Piero RUGGENENTI, M.D.[18], Annapaola CALLEGARO, M.D.[19], Lorenzo D'ANTIGA, M.D.[20], Luisa PASULO, M.D.[21], Fabio PEZZOLI, M.D.[22], Andrea GIANATTI, M.D.[23], Piercarlo PARIGI, M.D. [1], Claudio FARINA, M.D. [19], Antonio BELLASI, M.D., Ph.D.[24], Paolo SOLIDORO, M.D.[25], Sandro SIRONI, M.D.[26,29], §Fabiano DI MARCO, M.D., Ph.D[1,27], and §Stefano FAGIUOLI, M.D.[21],

on behalf of HPG23 Covid-19 Study Group

[1]Pulmonary Medicine Unit, ASST Papa Giovanni XXIII, Bergamo, Italy; [2]FROM Research Foundation, Bergamo, Italy; [3]Cardiovascular Department, ASST Papa Giovanni XXIII, Bergamo, Italy; [4]Cardiology Unit, Ferrarotto Hospital, Università degli Studi di Catania, Catania, Italy; [5]Department of Medical, Surgical and Experimental Sciences, Università degli Studi di Sassari, Sassari, Italy; [6]Department of Emergency and Critical Care Area, ASST Papa Giovanni XXIII, Bergamo, Italy; [7]Infectious Diseases Unit, ASST Papa Giovanni XXIII, Bergamo, Italy; [8]Department of Oncology and Hematology, ASST Papa Giovanni, Bergamo, Italy; [9]Department of Emergency, ASST Papa Giovanni XXIII, Bergamo, Italy; [10]Department of Neurorehabilitation sciences, Casa di Cura del Policlinico, Milan, Italy; [11]Department of Health and Social Care Professions, ASST Papa Giovanni XXIII, Bergamo, Italy; [12]General Surgery 3 Unit, Department of Organ Failure and Transplantation, ASST Papa Giovanni XXIII; Bergamo, Italy; [13]Neurology Unit, ASST Papa Giovanni XXIII, Bergamo, Italy;

[14]Immunohematology and Transfusion Unit, ASST Papa Giovanni XXIII, Bergamo; [15]Urology Unit, ASST Papa Giovanni XXIII, Bergamo, Italy; [16]Quality management, ASST Papa Giovanni XXIII, Bergamo, Italy; [17]Mario Negri Institute for pharmacological research IRCCS, Anna Maria Astori Centre, Science and Technology Park Kilometro Rosso, Bergamo, Italy; [18]Nephrology and Dialysis Unit, ASST Papa Giovanni XXIII, Bergamo, Italy; [19]Department of Laboratory Medicine, ASST Papa Giovanni XXIII, Bergamo, Italy; [20]Paediatric Hepatology Gastroenterology and Transplantation Unit, ASST Papa GiovannI XXIII, Bergamo, Italy; [21]Gastroenterology 1, Hepatology and Transplantation Unit, ASST Papa Giovanni XXIII, Bergamo, Italy; [22]Medical Direction, ASST Papa Giovanni XXIII, Bergamo, Italy; [23]Pathology Unit, Department of Laboratory Medicine, ASST Papa Giovanni XXIII, Bergamo, Italy, [24]Department of Research, Innovation and Brand Reputation, ASST Papa Giovanni XXIII, Bergamo, Italy; [25]Pneumology Unit, Department of Cardiovascular and Thoracic Surgery, Molinette Hospital, Città della Salute e della Scienza, Università degli Studi Torino, Turin, Italy; [26]Department of Diagnostic Radiology, ASST Papa Giovanni XXIII, Bergamo, Italy; [27]Università degli Studi di Milano, Milan, Italy; [28]Università degli Studi Federico II, Naples, Italy; [29]Università degli Studi di Milano-Bicocca, Milan, Italy.

*Corresponding Author: Prof. Fabiano Di Marco at Piazza OMS, 1 - 24127 Bergamo. fabiano.dimarco@unimi.it Phone: +39.035.267.3444

§Fabiano di Marco and Stefano Fagiuoli contributed to the manuscript equally

Abstract

Background. Findings from February, 2020, indicate that the clinical spectrum of Covid-19 can be heterogeneous, probably due to the infectious dose and viral load of SARS-CoV-2 within the first weeks of the outbreak. The aim of this study was to investigate predictors of overall 28-day mortality at the peak of the Italian outbreak.

Methods. Retrospective observational study of all Covid-19 patients admitted to the main hospital of Bergamo, from February 23 to March, 14, 2020.

Results. 508 patients were hospitalized , predominantly male (72.4%), mean age of 66±15 years; 49.2% were older than 70 years. Most of patients presented with severe respiratory failure (median value [IQR] of PaO_2/FiO_2 233 [149-281]). Mortality rate at 28 days resulted of 33.7% (N=171). 39.0% of patients were treated with continuous positive airway pressure (CPAP), 9.5% with non-invasive ventilation (NIV) and 13.6% with endotracheal intubation. 9.5% were admitted to semi-intensive respiratory care unit, and 18.9% to ICU. Risk factors independently associated with 28-day mortality were advanced age (≥78 years: odds ratio, OR, 95% confidence interval [CI] 38.91 [10.67-141.93], p<0.001; 70-77 years: 17.30 [5.40-55.38], p<0.001; 60-69 years: 3.20 [1.00-10.20], p=0.049), PaO_2/FiO_2 <200 at presentation (3.50 [1.70-7.20], p=0.001), need for CPAP/NIV in the first 24 hours (8.38 [3.63-19.35], p <0.001), and blood urea value at admission (1.01 [1.00-1.02], p=0.015).

Conclusions. At the peak of the outbreak, with a probable high infectious dose and viral load, older age, the severity of respiratory failure and renal impairment at presentation, but not comorbidities, are predictors of 28-day mortality in Covid-19.

Introduction

In Wuhan, China, an unprecedented outbreak of pneumonia of unknown origin was documented in December 2019[1]. The agent of the infection was eventually identified as a novel strain of beta coronavirus, which had never been identified in humans before, and was later named Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2)[2]. Global spread of the SARS-CoV-2, the causative agent of Covid-19 (Coronavirus Disease 2019), has been extremely rapid and relentless, reaching a pandemic status on 11 March 2020[3].

Findings from February, 2020, indicates that the clinical spectrum of Covid-19 can be very heterogeneous, probably due to the infectious dose and the viral load of SARS-CoV-2 within the first weeks of disease onset[4,5,6]. Compared to other European countries, Italy was earlier and hardly hit by the outbreak since late February, 2020. As of the end of June, 2020 over 240,570 positive cases and over 34,760 deaths have been reported by Italian Civil Protection Department and National Heath Institute (ISS)[7]. In Bergamo and its Province, one of the most affected area of Italy and Europe, there was an increase in mortality up to + 568% in March, 2020 compared with the same month in 2015-2019[8]. The harshness of local epidemic could be ascribed to delays in recognizing SARS-CoV-2 pneumonia cases in the small peripheral community hospitals as well as delays in activating lockdown measures in the Province. The Province was not locked down until March 8, which was 2 weeks after the first documented Covid-19 cases at the hospital of Alzano Lombardo on February 23[9]. This scenario allowed the virus to spread rapidly to the city of Bergamo, probably reaching large-scale interpersonal infection and extremely high environmental contamination. Papa Giovanni XXIII Hospital, a tertiary public hospital in Bergamo serving a Province of over 1.1 million inhabitants, faced a massive influx of patients presenting with severe respiratory failure due to Covid-19 over just few weeks, with peaks of nearly one hundred patients per day admitted to the Emergency Department (ED).

Nowadays, after almost six months since the Covid-19 outbreak, no etiological therapy is yet proven to work. Moreover, the more the time passes the more it becomes clear that SARS-CoV-2 infection has multiple organ involvement other than lungs[10,11]. There are increasing literature on Covid-19 describing thrombotic complications, indeed Covid-19 as well as hospitalization due to Covid-19, carry several potential risk factors for thrombosis: activation of inflammatory cascade, platelet activation, endothelial dysfunction, stasis and immobilization[12]. Given the uncertainties about treatment and pathophysiology, is of timely interest to know potential predictors of mortality, in order to identify patients at a greater risk of unfavourable outcome and possibly prioritize their treatment. So far, we have limited literature mainly coming from extra-European countries investigating predictors of mortality, with variable follow-up of in-hospital patients only [13,14,15,16,17,18,19,20].

The aim of this study was to investigate predictors of overall 28-day mortality of all confirmed Covid-19 cases admitted to our Hospital at the peak of the Italian outbreak.

Methods

This retrospective, observational study was approved by the local Ethical Committee (n°37/2020). In the light of the urgent need to treat critical patients, and to avoid paper contamination, oral consent was obtained when feasible, according to local protocol.

Source of data

We searched electronic medical records and collected the data of all patients with laboratory-confirmed SARS-CoV-2 infection, hospitalized at Papa Giovanni XXIII Hospital (a tertiary hospital of 1080 beds), and its affiliate hospital, San Giovanni Bianco (a community hospital of 130 beds), between February 23rd and March 14th, 2020. Follow-up stopped on April 11th, 2020, to

allow for a minimum of 28 days in all patients. We also included patients already hospitalized for other conditions, who developed Covid-19 disease in the same time period; some of them were referred from other hospitals. Covid-19 was diagnosed on the basis of the updated WHO interim guidance[21]. Demographic data, medical history, underlying comorbidities, history of exposure to the virus, clinical symptoms and/or signs, radiological and laboratory findings upon admission were derived from medical records, while information about family unit, healthcare job, pre-hospital medical contact, use of antibiotics and flu vaccine status were self-reported by the patient or relatives. Radiologic assessments and all laboratory tests were performed according to local clinical practice and based on clinical needs. At presentation, patients underwent arterial blood gas analysis, routine blood tests, and chest X-ray. For those presenting to the emergency room (ER), the most intense level of oxygen or ventilatory support (i.e. low flow oxygen nasal cannula [1-5 L/min of oxygen], Venturi mask [FiO_2 ranging from 31 to 60%], Non-rebreather mask [reservoir 15 L/min of oxygen], continuous positive airway pressure [CPAP], non-invasive mechanical ventilation [NIV], or endotracheal intubation [ETI] and invasive mechanical ventilation) during the first 24 hours was recorded. CPAP was achieved with high flow systems (Flow-meter™, Bergamo, Italy) and delivered by appropriately sized helmets (Dimar s.r.l., Modena, Italy). Date of presentation was defined as date of arrival to the ER or onset of respiratory symptoms for already hospitalized patients, while hospital admission was defined as the time of hospitalization in clinical wards, or in intensive care units (ICU)/respiratory sub-intensive care units.

Laboratory confirmation of SARS-COV-2 infection

SARS-CoV-2 genome from nasal swabs and respiratory samples was detected by two different molecular methods (GeneFinder COVID-19-Elitech Group, Allplex™ 2019-nCoV Assay - Seegene Inc) according to the manufacturer's instructions. After the purification of viral RNA from

clinical samples, the detection of RdRp, E and N viral genes was obtained by real time Polymerase Chain Reaction (RT-PCR) according to WHO protocol[22].

Outcome

The primary endpoint was 28-day all-cause mortality, occurring either during in-hospital stay or after discharge.

Statistical analysis

Descriptive statistics were used to summarize the baseline characteristics of Covid-19 patients. Continuous variables were expressed as mean and standard deviation (SD) or as median and interquartile range [IQR], depending on their parametric or non-parametric distribution. Categorical variables were expressed as absolute counts and percentages. No imputation was made for missing values. The chi-square test (or Fisher's exact test when appropriate) was used to test between-group differences for the categorical variables, whereas the t-test or the Wilcoxon-Mann-Whitney test (for normally and not normally distributed variables, respectively) were used to compare continuous variables. Time to death was calculated as the time (days) between ER admission or symptom's onset for patients already hospitalized and time of death. The distribution of deaths over time was reported by absolute number and by Kaplan-Meier 28-day cumulative mortality. Kaplan-Meier 28-day survival curves were plotted stratifying by respiratory support used in the first 24 hours with comparison by the log-rank test. Univariate logistic regression model was run to investigate predictors of 28-day mortality. A backward stepwise procedure was used to determine the best predictors to be included in the multivariable model. Results are presented as odds ratio (OR) with 95% confidence intervals (CI). Candidate predictors were variables regarding demographic and clinical characteristics of patients (Table I), intervals between symptoms and

clinical relevant episodes (Table II), and pre-hospital epidemiology and clinical features (Table III) that were available in at least 300 patients and significantly different between patients who died and those who did not at a p value level of 0.05. Variables selected in the final step of the model were simultaneously tested into a second model, where other variables regarding clinical characteristics, blood gas analysis at presentation, oxygen and ventilatory support in the first 24 hours (Table IV) and laboratory and radiological findings at hospital admission (Table S1) were selected on biological plausibility and clinical judgment were forced, to establish their incremental value. For all tested hypotheses, a two-tailed p-values <0.05 was considered significant. Analyses were performed using STATA software, release 16 (StataCorp LP, College Station, TX, USA).

Results

The demographic and clinical characteristics of 508 Covid-19 patients are reported in Table I. The majority of patients were Caucasian (98.4%) and male (72.4%), with a mean age of 66 years. Most patients were overweight (median BMI 26.9 [24.5-30.1]), with documented relevant comorbidities, especially systemic hypertension (54.5%), and diabetes (19.7%). The comorbidity burden, as estimated by the Charlson Comorbidity Index (CCI), attained a median value of 4.0 [2.0-5.0]. Medication history is shown in Table I; most patients were treated with antihypertensive drugs (53.2%).

Pre-hospital and presentation features

Time intervals between symptom onset and clinical relevant episodes are reported in Table II. The median time between symptom onset and arrival to the ER was 7.0 days [5.0- 10.0]. A history of contact with a confirmed case of Covid-19 was reported in 24.2% of the patients (Table III). Fever was the most frequent symptom at home (85.6%), whereas dyspnoea was present in about half of

the patients (56.3%), and gastrointestinal or systemic symptoms only in a minority (18.1% and 31.2%, respectively). Prior contact with healthcare facilities within 14 days occurred in 37.0% of cases. At presentation, most of the patients were alert (91.9%), and febrile (62.8%), with normal blood pressure and normal heart rate (Table IV). Arterial blood gas analysis showed a tendency to respiratory alkalosis, with a median pH of 7.47 [7.44-7.50], median PaCO2 of 33.0 mmHg [30.0-35.0], and median HCO3- of 24.1 mmol/l [22.0-26.0]. Laboratory and radiographic findings at admission are reported in Table S1. CRP was generally elevated, while coagulation parameters, liver and renal function were in the majority of cases in the range of normality.

Respiratory support in the first 24 hours

The type of support used to treat respiratory failure in the first 24 hours is shown in Table IV. The majority of patients was managed with low-flow oxygen nasal cannula, non-rebreather mask, and CPAP (26.1%, 21.3%, and 20.7%, respectively), while Venturi mask, ETI, and NIV were less common (12.1%, 3.3%, and 3.8%, respectively). 61 patients (12.7%) did not require oxygen support.

Clinical endpoints

Death at 28-day occurred in 171 patients (33.7%); distribution of deaths over time is shown in Figure 1. During hospitalization 198 were treated with CPAP (39.0%), 48 with NIV (9.5%) and 69 with ETI (13.6%). Forty-eight patients (9.5%) were admitted to semi-intensive respiratory care unit, and 96 patients (18.9%) to intensive care unit. Patients in ICU had a mortality rate of 30.2% (29/96). Pre-hospital dyspnoea, respiratory rate, lactate, PaO2/FiO2 <200 at presentation and CRP levels > 127 mg/L were significantly higher in patients who died (Tables III, IV and S1). Time from symptom onset to ER or CPAP/NIV treatment was shorter in deceased patients than in survivals (p=0.004, and 0.016, respectively, Table II). Intervals from symptom onset to ETI, hospitalization to ETI, and

CPAP/NIV to ETI were not different (Table II). The use of CPAP in the first 24 hours was more frequent in patients who died, while the use of low-flow oxygen nasal cannula was more common in patients who survived (Table IV). Kaplan-Meier estimates of survival according to the type of respiratory support used in the first 24 hours are shown in Figure 2. In-hospital drug therapy was similar between the groups, although a more frequent use of each treatment was observed in patients with severe disease (Table IV).

Predictors of mortality

Table V reports risk predictors for mortality. In the multivariable analysis, advanced age (≥78 years: odds ratio, OR, 95% confidence interval [CI] 38.91 [10.67-141.93], p<0.001; 70-77 years: 17.30 [5.40-55.38], p<0.001; 60-69 years: 3.20 [1.00-10.20], p=0.049), PaO2/FiO2 <200 at admission (3.50 [1.70-7.20], p=0.001), need for CPAP or NIV in the first 24 hours (8.38 [3.63-19.35], p <0.001), and urea value (mg/dl) at presentation (1.01 [1.00-1.02], p=0.015) were independent predictors of death. Conversely, other variables such as gender, being a former smoker, flu vaccine status, dyspnoea, time from symptoms to ER, comorbidities, including cardiac and cerebrovascular disease, and pharmacologic therapies at home, were not associated with the risk of death.

Discussion

The main results from this study involving Covid-19 hospitalized patients in one of the most seriously affected outbreak areas in Western countries at the peak of the outbreak can be summarized as follows. First, several hundred patients with severe respiratory failure required hospital admission in a limited period of time. Second, 57% of patients suffered from severe disease, requiring either intensive or semi-intensive care units, or advanced respiratory support (CPAP, NIV, or ETI) or eventually dying. Third, the 28-day mortality was 33.7%, higher than earlier

experiences from China and recent reports from United Kingdom (UK) and United States (USA) [18,19,20]. Fourth, age over 60 years, PaO_2/FiO_2 <200 at presentation, need for ventilatory support with CPAP or NIV in the first 24 hours and increased blood urea values at admission, but not comorbidities, were independent predictors of death.

The condition of Bergamo and its Province, characterized by elevated concentration of severely compromised patients over a limited interval of time at the start of SARS-CoV2 outbreak, could be reasonably related to high infectious dose and viral load of the patients. Despite it is technically difficult to contemporary measure viral density, viability, and viral contamination, there are many indirect evidence that viral load should influence the incidence and severity of disease[23]. Firstly, patients with SARS-CoV-2 infection cause significant environmental contamination through respiratory droplets and fecal shedding, not only suggesting interpersonal contacts as a medium of transmission, but also the environment[24]. Secondly, experiments under controlled conditions in animal models showed a clear dose-response relation between the infecting viral dose and disease[25,26], as already demonstrated in mouse models infected with SARS-CoV-1, where consistent dose-response relations are observed with the severity of the infection[27]. Furthermore, recent data from Covid-19 have shown that compared with patients with mild disease, those with severe infections showed longer duration of persistence of SARS-CoV-2 in respiratory samples, higher viral load and a later shedding peak[6]. These data suggests that the magnitude of the initial viral load is likely to be a relevant factor for severe disease development in Covid-19.

By analyzing our cohort in this peculiar scenario, we investigated predictors of 28-day mortality and compared them with the available international literature. As shown by recent reports from different Countries[18,19,20], increasing age and chronic comorbidities, especially chronic cardiac disease, are well recognized risk factors for in hospital mortality of Covid-19 patients. Other potential predictors of mortality include: male sex, non-asthmatic chronic pulmonary disease,

chronic kidney disease, liver disease, obesity, hypoxemia, secondary bacterial infection, higher neutrophil to lymphocyte ratio (NLR), elevated inflammatory indicators in blood, high SOFA score, d-dimer greater than 1 μg/mL, CD3+ CD8+ T cells ≤ 75 cell/μL, and cardiac troponin I ≥ 0.05 ng/mL [13,14,15,16,17,18,19,20]. Given the heterogeneity of severity and disease manifestations[10] as well as the multiple and different findings in predictors of mortality, is important to collect information from various scenarios in order to optimize patient care and appropriately deploy health care resources during this Covid-19 pandemic.

Demographic and clinical characteristics of our study population differed in some way from previous reports from China. Compared to the Covid-19 Chinese population, which had a mean age ranging from 41 to 57 years, the patients hospitalized in Bergamo were on average 66 year-old, with half of them being over 70s[14,18,28,29,30,31,32,33]. Considering age distribution, our data are similar to those from large reports from United Kingdom and USA, where median age was 72.9 and 63 years respectively; in these cohorts increasing age has been identified as an independent predictor of mortality[19,20]. Our analysis, in accordance with literatures from China and Western countries, confirmed that advancing age, starting from the 60s, is an independent predictor of death, with a steep increase in odds ratio per decade.

Male sex has been found to be an independent risk factor in a large prospective cohort study on 20,133 British patients. In our cohort, even if males were prevalent (72.4% compared with 50-66% observed in China, 49.5% from New York City and 59.9% from UK) sex did not result *per se* as a factor associated with death. Actually, in our multivariable analysis gender resulted an independent risk factor for 28-day mortality up to the inclusion in the model of the severity of the disease. Of note, similar results were observed during the SARS-CoV-1 outbreak in Hong Kong, where it was demonstrated that age, but not sex, was associated with mortality[34].

In our study, most of the patients presented with severe respiratory failure, with 37.2% having a PaO2/FiO2 <200 at hospital admission (Table 4). At multivariable analysis, PaO2/FiO2 <200 at presentation and early need for ventilatory support (i.e. CPAP or NIV) were strong predictors of mortality (Table V, Figure 2). The severity of respiratory failure at presentation observed in our study was on odd with official reports from China, although comparisons between data may be difficult due to differences in hospitalization criteria, severity definition and admission criteria to high dependency unit (HDU) or ICU. In China, about 19% of patients suffered from either severe (i.e. PaO2/FiO2<300, blood oxygen saturation ≤93%, dyspnoea, respiratory rate ≥ 30/minute, and/or lung infiltrates >50% within 24–48 hours), or critical (i.e. respiratory failure, septic shock, and/or multiple organ dysfunction/failure) disease, with a mortality rate of 0% and 49 %, respectively[35]. In UK cohort, only 17% required admission to ICU or HDU and 32% of them eventually died, while in the New York cohort 36.1% experienced a critical illness (i.e. ICU admission, mechanical ventilation, discharge to hospice or death).

The treatment of respiratory failure during an outbreak with a shortage of critical care beds is the main hospital issue during a pandemic[36]. Conventional approaches include, according to severity, low-flow oxygen with nasal cannula or mask, non-invasive respiratory support (i.e. high-flow nasal cannula [HFNC], CPAP or NIV), and ETI and mechanical ventilation. Due to the lack of evidence, the European Respiratory Society and American Thoracic Society clinical practice guidelines were unable to provide a recommendation on the use of non-invasive ventilation for type 1 respiratory failure, such as in case of Covid-19[37]. The use of NIV for SARS and other airborne diseases has been assessed in several observational studies and remains controversial[38,39]. HFNC, which has been demonstrated to be an option in patients with non-hypercapnic acute respiratory failure, has been used in Covid-19 patients [40,41,42]. This option was not considered feasible and convenient in our emergency setting mainly because of the imbalance between the number of

patients to treat and the scarce availability of active humidifiers as well as the uncertainties about the effectiveness in providing adequate positive end expiratory pressure (PEEP). However, since in Covid-19 the effect of high PEEP could be detrimental, the role of HFNC needs to be actively investigated[43]. The main risk of non-invasive respiratory support, such as HFNC, CPAP, and NIV for de novo acute respiratory failure is delaying intubation, and promoting the so called "self-inflicted lung injury"[43,44]. Interestingly, in our cohort, the interval between CPAP/NIV and ETI (Table II) was not associated with mortality. Thus, our experience suggests that during an outbreak with a shortage of critical care beds, the use of CPAP, although not validated, can be a bridge to intubation[36].

Our multivariable analysis showed that urea is an independent predictor of death in Covid-19 (Table V). The same evidence has been obtained from community acquired pneumonia (CAP)[45,46,47]. For this reason, validated prognostic scores predicting 30-day mortality in CAP, such as Pneumonia Severity Index (PSI), and CURB-65 include blood urea nitrogen value (cut off ≥30 mg/dl and >19 mg/dl respectively). Furthermore, renal function impairment as evaluated by serum creatinine and/or reduced urinary output, is part of the Sequential Organ Failure Assessment (SOFA), which describes the burden of multi organ dysfunction/failure in critically ill patients[48]. SOFA has been recently identified as a possible predictor of mortality for Covid-19 patients, according to a Chinese retrospective study[14].

Our study has several limitations. First, it must be acknowledged that it is a single center, retrospective study based on electronic medical records, which were collected during a medical emergency, with almost overwhelmed hospital resources. Thus, the accuracy and completeness of data may be reasonably questioned. Nevertheless, this is a large series of cases coming from the forefront of the Italian outbreak, providing a definite follow-up length on hard endpoints considering also mortality after discharge. Second, we do not measure the ribonucleic acid (RNA)

viral load in respiratory samples or in the environment, neither assess the viability of the virus, therefore we can only speculate about the association between infectious dose, viral load and disease severity. However, taking into account the evidence from previous studies, it is reasonable not to exclude the role of viral load and the unique epidemiological condition in Bergamo and its Province.

Third, increased level of d-dimer and troponin I and low CD3+ CD8+ T cells recently emerged as a potential predictor of mortality in hospitalized patients with Covid-19; unfortunately, these biomarkers were not adequately investigated in our study, being not part of the standard admission laboratory panel in ER. Finally, due to the absolute prevalence of the Caucasian population (98.4%), the study may have not fully addressed the role of ethnicity on mortality from Covid-19 infection. This aspect may be relevant in regions with significant ethnical heterogeneity .

Conclusion

In conclusion, we described the heavy burden of hospitalized patients, their challenging clinical characteristics and their outcome at the Italian forefront of the first three weeks of Covid-19 outbreak. These results, together with other international evidence, may help guide the strategic allocation of limited critical care resources, particularly in settings of massive influx of severely compromised patients. At the peak of the outbreak, with a probable very high infectious dose and viral load, increasing age (i.e. over 60 years) and the severity of the disease at presentation, but not comorbidities, are the most important risk factor for mortality.

Figures Footnotes

Figure 1. Distribution of deaths and Kaplan-Meier 28-day cumulative mortality.

Histogram of single-day number of deaths and 28-day cumulative mortality.

Figure 2. Kaplan-Meier survival curves by respiratory support in the first 24 hours of treatment.

Oxygen and Ventilatory support in the first 24 hours by the ER presentation intended as the highest between Low flow oxygen nasal cannula (≤5 L/min of Oxygen), Venturi mask (FiO_2 ranging from 31 to 60%), Non-rebreather mask (reservoir) 15L/min of Oxygen, Continuous Positive Airway Pressure (CPAP), Non-invasive ventilation (NIV).

Authors' contribution

Luca Novelli, Federico Raimondi and Fabiano Di Marco conceived the idea and designed the research. Luca Novelli, Federico Raimondi, Roberta Civiletti and Caterina Conti collected clinical records data. Annapaola Callegaro and Claudio Farina performed and supervised all molecular and biological analyses. Arianna Ghirardi and Davide Capodanno analysed study data and developed statistical models and design of methodology. Fabiano Di Marco and Stefano Fagiuoli were the responsible for the research activity, management and coordination. Luca Novelli, Federico Raimondi, Fabiano Di Marco, Stefano Fagiuoli, Roberta Civiletti and Arianna Ghirardi created and wrote the initial draft. All the authors critically analysed data and revised the draft. Luca Novelli, Federico Raimondi, Fabiano Di Marco and Stefano Fagiuoli prepared the final version of manuscript after revision and final approval by all the authors. §Fabiano DI Marco and Stefano Fagiuoli contributed to the manuscript equally. All the members of HPG23 Covid-19 Study Group are listed in Supplementary material. All authors read and approved the final version of the manuscript.

Founding

None

Conflict of interest

Authors have nothing to disclose about the work under consideration. Only Alessandro Rambaldi and Fabiano Di Marco received financial activities outside this work, as declared in ICMJE form.

Table I. Demographic and clinical characteristics by death and severe disease status.

	N	All patients (N=508)	Death		
			No (N=337)	Yes (N=171)	p
Male gender – *no. (%)*	508	368 (72.4)	232 (68.8)	136 (79.5)	0.011
Age - *y mean (SD)*	508	66.3 (15.8)	61.7 (16.5)	75.2 (9.2)	<0.001
≤ 59 – *no. (%)*	508	139 (27.4)	127 (37.7)	12 (7.0)	<0.001
60-69 – *no. (%)*		119 (23.4)	93 (27.6)	26 (15.2)	
70-77 – *no. (%)*		124 (24.4)	68 (20.2)	56 (32.7)	
≥ 78 – *no. (%)*		126 (24.8)	49 (14.5)	77 (45.0)	
Caucasian ethnicity – *no. (%)*	508	500 (98.4)	329 (97.6)	171 (100.0)	0.042
BMI - *median [IQR]*	419	26.9 [24.5-30.1]	26.9 [24.4-30.4]	26.9 [24.7-29.7]	0.56
≥ 30 – *no. (%)*	419	108 (25.8)	77 (26.6)	31 (24.0)	0.59
Smoking history – *no. (%)*					
Current smoker	373	22 (5.9)	18 (6.9)	4 (3.5)	0.20
Former smoker	373	99 (26.5)	57 (21.9)	42 (37.2)	0.002
Never smoker	373	252 (67.6)	185 (71.2)	67 (59.3)	0.025
Comorbidities – *no. (%)*					
Hypertension	497	271 (54.5)	151 (45.6)	120 (72.3)	<0.001
Diabetes	493	97 (19.7)	53 (16.2)	44 (26.7)	0.006
Chronic Kidney Failure	491	41 (8.4)	17 (5.2)	24 (14.7)	<0.001
COPD	490	48 (9.8)	23 (7.1)	25 (15.2)	0.004
Long-term oxygen therapy	491	12 (2.4)	5 (1.5)	7 (4.3)	0.064
Active solid neoplasm	492	26 (5.3)	15 (4.6)	11 (6.7)	0.32
Active hematologic malignancy	492	16 (3.3)	4 (1.2)	12 (7.3)	<0.001
Cerebrovascular disease	494	39 (7.9)	21 (6.4)	18 (11.0)	0.073
Previous Myocardial Infarction	492	70 (14.2)	30 (9.1)	40 (24.5)	<0.001
Chronic heart failure	494	26 (5.3)	10 (3.0)	16 (9.7)	0.002
Vasculopathy	495	69 (13.9)	31 (9.4)	38 (23.0)	<0.001
Rheumatic pathology	491	30 (6.1)	16 (4.9)	14 (8.5)	0.11
CCI score - *median [IQR]*	497	4.0 [2.0-5.0]	3.0 [1.0-4.0]	5.0 [4.0-6.0]	<0.001
CCI=0 – no. (%)	497	49 (9.9)	48 (14.5)	1 (0.6)	<0.001
CCI=1-2 – no. (%)		116 (23.3)	105 (31.7)	11 (6.6)	
CCI=3+ – no. (%)		332 (66.8)	178 (53.8)	154 (92.8)	
CCI=4+ – no. (%)	497	259 (52.1)	126 (38.1)	133 (80.1)	<0.001
Medications history – *no. (%)*					
Antihypertensives	476	253 (53.2)	146 (45.5)	107 (69.0)	<0.001
ACE-inhibitors	483	84 (17.4)	47 (14.4)	37 (23.6)	0.013
ARBs	482	80 (16.6)	47 (14.5)	33 (21.0)	0.070
Steroids	476	24 (5.0)	15 (4.6)	9 (5.9)	0.56
Oral antidiabetics	478	66 (13.8)	41 (12.7)	25 (16.1)	0.31
Insulin	478	32 (6.7)	15 (4.6)	17 (11.0)	0.010
OAT/DOACs	477	63 (13.2)	31 (9.6)	32 (20.8)	<0.001
Antiplatelets	477	126 (26.4)	59 (18.3)	67 (43.5)	<0.001
Immunosuppression – *no. (%)*	492	35 (7.1)	15 (4.6)	20 (12.1)	0.002
Iatrogenic	492	34 (6.9)	14 (4.3)	20 (12.1)	0.002
HIV	492	1 (0.2)	1 (0.3)	0 (0.0)	1.00

Flu vaccine – *no. (%)*	337	164 (48.7)	101 (42.8)	63 (62.4)	<0.001

Data expressed as column percentages. Percentages may not total 100 because of rounding.
Body Weight and Height as referred by patient, BMI (Body Mass Index),
COPD (Chronic Obstructive Pulmonary Disease),
CCI (Charlson Comorbidity Index score),
Antihypertensives included ACE-inhibitors, ARBs (Angiotensin Receptor Blockers), Calcium channels blockers, Diuretics, Beta-blockers, Alpha-blockers, Alpha-2 agonists,
OAT (Oral Anticoagulant Therapy),
DOACs (Direct Oral Anticoagulants),
Iatrogenic immunosuppression (due to chemotherapy, solid organ transplantation, autoimmune diseases), HIV (Human Immunodeficiency Virus),
SD (Standard Deviation), IQR [Interquartile Range], p-values obtained by Chi-square test (or Fisher's exact test when appropriate) for categorical variables and t-test (or Wilcoxon-Mann-Whitney test when appropriated) for continuous variables.

Table II. Intervals in terms of days between symptoms and clinical relevant episodes.

	N	All patients (N=508)	Death		
			No (N=337)	Yes (N=171)	p
Median days [IQR] between					
Symptoms onset – ER§	427	7.0 [5.0-10.0]	8.0 [5.0-10.0]	7.0 [4.0-9.0]	0.004
Symptoms onset – CPAP/NIV§	191	9.0 [6.0-11.0]	9.0 [7.0-12.0]	8.0 [6.0-10.0]	0.016
Symptoms onset – ETI§	63	10.0 [8.0-14.0]	9.0 [7.0-15.0]	10.0 [9.0-13.0]	0.53
ER - Hospitalization§	438	2.0 [1.0-2.0]	2.0 [1.0-2.0]	2.0 [1.0-2.0]	0.57
Hospitalization – CPAP/NIV§	197	1.0 [1.0-3.0]	2.0 [1.0-4.0]	1.0 [0.0-2.0]	<0.001
Hospitalization – ETI§	64	3.5 [2.0-5.0]	4.0 [2.0-5.0]	3.0 [2.0-4.0]	0.45
CPAP/NIV – ETI	67	3.0 [2.0-4.0]	2.0 [2.0-4.5]	3.0 [2.0-4.0]	0.63

§ Only for patients not already hospitalized for other conditions (n=438)

Continuous Positive Airway Pressure (CPAP), Non-invasive ventilation (NIV), Endotracheal Intubation (ETI)

Median time between symptoms onset and Emergency Room (ER) admission, between symptoms onset and CPAP/NIV initiation, between symptoms onset and Endotracheal Intubation (ETI), between ER admission and hospitalization in a ward, between hospitalization after ER admission and CPAP/NIV initiation, between hospitalization after ER admission and ETI, between CPAP/NIV initiation and ETI,

IQR [Interquartile Rang], p-values obtained by Wilcoxon-Mann-Whitney test for continuous variables.

Table III. Pre-hospital epidemiology and clinical features.

	N	All patients (N=508)	Death		
			No (N=337)	Yes (N=171)	p
Pre-hospital antibiotic – *no. (%)*	442	208 (47.1)	139 (47.1)	69 (46.9)	0.97
Contact with healthcare facilities in the last 14 days – *no. (%)*	441	163 (37.0)	103 (34.8)	60 (41.4)	0.18
Contact with minors in the last 14 days – *no. (%)*	314	116 (36.9)	87 (38.8)	29 (32.2)	0.27
Family members, *median [IQR]*	343	2.0 [2.0-3.0]	2.0 [2.0-3.0]	2.0 [2.0-3.0]	0.75
Family member infected by Covid-19 – *no. (%)*	339	51 (15.0)	40 (16.9)	11 (10.8)	0.15
Contact with confirmed case of Covid-19 – *no. (%)*	364	88 (24.2)	66 (25.6)	22 (20.8)	0.33
Healthcare professional – *no. (%)*	447	29 (6.5)	23 (7.6)	6 (4.1)	0.16
Already hospitalized – *no. (%)*	508	69 (13.6)	48 (14.2)	21 (12.3)	0.54
Symptoms – *no. (%)*					
Fever	492	421 (85.6)	282 (86.0)	139 (84.8)	0.72
Cough	491	231 (47.0)	164 (50.2)	67 (40.9)	0.052
Dyspnoea	492	277 (56.3)	169 (51.7)	108 (65.5)	0.004
Sore throat	491	14 (2.9)	11 (3.4)	3 (1.8)	0.40
Dizziness	491	21 (4.3)	15 (4.6)	6 (3.7)	0.63
Abdominal pain	491	13 (2.6)	10 (3.1)	3 (1.8)	0.42
Chest pain	491	22 (4.5)	14 (4.3)	8 (4.9)	0.76
Systemic (asthenia, myalgia)	491	153 (31.2)	111 (33.9)	42 (25.6)	0.060
Gastrointestinal	491	89 (18.1)	67 (20.5)	22 (13.4)	0.055

Data expressed as column percentages. Percentages may not total 100 because of rounding.
Pre-hospital antibiotic therapy prescribed for onset of symptoms connected to Covid-19 disease,
Access to healthcare facilities (i.e. outpatient clinic consultations, dialysis, previous hospitalization, assistance or visits to hospitalized or retirement home people),
Family member number intended as cohabitants,
Already hospitalized (patients already hospitalized for other conditions),
Symptoms referred by patients to Emergency Room (ER) physician as described in admission dossier,
Gastrointestinal symptoms include anorexia, nausea, vomiting, and diarrhoea
IQR [Interquartile Range], p-values obtained by Chi-square test (or Fisher's exact test when appropriate) for categorical variables.

Table IV. Clinical characteristics, blood gas analysis at presentation and in-hospital treatments.

	N	All patients (N=508)	Death		
			No (N=337)	Yes (N=171)	p
At entry in Emergency Room					
AVPU – *no. (%)*					
A (alert)	484	445 (91.9)	301 (93.5)	144 (88.9)	0.039
V (verbal)		7 (1.4)	5 (1.6)	2 (1.2)	
P (pain)		9 (1.9)	7 (2.2)	2 (1.2)	
U (unresponsive)		23 (4.8)	9 (2.8)	14 (8.6)	
HR, *bpm* **-** *median [IQR]*	446	84 [75-94]	84 [75-95]	82 [74-93]	0.18
SBP, *mmHg* **-** *median [IQR]*	438	125 [112-140]	125 [110-140]	126 [115-142]	0.14
RR, *acts/min* **-** *median [IQR]*	239	20 [16-26]	18 [16-24]	22 [18-28]	<0.001
Fever – *no. (%)*	452	284 (62.8)	189 (64.1)	95 (60.5)	0.46
pH - *median [IQR]*	299	7.47 [7.44-7.50]	7.47 [7.45-7.50]	7.46 [7.42-7.50]	0.040
PaO_2/FiO_2 - *median [IQR]*	317	233 [149-282]	257 [193-295]	179 [97-240]	<0.001
<200 – no. [%]	317	118 [37.2]	52 [25.9]	66 [56.9]	<0.001
$PaCO_2$, *mmHg - median [IQR]*	313	33.0 [30.0-35.0]	33.0 [30.0-35.0]	33.0 [29.0-35.0]	0.76
HCO_3^-, *mmol/L - median [IQR]*	164	24.1 [22.0-26.0]	24.2 [22.5-26.2]	23.9 [21.6-25.0]	0.10
Lac, *mmol/L - median [IQR]*	203	1.38 [1.02-1.79]	1.23 [0.96-1.56]	1.62 [1.19-2.09]	<0.001
In the first 24h					
Oxygen and ventilatory support – *no. (%)*					
Low flow oxygen cannula	479	125 (26.1)	104 (32.6)	21 (13.1)	<0.001
Venturi mask	479	58 (12.1)	43 (13.5)	15 (9.4)	0.19
Non-rebreather mask	479	102 (21.3)	62 (19.4)	40 (25.0)	0.16
CPAP	479	99 (20.7)	35 (11.0)	64 (40.0)	<0.001
NIV	479	16 (3.3)	9 (2.8)	7 (4.4)	0.37
ETI	479	18 (3.8)	15 (4.7)	3 (1.9)	0.20
FiO_2 - *median [IQR]*	422	60 [33-70]	50 [30-70]	60 [50-70]	<0.001
PEEP, *cmH_2O - median [IQR]*	120	15 [11-15]	13 [10-15]	15 [12-15]	0.13
IPAP, *cmH_2O - median [IQR]*	19	21 [16-24]	21 [16-25]	20 [16-24]	0.67
Antiviral – *no. (%)*	452	354 (78.3)	247 (80.5)	107 (73.8)	0.11
Hydroxychloroquine – *no. (%)*	444	332 (74.8)	232 (75.8)	100 (72.5)	0.45
Steroid – *no. (%)*	446	42 (9.4)	26 (8.5)	16 (11.3)	0.34
Antibiotics – *no. (%)*	458	410 (89.5)	274 (87.8)	136 (93.2)	0.083
IL-6 Inhibitors – *no. (%)*	438	18 (4.1)	15 (5.0)	3 (2.2)	0.20

* As described in materials and methods. Data expressed as column percentages. Percentages may not total 100 because of rounding..
AVPU as level of consciousness,
HR (Heart Rate), RR (Respiratory Rate), SBP (Systolic Blood Pressure), DBP (Systolic Blood Pressure),
Emergency Room (ER) admission Blood gas analysis performed in Room air shown as pH, Inspired Oxygen Ratio (FiO_2), partial pressure of Oxygen (PaO_2), oxygen arterial saturation (SaO_2), partial pressure of Carbon Dioxide ($PaCO_2$), Bicarbonate (HCO_3^-) and Lactate (Lac) concentration,
Oxygen and Ventilatory support in the first 24 hours by the ER presentation intended as the highest between Low flow oxygen nasal cannula (≤5 L/min of Oxygen), Venturi mask (FiO_2 ranging from 31 to 60%), Non-rebreather mask (reservoir) 15 L/min of Oxygen, Continuous Positive Airway Pressure (CPAP) with helmet, Non-invasive ventilation (NIV) and Endotracheal Intubation (ETI). Positive End Expiratory Pressure (PEEP), IPAP (Inspiratory Positive Airway Pressure),
Antiviral therapy intended as at least one of the following: Oseltamivir, Lopinavir/Ritonavir, Remdesivir and Darunavir/Cobicistat,
Antibiotic Therapy was prescribed at Physician's discretion and at least one of the following: Ceftriaxone, Cefixime, Azithromycin or Levofloxacin

Steroid therapy intended as Methylprednisolone, Hydrocortisone and Dexamethasone,
IL-6 pathway inhibitors intended as Tocilizumab or Siltuximab were prescribed in according to shared local clinical protocol.
IQR [Interquartile Range], p-values obtained by Chi-square test (or Fisher's exact test when appropriate) for categorical variables and Wilcoxon-Mann-Whitney test for continuous variables.

Table V. Univariate and multivariable predictors of 28-day mortality.

	UNIVARIATE MODEL *(all candidate predictors)*		MULTIVARIABLE MODEL *(selected predictors*)*	
	OR (95% CI)	P	OR (95% CI)	p
Male gender	1.76 (1.14-2.72)	0.011	1.25 (0.55-2.85)	0.593
Age – y				
≤ 59	1.00 (Ref.)	--	1.00 (Ref.)	
60-69	2.96 (1.42-6.17)	0.004	3.20 (1.00-10.20)	0.049
70-77	8.72 (4.37-17.37)	<0.001	17.30 (5.40-55.38)	<0.001
≥ 78	16.63 (8.33-33.22)	<0.001	38.91 (10.67-141.93)	<0.001
Former smoker	2.11 (1.30-3.41)	0.002	-	-
Hypertension	3.11 (2.08-4.65)	<0.001	-	-
Diabetes				
No diabetes	1.00 (Ref.)	-	-	-
Diabetes, not insulin dependent	1.51 (0.86-2.63)	0.148	-	-
Diabetes, insulin dependent	3.12 (1.47-6.64)	0.003	-	-
Chronic Kidney Failure	3.16 (1.64-6.07)	0.001	-	-
COPD	2.37 (1.30-4.32)	0.005	-	-
Active hematologic malignancy	6.39 (2.03-20.15)	0.002	-	-
Previous Myocardial Infarction	3.24 (1.93-5.44)	<0.001	-	-
Chronic heart failure	3.43 (1.52-7.73)	0.003	-	-
Vasculopathy	2.89 (1.72-4.84)	<0.001	-	-
ACE-inhibitors	1.83 (1.13-2.96)	0.014	-	-
OAT/DOACs	2.47 (1.44-4.23)	0.001	-	-
Antiplatelets	3.45 (2.25-5.27)	<0.001	-	-
Immunosuppression	2.87 (1.43-5.76)	0.003	2.26 (0.73-6.97)	0.157
Flu vaccine	2.22 (1.37-3.57)	0.001	-	-
Time from symptoms to ER, per 1-day increase	0.93 (0.88-0.97)	0.003	-	-
Dyspnoea before admission	1.77 (1.20-2.61)	0.004	-	-
CPAP or NIV in the first 24 hours	5.41 (3.37-8.68)	<0.001	8.38 (3.63-19.35)	<0.001
PaO_2/FiO_2 <200	3.78 (2.33-6.14)	<0.001	3.50 (1.70-7.20)	0.001
CRP, per 1-unit increase	1.05 (1.03-1.07)	<0.001	-	-
Blood urea, per 1-unit increase	1.02 (1.01-1.03)	<0.001	1.01 (1.00-1.02)	0.015

Ethnicity was not included in the model since only Caucasian patients died.
COPD (Chronic Obstructive Pulmonary Disease),
OAT (Oral Anticoagulant Therapy),
DOACs (Direct Oral Anticoagulants),
ER (Emergency Room),
CPAP (Continuous Positive Airway Pressure) or NIV (Non-invasive ventilation) in the first 24 hours (<24 hours),
CRP (C-reactive Protein),
PaO_2/FiO_2 (Inspired Oxygen Ratio (FiO_2) and Partial pressure of Oxygen (PaO_2) Ratio)
OR (Odds Ratio), CI (Confidence Interval), p-values obtained by the univariate/multivariable logistic regression model

References

1. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 2020;395:497-506.
2. Zhu N, Zhang D, Wang W, et al. A novel coronavirus from patients with pneumonia in China, 2019. N Engl J Med 2020;382:727-733.
3. WHO. WHO Director-General's opening remarks at the media briefing on COVID-19 - 11 March 2020; [Internet]. Available from: https://www.who.int/dg/speeches/detail/who-director-general-s-opening-remarks-at-the-media-briefing-on-covid-19---11-march-2020 [cited 2020, Jul 23].
4. Pan Y, Zhang D, Yang P, Poon LLM, Wang Q. Viral load of SARS-CoV-2 in clinical samples. Lancet Infect Dis 2020;20(4):411-412.
5. Zou L, Ruan F, Huang M, et al. SARS-CoV-2 viral load in upper respiratory specimens of infected patients. N Engl J Med 2020;382:1177-1179.
6. Zheng S, Fan J, Yu F, et al. Viral load dynamics and disease severity in patients infected with SARS-CoV-2 in Zhejiang province, China, January-March 2020: Retrospective cohort study. BMJ 2020;369:m1443.
7. Italian Prime Minister office - Department of Civil Protection. Presidenza del Consiglio dei Ministri – Dipartimento di Protezione Civile: Covid-19 Dati andamento Nazionale; 2020 [Internet]. Available from: https://github.com/pcm-dpc/COVID-19/blob/master/dati-andamento-nazionale/dpc-covid19-ita-andamento-nazionale.csv [cited 2020, Jul 23].
8. Italian Institute of Statistics Report. Istituto Nazionale di Statistica (ISTAT); 2020 [Internet]. Available from: https://www.istat.it/it/files/2020/05/Rapporto_Istat_ISS.pdf [cited 2020, Jul 23].
9. Fagiuoli S, Lorini FL, Remuzzi G. Adaptations and lessons in the province of Bergamo. N Engl J

Med 2020;382:e71.

10. Renu K, Prasanna PL, Valsala Gopalakrishnan A. Coronaviruses pathogenesis, comorbidities and multi-organ damage – A review. Life Sci 2020;255:117839.

11. Tuttolomondo D, Frizzelli A, Aiello M, Bertorelli G, Majori M, Chetta A. Beyond the lung involvement in COVID-19 patients. A review. Minerva Med 2020;10.23736/S0026-4806.20.06719-1.

12. Casale M, Dattilo G, Imbalzano E, et al. The thromboembolism in COVID-19: the unsolved problem. Panminerva Med 2020;10.23736/S0031-0808.20.03999-3.

13. Ruan Q, Yang K, Wang W, Jiang L, Song J. Clinical predictors of mortality due to COVID-19 based on an analysis of data of 150 patients from Wuhan, China. Intensive Care Med 2020;46(5):846-848.

14. 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;395:1054–62.

15. Liu Y, Du X, Chen J, et al. Neutrophil-to-lymphocyte ratio as an independent risk factor for mortality in hospitalized patients with COVID-19. J Infect 2020;81(1):e6-e12.

16. Xie J, Covassin N, Fan Z, et al. Association Between Hypoxemia and Mortality in Patients With COVID-19. Mayo Clin Proc 2020;95(6):1138-1147.

17. Tian W, Jiang W, Yao J, et al. Predictors of mortality in hospitalized COVID-19 patients: A systematic review and meta-analysis. J Med Virol 2020;92:1875–1883.

18. Du RH, Liang LR, Yang CQ, et al. Predictors of mortality for patients with COVID-19 pneumonia caused by SARSCoV- 2: A prospective cohort study. Eur Respir J 2020;55(5):2000524.

19. Docherty AB, Harrison EM, Green CA, et al. Features of 20 133 UK patients in hospital with covid-19 using the ISARIC WHO Clinical Characterisation Protocol: Prospective observational

cohort study. BMJ 2020;369:m1985.

20. Petrilli CM, Jones SA, Yang J, et al. Factors associated with hospital admission and critical illness among 5279 people with coronavirus disease 2019 in New York City: Prospective cohort study. BMJ 2020;369:m1966.

21. WHO – Laboratory testing strategy recommendations for COVID-19: interim guidance; 2020 [Internet]. Available from: https://www.who.int/publications/i/item/laboratory-testing-strategy-recommendations-for-covid-19-interim-guidance [cited 2020, Jul 23].

22. Corman VM, Landt O, Kaiser M, et al. Detection of 2019 novel coronavirus (2019-nCoV) by real-time RT-PCR. Euro Surveill 2020;25(3):2000045.

23. Little P, Read RC, Amlôt R, et al. Reducing risks from coronavirus transmission in the home-the role of viral load. BMJ 2020;369:m1728.

24. Ong SWX, Tan YK, Chia PY, et al. Air, Surface Environmental, and Personal Protective Equipment Contamination by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) from a Symptomatic Patient. JAMA 2020;323(16):1610-1612.

25. Niederwerder MC, Stoian AMM, Rowland RRR, et al. Infectious dose of African swine fever virus when consumed naturally in liquid or feed. Emerg Infect Dis 2019;25(5):891-897.

26. McKenney DG, Kurath G, Wargo AR. Characterization of infectious dose and lethal dose of two strains of infectious hematopoietic necrosis virus (IHNV). Virus Res 2016;214:80-89.

27. Roberts A, Deming D, Paddock CD, et al. A mouse-adapted SARS-coronavirus causes disease and mortality in BALB/c mice. PLoS Pathog. 2007;3(1):e5.

28. Guan W, Ni Z, Hu Y, et al. Clinical characteristics of coronavirus disease 2019 in China. N Engl J Med 2020;382(18):1708-1720.

29. 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.

30. Wang D, Hu B, Hu C, et al. Clinical Characteristics of 138 Hospitalized Patients with 2019 Novel Coronavirus-Infected Pneumonia in Wuhan, China. JAMA 2020;323(11):1061-1069.

31. 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;180(7):934-943.

32. Xu XW, Wu XX, Jiang XG, et al. Clinical findings in a group of patients infected with the 2019 novel coronavirus (SARS-Cov-2) outside of Wuhan, China: Retrospective case series. BMJ 2020;368:m606.

33. Zhang J jin, Dong X, Cao Y yuan, et al. Clinical characteristics of 140 patients infected with SARS-CoV-2 in Wuhan, China. Allergy 2020;75(7):1730-1741.

34. Lee N, Hui D, Wu A, et al. A major outbreak of severe acute respiratory syndrome in Hong Kong. N Engl J Med 2003;348(20):1986-1994.

35. Wu Z, McGoogan JM. Characteristics of and Important Lessons From the Coronavirus Disease 2019 (COVID-19) Outbreak in China. JAMA 2020;323(13):1239-1242.

36. Truog RD, Mitchell C, Daley GQ. The toughest triage — Allocating ventilators in a pandemic. N Engl J Med 2020;382:1973-1975.

37. Rochwerg B, Brochard L, Elliott MW, et al. Official ERS/ATS clinical practice guidelines: Noninvasive ventilation for acute respiratory failure. Eur Respir J 2017;50(2):1602426.

38. Cheung TMT, Yam LYC, So LKY, et al. Effectiveness of noninvasive positive pressure ventilation in the treatment of acute respiratory failure in severe acute respiratory syndrome. Chest 2004;126(3):845-850.

39. Han F, Jiang YY, Zheng JH. [Acute respiratory failure and noninvasive positive pressure ventilation treatment in patients with severe acute respiratory syndrome]. Zhonghua Jie He He Hu Xi Za Zhi 2004;27(9):593-597.

40. Arentz M, Yim E, Klaff L, et al. Characteristics and Outcomes of 21 Critically Ill Patients with COVID-19 in Washington State. JAMA 2020;323(16):1612-1614.

41. Bhatraju PK, Ghassemieh BJ, Nichols M, et al. COVID-19 in critically ill patients in the Seattle region — Case series. N Engl J Med 2020;382(21):2012-2022.

42. 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;323(16):1574-1581.

43. Gattinoni L, Coppola S, Cressoni M, Busana M, Rossi S, Chiumello D. COVID-19 Does Not Lead to a "Typical" Acute Respiratory Distress Syndrome. Am J Respir Crit Care Med 2020;201(10):1299-1300.

44. Brochard L, Lefebvre JC, Cordioli RL, Akoumianaki E, Richard JCM. Noninvasive ventilation for patients with hypoxemic acute respiratory failure. Semin Respir Crit Care Med 2014;35:492–500.

45. Farr BM, Sloman AJ, Fisch MJ. Predicting death in patients hospitalized for community-acquired pneumonia. Ann Intern Med 1991;115(6):428-436.

46. Lim WS, Van Der Eerden MM, Laing R, et al. Defining community acquired pneumonia severity on presentation to hospital: An international derivation and validation study. Thorax 2003;58(5):377-382.

47. Raz R, Dyachenko P, Levy Y, Flatau E, Reichman N. A predictive model for the management of community-acquired pneumonia. Infection 2003;31(1):3-8.

48. Vincent J-L, Moreno R, Takala J, et al. The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. Intensive Care Medicine 1996 Jul;22(7):707-710.

Figure 1. Distribution of deaths and Kaplan-Meier 28-day cumulative mortality.

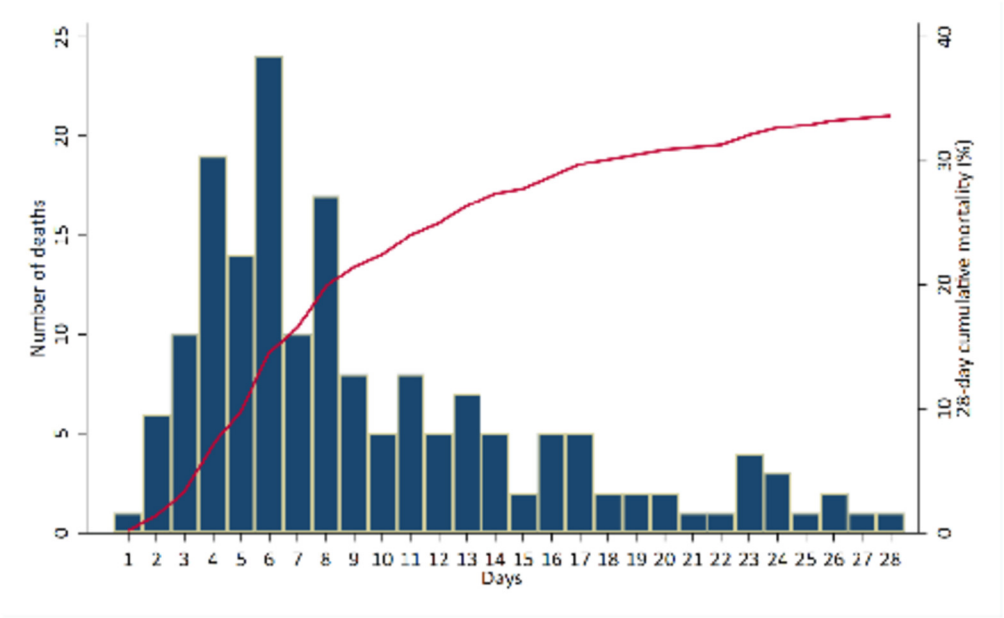
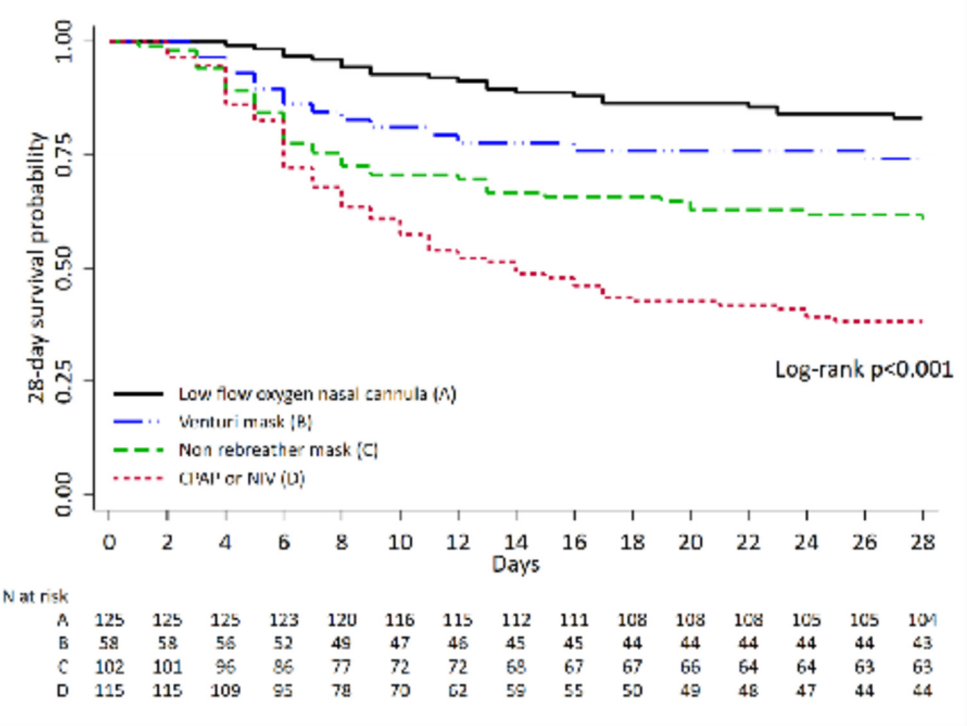


Figure 2. Kaplan-Meier survival curves by respiratory support in the first 24 hours of treatment.



Oxygen and Ventilatory support in the first 24 hours by the ER presentation intended as the highest between Low flow oxygen nasal cannula (≤5 L/min of Oxygen), Venturi mask (FiO_2 ranging from 31 to 60%), Non-rebreather mask (reservoir) 15L/min of Oxygen, Continuous Positive Airway Pressure (CPAP), Noninvasive ventilation (NIV).

Supplementary Digital Material

Download supplementary material file: Panminerva Med-4063_Supplementary Digital Material1_V1_2020-07-23.docx

Supplementary Digital Material

Download supplementary material file: Panminerva Med-4063_Supplementary Digital Material2_V1_2020-07-23.docx

Supplementary Digital Material

Download supplementary material file: Panminerva Med-4063_Supplementary Digital Material3_V1_2020-07-23.pdf

Supplementary Digital Material

Download supplementary material file: Panminerva Med-4063_Supplementary Digital Material4_V1_2020-10-10.pdf

Supplementary Digital Material

Download supplementary material file: Panminerva Med-4063_Supplementary Digital Material5_V1_2020-10-10.pdf

Supplementary Digital Material

Download supplementary material file: Panminerva Med-4063_Supplementary Digital Material6_V1_2020-10-10.pdf

Supplementary Digital Material

Download supplementary material file: Panminerva Med-4063_Supplementary Digital Material7_V1_2020-10-10.pdf