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Severity of respiratory failure at admission and in-hospital mortality in patients with COVID-19: a prospective observational multicentre study

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ABSTRACT

Objectives COVID-19 causes lung parenchymal and endothelial damage that lead to hypoxic acute respiratory failure (hARF). The influence of hARF severity on patients' outcomes is still poorly understood.

Design Observational, prospective, multicentre study.

Setting Three academic hospitals in Milan (Italy) involving three respiratory high dependency units and three general wards.

Participants Consecutive adult hospitalised patients with a virologically confirmed diagnosis of COVID-19. Patients aged <18 years or unable to provide informed consent were excluded.

Interventions Anthropometrical, clinical characteristics and blood biomarkers were assessed within the first 24 hours from admission. hARF was graded as follows: severe (partial pressure of oxygen to fraction of inspired oxygen ratio (PaO2/FiO2) <100 mm Hg); moderate (PaO2/FiO2 101–200 mm Hg); mild (PaO2/FiO2 201–300 mm Hg) and normal (PaO2/FiO2 >300 mm Hg).

Primary and secondary outcome measures The primary outcome was the assessment of clinical characteristics and in-hospital mortality based on the severity of respiratory failure. Secondary outcomes were intubation rate and application of continuous positive airway pressure during hospital stay.

Results 412 patients were enrolled (280 males, 68%). Median (IQR) age was 66 (55–76) years with a PaO2/FiO2 at admission of 262 (140–343) mm Hg. 50.2% had a cardiovascular disease. Prevalence of mild, moderate and severe hARF was 24.4%, 21.9% and 15.5%, respectively. In-hospital mortality proportionally increased with increasing impairment of gas exchange (p<0.001). The only independent risk factors for mortality were age ≥65 years (HR 3.41; 95% CI 2.00 to 5.78, p<0.0001), PaO2/FiO2 ratio ≤200 mm Hg (HR 3.57; 95% CI 2.20 to 5.77, p<0.0001) and respiratory failure at admission (HR 3.58; 95% CI 1.05 to 12.18, p=0.04).

Conclusions A moderate-to-severe impairment in PaO2/FiO2 was independently associated with a threefold increase in risk of in-hospital mortality. Severity of respiratory failure is useful to identify patients at higher risk of mortality.

Strengths and limitations of this study

- This was a multicentre, prospective study.
- The study has enrolled a conspicuous number of well-characterised patients hospitalised with COVID-19 pneumonia.
- A selection bias may be due to the high number of severe patients due to the hub characteristics of the participating centres.
- Not all patients were evaluated in room air conditions at admittance, thus potentially underestimating the severity of the study sample.

Trial registration number NCT04307459

INTRODUCTION

SARS-CoV-2 and the related COVID-19 has caused a pandemic and ~860 000 deaths worldwide.[1] The clinical spectrum can range from mild symptoms (eg, fever and malaise) to severe hypoxic respiratory failure, sepsis, multiorgan involvement and death. The infection appears to induce an inflammatory reaction with pulmonary infiltrates generating hypoxaemia secondary to intraparenchymal shunt and ventilation/perfusion mismatch, favoured by endothelial damage and dysfunction, and altered regulation of perfusion and associated with macroembolism and/or microembolism.[2 3] So far, risk factors such as older age,[4–6] severity of clinical presentation,[4–7] increased D-dimer values,[4] cardiovascular disease (CVD)[4 5] and hypertension[5–8] have been associated with unfavourable outcomes.

It has been proposed that clinical severity of COVID-19 should depend on the presence of any of the following criteria: a partial pressure of oxygen to fraction of inspired oxygen

(PaO2/FiO2) ratio <300 mm Hg, a respiratory rate >30 per min and a peripheral oxygen saturation (SpO2) <93%.[4 9–12] Several consensus statements recommend different PaO2 and SpO2 thresholds to prescribe continuous positive airway pressure (CPAP),[13–15] non-invasive ventilation or intubation.[16] Data on the association between severity of respiratory failure at admission and patients' outcomes are still limited.

The aim of the present study was to assess the clinical characteristics of patients with COVID-19 based on the severity of respiratory failure, and to explore the relationship between the degree of gas exchange impairment and clinical outcomes (CPAP initiation and mortality).

METHODS

An observational, prospective, multicentre study was conducted in three academic hospitals in Milan (Italy) from 7 March to 7 May 2020, involving three respiratory high dependency units and three general wards. A detailed list of participating centres is reported in the online supplemental file. The authors received no specific funding for this work.

Patient and public involvement

Participants were not involved in the design and conduct of the research, interpretation of results and writing of the manuscript. The results of the study will be shared with local patients' organisations by social media and summary reports on organisations' websites.

Patients

Adult hospitalised patients with a virologically confirmed diagnosis of SARS-CoV-2 infection were considered eligible for study enrolment. Patients aged <18 years or unable to provide informed consent were excluded from the study. Hospitalisation criteria are reported in the online supplemental file.

Procedures

Anthropometrical and clinical characteristics were collected at admission. The PaO2/FiO2 ratio was calculated from the first available arterial blood gas analysis performed in the emergency department. PaO2/FiO2 thresholds to grade severity of respiratory failure were taken from the acute respiratory distress syndrome (ARDS) Berlin definition, and were[17]: normal (PaO2/FiO2 >300 mm Hg); mild (PaO2/FiO2 201–300 mm Hg); moderate (PaO2/FiO2 101–200 mm Hg); severe (PaO2/FiO2 ≤100 mm Hg). Blood count and biochemistry parameters were assessed during the first 24 hours after hospital admission.

Outcomes

The primary outcome was the description of patients' clinical characteristics at admission and the assessment of in-hospital mortality based on the severity of respiratory failure.

Secondary outcomes were the assessment of intubation rate and application of CPAP during the hospital stay.

Study definitions

SARS-CoV-2 infection and co-infections

The COVID-19 diagnosis was based on a positive nasopharyngeal swab collected in the emergency department. *SARS-CoV-2* infection was proved by means of reverse transcriptase PCR (RT-PCR). In case a first swab was negative, and the clinical picture was highly suggestive for COVID-19, the swab was repeated. Co-infection with *influenza virus* A and B, *adenovirus*, *human rhinovirus*, *respiratory syncytial virus*, *human metapneumovirus* were also investigated and analysed by means of RT-PCR or rapid influenza diagnostic tests.[18] Microbiological testing for bacteria and fungi in blood, upper and lower airway tract, sputum and urinary antigens for *Streptococcus pneumoniae* and *Legionella pneumophila* were performed according to standard operating protocols.

Management of respiratory failure

Helmet CPAP was the only non-invasive respiratory support used in patients with confirmed or suspected COVID-19 pneumonia not responsive to oxygen masks in order to reduce the viral exposure of the healthcare workers in rooms without negative pressure.[19] Patients with a PaO2/FiO2 ratio <300 mm Hg in room air were administered oxygen with nasal cannulae to reach a SpO2 of 94% or PaO2 >60 mm Hg; in case of unsuccessful intervention within 30 min, patients were put on reservoir masks with 90%–100% FiO2 or helmet CPAP was initiated with positive end expiratory pressure (PEEP) up to 12 cmH_2O based on the respiratory distress and comorbidities following standard operating procedures as previously described.[14] CPAP failure after 2 hours with the maximal tolerable PEEP and a FiO2 of 100% was considered in case of: a) persistence of PaO2/FiO2 <300 mm Hg; b) haemodynamic instability (systolic blood pressure <90 mm Hg despite adequate fluid support) or altered consciousness; d) respiratory distress, fatigue and/or a respiratory rate >30 bpm.[20] Patients who fulfilled CPAP failure criteria were evaluated by an ICU physician for potential intubation. A do not intubate (DNI) order was established by the treating attending physician following a multidisciplinary discussion with the unit staff and the ICU and based on patient's age, comorbidities and clinical status.

In-hospital treatment

Unless contraindicated, patients received hydroxychloroquine and lopinavir/ritonavir following local standard and Italian guidelines.[21 22] In patients with severe pneumonia, methylprednisolone was given at a maximal dose of 1 mg/kg according to the American Thoracic Society/Infectious Diseases Society of America (ATS/IDSA) guidelines[23] and local standard operating procedures. Criteria for methylprednisolone initiation included age <80 years, PaO2/FiO2<250 mm Hg, bilateral infiltrates at the chest

X-ray or CT scan, a C reactive protein >100 mg/L and/or a diagnosis of ARDS according to the Berlin definition.[17] Immunomodulation with off-label tocilizumab at a dosage of 8 mg/kg body weight was administered in patients with signs of hyperinflammatory syndrome and elevated interleukin-6.[21] Unless contraindicated, patients received prophylactic low molecular weight heparin (LMWH) or were switched to therapeutic LMWH dosage if already on chronic anticoagulant therapy. Patients with signs of deep vein thrombosis, pulmonary embolism or D-dimer values >5000 received a therapeutic dose of LMWH.

Statistical analysis

Qualitative variables were summarised with absolute and relative (percentage) frequencies. Parametric and non-parametric quantitative variables were described with means (SD) and medians (IQRs), respectively. Fisher's exact and χ^2 tests were used to compare qualitative variables, whereas Student's t-test or Mann-Whitney U test, analysis of variance or Kruskall-Wallis, corrected with Sidak adjustment, were used to compare quantitative variables with normal or non-normal distribution, respectively. Cox proportional hazard regression analysis was performed to assess the relationship between clinical outcomes and independent variables. Kaplan-Meier survival curves were plotted to show differences for the outcome mortality, considering the confounding variables age, respiratory failure, PaO2/FiO2 and antihypertensive treatment; log-rank test was computed to assess the presence of any statistically significant differences. A two-tailed p value <0.05 was considered statistically significant. All statistical computations were performed with the statistical software STATA V.16 (StatsCorp, Texas, USA).

RESULTS

Clinical characteristics of the whole sample size

A total of 412 patients were enrolled (280 males, 68%) (table 1). The median (IQR) age at admission was 66 (55–76) years, and 54.6% of patients were ≥65 years of age; 61.8% of patients had a PaO2/FiO2 <300 mm Hg, with a median (IQR) PaO2/FiO2 of 262 (140–343) mm Hg; 24.4% had mild, 21.9% moderate and 15.5% had severe respiratory failure. CPAP was prescribed in the emergency department in 9.7% of cases, whereas only three patients were immediately intubated. Median (IQR) white blood cell (WBC) count was 6.7 (5.1–9.4) per 10^9/µL, 10.9% had leucopenia and 45.9% had lymphocytopenia. Median (IQR) D-dimer values were 890.5 (470–2157) mg/L fibrinogen-equivalent units (FEU) and 34% had a D-dimer >1000 mg/L FEU (table 1).

Half of the patients (50.2%) showed cardiovascular comorbidities, with hypertension being the most prevalent (38.8%). Diabetes and chronic kidney disease were observed in 16.8% and 13.6% of the cases, respectively. Chronic obstructive pulmonary disease (COPD) and asthma accounted for the 6.1% and 3.2% of the study

Table 1 Characteristics and outcomes of patients at admission

	Patients with COVID-19 (n=412)
Age at admission, years	66 (55–76)
Males, n (%)	280 (68.0)
SARS-COV-2-positive swab, n (%)	412 (100.0)
PaO2/FiO2 at admission, mm Hg	262 (140–343)
PaO2/FiO2 severity, n (%)	
≤100 mm Hg	64 (15.5)
101–200 mm Hg	90 (21.9)
201–300 mm Hg	101 (24.4)
>300, mm Hg	157 (38.2)
Respiratory support at admission, n (%)	
Room air	125 (30.3)
Nasal cannulae	93 (22.6)
Venturi mask	78 (18.9)
Reservoir mask	68 (16.5)
CPAP	40 (9.7)
NIV	5 (1.2)
IMV	3 (0.7)
Blood count and biochemistry	
Haemoglobin, g/L (n=401)	13.4 (12.4–14.6)
Platelets, per 10^9/µL (n=401)	203 (156–270)
Platelets <100 per 10^9/µL, n (%) (n=401)	17 (4.1)
White blood cells, per 10^9/µL (n=401)	6.7 (5.1–9.4)
White blood cells <4.0 per 10^9/µL, n (%) (n=401)	45 (10.9)
Neutrophils, per 10^9/µL (n=401)	5.1 (3.3–8.1)
Neutrophils <1.5 per 10^9/µL, n (%) (n=401)	7 (1.7)
Lymphocytes, per 10^9/µL (n=401)	0.98 (0.67–1.33)
Lymphocytes <1.0 per 10^9/µL, n (%) (n=401)	189 (45.9)
Lymphocytes <0.5 per 10^9/µL, n (%) (n=401)	44 (10.7)
Blood urea nitrogen, mg/dL (n=372)	37.5 (27–56)
Creatinine, mg/dL (n=401)	0.93 (0.75–1.19)

Continued

Table 1 Continued

	Patients with COVID-19 (n=412)
Creatinine >1.2 mg/dL, n (%) (n=401)	95 (23.1)
D-dimer, mg/L FEU (n=400)	890.5 (470–2157)
D-dimer ≥1000 mg/L FEU, n (%) (n=195)	140 (34.0)
Troponin T, ng/L (n=125)	13 (7.0–22.4)
C reactive protein, mg/L (n=400)	84.6 (36.2–158.0)
Albumin, g/L (n=151)	28 (23–35)
Interleukin-6 pg/mL (n=83)	86 (31–693)
Ferritin, µg/L (n=145)	1063 (408–2145)
Comorbidities	
Cardiovascular diseases	
Any cardiovascular disease*, n (%)	207 (50.2)
Hypertension, n (%)	160 (38.8)
Arrhythmia, n (%)	49 (11.9)
Ischaemic heart disease, n (%)	43 (10.4)
Vasculopathy, n (%)	32 (7.8)
Heart failure, n (%)	17 (4.1)
Valvulopathy, n (%)	15 (3.6)
Other	
Diabetes mellitus, n (%)	69 (16.8)
Endocrinology disease, n (%)	57 (13.9)
Neurological disease, n (%)	49 (11.9)
Immune depression, n (%)	39 (9.5)
Hypothyroidism, n (%)	32 (7.8)
Kidney disease, n (%)	31 (7.5)
Orthopaedic disease, n (%)	31 (7.5)
Gastrointestinal disease, n (%)	28 (6.8)
Severe obesity, n (%)	26 (6.3)
COPD, n (%)	25 (6.1)
CKD, n (%)	25 (6.1)
BPH, n (%)	25 (6.1)
Active solid cancer, n (%)	20 (4.9)
Previous cancer, n (%)	18 (4.4)
Stroke, n (%)	17 (4.1)
Other neurological disease, n (%)	14 (3.4)
Asthma, n (%)	13 (3.2)
Chronic treatments	
ACEi at admission, n (%)	59 (14.3)
ACEi name, n (%)	34 (56.7)
	16 (26.7)
	3 (5.0)
	3 (5.0)
	2 (3.3)
	1 (1.7)
	1 (1.7)
ARBs, n (%)	61 (14.8)
ARB name, n (%)	25 (39.7)
	11 (17.5)
	11 (17.5)
	10 (15.9)
	6 (9.5)
ACEi or ARBs, n (%)	119 (28.9)
In-hospital treatments	
Hydroxychloroquine, n (%)	336 (81.6)
Lopinavir/Ritonavir, n (%)	242 (58.7)
Corticosteroids, n (%)	105 (25.5)
LMWH, n (%)	249 (60.4)
Tocilizumab, n (%)	88 (21.6)
Experimental drugs, n (%)†	3 (0.7)
Outcomes	
CPAP during hospitalisation, n (%)	176 (42.7)
CPAP max PEEP	10 (10.0–12.5)
Discharge at home, n (%)	180 (43.7)
Discharge to other facility, n (%)	41 (10.0)
In-hospital mortality, n (%)	105 (25.5)
Intubation, n (%)	36 (8.7)
Still hospitalised, n (%)	50 (12.1)

Demographic, clinical characteristics, respiratory failure parameters at admission and clinical outcomes in 412 patients hospitalised with COVID-19 pneumonia. Data are expressed as frequencies or medians (IQR). Comorbidities with ≥3% prevalence were reported. A complete list of comorbidities is reported in table 1 of the online supplemental file. Missing values, if present, are reported next to each variable.
*At least one of the following: hypertension, arrhythmia, ischaemic heart disease, vasculopathy, heart failure, valvulopathy.
†Remdesivir.
ACEi, ACE inhibitor; ARB, angiotensin receptor blocker; BPH, benign prostatic hyperplasia; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; CPAP, continuous positive airway pressure; FEU, fibrinogen-equivalent unit; IMV, invasive mechanical ventilation; LMWH, low molecular weight heparin; NIV, non-invasive ventilation; PaO2/FiO2, partial pressure of oxygen to fraction of inspired oxygen ratio; PEEP, positive end expiratory pressure.

Table 2 Patients' characteristics and outcomes depending on the severity of respiratory failure

Variables	Severe (PaO2/FiO2 ≤100 mm Hg (n=63)	Moderate (PaO2/FiO2 101–200 mm Hg (n=89)	Mild (PaO2/FiO2 201–300 mm Hg (n=99)	Normal (PaO2/FiO2 >300 mm Hg (n=155)	P value
Age at admission, years	75 (64–81)	72 (63–81)	67 (57–76)	58 (48–70)	0.0001†
Males, n (%)	51 (81.0)	67 (75.3)	65 (65.7)	95 (61.3)	0.02‡
Respiratory support at admission, n (%)					
Room air	1 (1.6)	5 (5.6)	23 (23.2)	93 (60.0)	<0.0001§
Nasal cannulae	11 (17.5)	14 (15.7)	32 (32.3)	35 (22.6)	0.03¶
Venturi mask	6 (9.5)	27 (30.3)	23 (23.2)	20 (12.9)	0.001**
Reservoir mask	29 (46.0)	31 (34.8)	5 (5.1)	3 (1.9)	<0.0001††
CPAP	14 (22.2)	9 (10.1)	13 (13.1)	4 (2.6)	<0.0001‡‡
NIV	1 (1.6)	2 (2.3)	2 (2.0)	0 (0.0)	0.16
IMV	1 (1.6)	1 (1.1)	1 (1.0)	0 (0.0)	0.26
Blood count					
Haemoglobin, g/L	13.4 (12.5–14.5)	12.9 (11.8–14.6)	13.4 (12.5–14.7)	13.7 (12.7–14.8)	0.05
Platelets, per 10^9/µL	206 (151–286)	225 (160–292)	205.5 (161–264)	192 (152–247)	0.12
White blood cells, per 10^9/µL	8.3 (6.2–12.2)	8.1 (6.0–11.0)	6.5 (5.1–9.0)	5.9 (4.8–7.7)	0.0001§§
Neutrophils, per 10^9/µL	6.9 (5.0–10.7)	7.0 (4.5–10.0)	4.9 (3.2–7.3)	4.0 (3.0–5.6)	0.0001¶¶
Lymphocytes, per 10^9/µL	0.74 (0.57–0.99)	0.84 (0.62–1.14)	1.07 (0.65–1.37)	1.13 (0.84–1.50)	0.0001***
Blood urea nitrogen, mg/dL	55 (39–74)	49 (34–78)	37 (29–52)	29 (23–39)	0.0001†††
Creatinine, mg/dL	0.91 (0.8–1.3)	1.04 (0.76–1.39)	0.92 (0.74–1.15)	0.89 (0.72–1.05)	0.007‡‡‡
D-dimer, mg/L FEU	1990 (701–6210)	1355 (814–4025)	971 (556–1830)	579 (336–953)	0.0001§§§
Troponin T, ng/L	20 (15–44)	15.5 (9.0–31.5)	14 (9–18)	8 (6–12)	0.0001¶¶¶
C reactive protein, mg/L	153 (86–219)	119 (59–198)	94.2 (40.5–148)	44.2 (20–89.7)	0.0001****
Albumin, g/L	24 (20–37)	27 (22–59)	27 (23–34)	31 (27–34)	0.004††††
Interleukin-6, pg/mL	167 (44–968)	309 (42–1113)	64 (27–496)	47 (23–183)	0.003‡‡‡‡
Ferritin, µg/L	1271 (499–2653)	958 (423–2184)	1513.5 (817–2824)	775 (238–1484)	0.06
Comorbidities					
Cardiovascular diseases					
Cardiovascular disease*, n (%)	38 (60.3)	59 (66.3)	56 (56.6)	51 (32.9)	<0.0001§§§§
Hypertension, n (%)	30 (47.6)	42 (47.2)	47 (47.5)	39 (25.2)	<0.0001¶¶¶¶
Ischaemic heart disease, n (%)	8 (12.7)	14 (15.7)	11 (11.1)	8 (5.2)	0.05
Arrythmia, n (%)	8 (12.7)	16 (18.0)	9 (9.1)	14 (9.0)	0.16
Vasculopathy, n (%)	8 (12.7)	8 (9.0)	9 (9.1)	7 (4.5)	0.19
Valvulopathy, n (%)	2 (3.2)	5 (5.6)	3 (3.0)	4 (2.6)	0.67
Heart failure, n (%)	3 (4.8)	7 (7.9)	4 (4.0)	2 (1.3)	0.07
Other					
Diabetes mellitus, n (%)	9 (14.3)	21 (23.6)	20 (20.0)	18 (11.6)	0.07
Endocrinology disease, n (%)	7 (11.1)	17 (19.1)	13 (13.1)	18 (11.7)	0.37
Neurological disease, n (%)	8 (12.7)	16 (18.0)	13 (13.1)	12 (7.7)	0.12
Immune depression, n (%)	3 (4.8)	12 (13.5)	11 (11.1)	12 (7.7)	0.24
Hypothyroidism, n (%)	2 (3.2)	9 (10.1)	9 (9.1)	10 (6.5)	0.35
Kidney disease, n (%)	5 (7.9)	8 (9.0)	7 (7.1)	8 (5.2)	0.70
Orthopaedic disease, n (%)	3 (4.8)	7 (7.9)	8 (8.1)	13 (8.4)	0.86
Gastrointestinal disease, n (%)	6 (9.5)	8 (9.0)	4 (4.0)	10 (6.5)	0.42

Continued

Table 2 Continued

Variables	Severe (PaO2/FiO2 ≤100 mm Hg (n=63)	Moderate (PaO2/FiO2 101–200 mm Hg (n=89)	Mild (PaO2/FiO2 201–300 mm Hg (n=99)	Normal (PaO2/FiO2 >300 mm Hg (n=155)	P value
Severe obesity, n (%)	6 (9.5)	12 (13.5)	1 (1.0)	7 (4.5)	0.002*****
COPD, n (%)	7 (11.1)	9 (10.1)	4 (4.0)	5 (3.2)	0.04†††††
CKD, n (%)	3 (4.8)	9 (10.1)	5 (5.1)	6 (3.9)	0.26
BPH, n (%)	7 (11.1)	9 (10.1)	4 (4.0)	5 (3.2)	0.04‡‡‡‡‡
Active solid cancer, n (%)	2 (3.2)	7 (7.9)	4 (4.0)	7 (4.5)	0.59
Previous cancer, n (%)	4 (6.4)	4 (4.5)	2 (2.0)	8 (5.2)	0.52
Stroke, n (%)	3 (4.8)	6 (6.7)	4 (4.0)	4 (2.6)	0.44
Other neurological disease, n (%)	4 (6.4)	5 (5.6)	4 (4.0)	1 (0.7)	0.03§§§§§
Asthma, n (%)	1 (1.6)	3 (3.4)	4 (4.0)	5 (3.2)	0.90
Chronic treatments					
ACEi at admission, n (%)	12 (19.1)	13 (14.6)	24 (24.2)	9 (5.8)	<0.0001¶¶¶¶¶
ACEi name, n (%)					
Ramipril	6 (50.0)	9 (64.3)	13 (54.2)	5 (55.6)	0.90
Enalapril	2 (16.7)	3 (21.4)	8 (33.3)	3 (33.3)	0.71
Lisinopril	1 (8.3)	1 (7.1)	1 (4.2)	0 (0.0)	–
Perindopril	1 (8.3)	1 (7.1)	0 (0.0)	1 (11.1)	
Zofenpril	1 (8.3)	0 (0.0)	1 (4.2)	0 (0.0)	
Captopril	1 (8.3)	0 (0.0)	0 (0.0)	0 (0.0)	
Zanipril	0 (0.0)	0 (0.0)	1 (4.2)	0 (0.0)	
ARBs, n (%)	9 (14.3)	16 (18.0)	10 (10.1)	26 (16.8)	0.41
ARB name, n (%)					
Olmesartan	6 (66.7)	6 (35.3)	2 (20.0)	11 (40.7)	0.23
Telmisartan	1 (11.1)	3 (17.7)	3 (30.0)	4 (14.8)	0.71
Valsartan	1 (11.1)	4 (23.5)	1 (10.0)	5 (18.5)	0.84
Irbesartan	0 (0.0)	3 (17.7)	3 (30.0)	4 (14.8)	–
Losartan	1 (1.1)	1 (5.9)	1 (10.0)	3 (11.1)	
ACEi or ARBs, n (%)	21 (33.3)	29 (32.6)	34 (34.3)	34 (21.9)	0.10
In-hospital treatments					
Lopinavir/Ritonavir, n (%)	40 (63.5)	50 (56.2)	64 (64.6)	87 (56.1)	0.45
Hydroxychloroquine, n (%)	51 (81.0)	74 (83.2)	89 (89.9)	120 (77.4)	0.09
Corticosteroids, n (%)	26 (41.3)	37 (41.6)	24 (24.2)	18 (11.6)	<0.0001******
Tocilizumab, n (%)	17 (27.0)	21 (23.6)	27 (27.3)	22 (14.2)	0.03††††††
LMWH, n (%)	48 (76.2)	66 (74.2)	62 (62.6)	73 (47.1)	<0.0001‡‡‡‡‡‡
Experimental drugs, n (%)	1 (1.6)	0 (0.0)	0 (0.0)	2 (1.3)	0.74
Outcomes					
CPAP during hospitalisation, n (%)	45 (71.4)	50 (56.2)	49 (49.5)	32 (20.7)	<0.0001§§§§§§
Median (IQR) CPAP max PEEP	12 (10–14)	10 (10.0–12.3)	10 (10.0–12.5)	10 (10.0–12.5)	0.02¶¶¶¶¶¶
Intubation, n (%)	11 (17.5)	5 (5.6)	9 (9.1)	11 (7.1)	0.06
In-hospital mortality, n (%)	35 (55.6)	43 (48.3)	16 (16.2)	10 (6.5)	<0.0001*******
Days from admission to death	15 (6–37)	25 (7–34)	35 (24–41)	36 (30–41)	0.0001†††††††

Continued

Table 2 Continued

Variables	Severe (PaO2/FiO2 ≤100 mm Hg (n=63)	Moderate (PaO2/FiO2 101–200 mm Hg (n=89)	Mild (PaO2/FiO2 201–300 mm Hg (n=99)	Normal (PaO2/FiO2 >300 mm Hg (n=155)	P value

Data are expressed as frequencies or medians (IQR). Comorbidities with ≥3% prevalence were reported. A complete list of comorbidities is reported in table 1 of the online supplemental file.
*At least one of the following: hypertension, arrhythmia, ischaemic heart disease, vasculopathy, heart failure, valvulopathy.
†Severe vs Mild p=0.02; Severe vs Normal p<0.0001; Moderate vs Normal p<0.0001; Mild vs Normal p<0.0001.
‡Severe vs Mild p=0.04; Severe vs Normal p=0.005; Moderate vs Normal p=0.03.
§Severe vs Mild p=0.0002; Severe vs Normal p<0.0001; Moderate vs Mild p=0.0007; Moderate vs Normal p<0.0001; Mild vs Normal p<0.0001.
¶Severe vs Mild p=0.04; Moderate vs Mild p=0.008.
**Severe vs Moderate p=0.002; Severe vs Mild p=0.03; Moderate vs Normal p=0.0009; Mild vs Normal p=0.03.
††Severe vs Mild p<0.0001; Severe vs Normal p<0.0001; Moderate vs Mild p<0.0001; Moderate vs Normal p<0.0001.
‡‡Severe vs Moderate p=0.04; Severe vs Normal p<0.0001; Moderate vs Normal p=0.01; Mild vs Normal p=0.001.
§§Severe vs Mild p=0.03; Severe vs Normal p<0.0001; Moderate vs Normal p<0.0001.
¶¶Severe vs Mild p=0.008; Severe vs Normal p<0.0001; Moderate vs: Mild p=0.01; Moderate vs Normal p<0.0001; Mild vs Normal p=0.02.
***Severe vs Mild p=0.01; Severe vs Normal p<0.0001; Moderate vs Normal p=0.0006.
†††Severe vs Mild p=0.002; Severe vs Normal p-value<0.0001; Moderate vs: Mild p=0.02; Moderate vs Normal p<0.0001; Mild vs Normal p=0.0006.
‡‡‡Moderate vs Normal p=0.004.
§§§Severe vs Mild p=0.02; Severe vs Normal p<0.0001; Moderate vs: Mild p=0.02; Moderate vs Normal p<0.0001; Mild vs Normal p=0.003.
¶¶¶Severe vs Normal p<0.0001; Moderate vs: Normal p=0.001; Mild vs Normal p=0.01.
****Severe vs Mild p=0.003; Severe vs Normal p<0.0001; Moderate vs Normal p<0.0001; Mild vs Normal p=0.0002.
††††Severe vs Normal p=0.002.
‡‡‡‡Severe vs Normal p=0.02; Moderate vs: Normal p=0.004.
§§§§Severe vs Normal p=0.0002; Moderate vs Normal p<0.0001; Mild vs Normal p=0.0002.
¶¶¶¶Severe vs Normal p=0.001; Moderate vs Normal p=0.0004; Mild vs Normal p=0.0003.
*****Severe vs Moderate p=0.009; Moderate vs Mild p=0.0007; Moderate vs Normal p=0.01; Mild vs Normal p=0.01.
†††††Severe vs Normal p=0.02; Moderate vs Normal p=0.03.
‡‡‡‡‡Severe vs Normal p=0.02; Moderate vs Normal p=0.03.
§§§§§NA.
¶¶¶¶¶Severe vs Normal p=0.003; Moderate vs Normal p=0.02; Mild vs Normal p<0.0001.
******Severe vs Mild p=0.02; Severe vs Normal p<0.0001; Moderate vs Mild p=0.01; Mild vs Normal p=0.008.
††††††Severe vs Normal p=0.03; Mild vs Normal p=0.01.
‡‡‡‡‡‡Severe vs Normal p<0.0001; Moderate vs Mild p=0.02; Moderate vs Normal p<0.0001; Mild vs Normal p<0.0001.
§§§§§§Severe vs Mild p=0.006; Severe vs Normal p<0.0001; Moderate vs Normal p<0.0001; Mild vs Normal p<0.0001.
¶¶¶¶¶¶Severe vs Moderate p=0.005.
*******Severe vs Mild p<0.0001; Severe vs Normal p<0.0001; Moderate vs Mild p<0.0001; Moderate vs Normal p<0.0001; Mild vs Normal p=0.01.
†††††††Severe vs Mild p<0.0001; Severe vs Normal p<0.0001; Moderate vs Normal p<0.0001.
ACEi, ACE inhibitor; ARB, angiotensin receptor blocker; BPH, benign prostate hypertrophy; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; CPAP, continuous positive airway pressure ; FEU, fibrinogen-equivalent units; IMV, invasive mechanical ventilation; LMWH, low molecular weight heparin ; NIV, non-invasive ventilation; PEEP, positive end expiratory pressure; P/F, partial pressure of oxygen to fraction of inspired oxygen ratio (PaO2/FiO2).

sample. A complete list of observed comorbidities is reported in table 1 of the online supplemental file.

The most frequently administered therapy was hydroxychloroquine (81.6%), whereas corticosteroids and tocilizumab were prescribed in 25.5% and 21.6% of the patients, respectively.

During the hospital stay, 42.7% were exposed to CPAP, 8.7% underwent mechanical ventilation and were transferred to the ICU.

Characteristics based on severity of respiratory failure

The cohort was divided in four groups based on the severity of respiratory failure (table 2). Advanced age and male were more prevalent in patients with severe respiratory failure (p=0.0001 and 0.02, respectively).

WBC, neutrophils, C reactive protein and D-dimer values were higher in severe cases (all p=0.0001). Impaired gas exchange was associated with a decreased lymphocyte counts, ranging from a median (IQR) value of 1.13 (0.84–1.50) per 10^9/µL in patients with PaO2/FiO2 >300 mm Hg to 0.74 (0.57–0.99) per 10^9/µL in patients with severe respiratory failure (p=0.0001).

The proportion of patients with cardiovascular comorbidities and hypertension was significantly higher in patients with a respiratory failure if compared with that of patients with a PaO2/FiO2 >300 mm Hg (p<0.0001). Obesity was more prevalent in patients with moderate and severe respiratory failure if compared with obesity prevalence in patients with PaO2/FiO2 ≥201 mm Hg (23% vs 5.5%; p=0.002); similar differences were found for COPD (22.2% vs 7.2%; p=0.04). Chronic use of ACEi was more prevalent in patients with respiratory failure (p<0.0001).

The highest proportion of intubated patients was in the severe group (17.5%) (table 2).

Impact of cardiovascular diseases and renin-angiotensin-aldosterone system inhibitors

Overall, chronic therapy with ACEi was associated with worse PaO2/FiO2 at admission (median value 223.5 vs 273.0; p=0.004) (table 2 of the online supplemental file) and higher in-hospital mortality (35.6% vs 23.5%; p=0.048) (table 2 of the online supplemental file and figure 1). Severity of respiratory failure at admission, intubation and mortality rates were not associated with

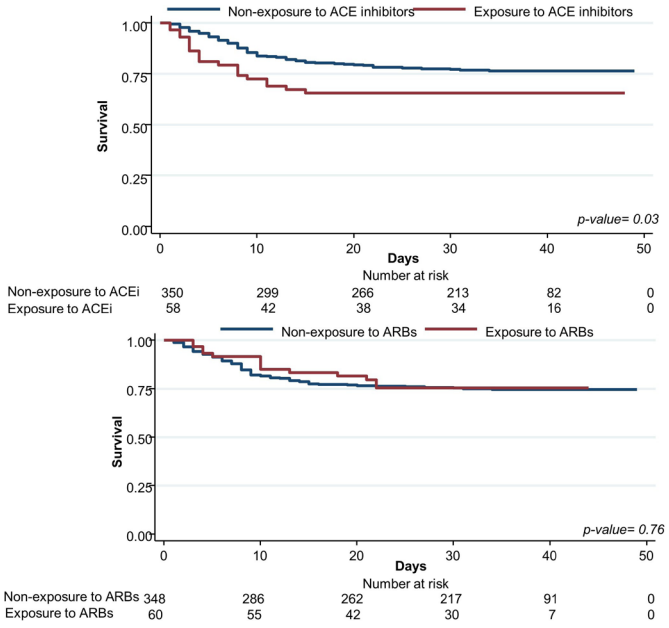

Figure 1 Survival curves based on ACE inhibitors (ACEi) or angiotensin receptor blockers (ARBs) exposure. Survival in patients hospitalised with COVID-19 pneumonia (n=412) based on the chronic exposure to ACEi (upper panel) or ARBs (lower panel).

ARBs therapy (table 3 of the online supplemental file and figure 1).

Patients with CVD or hypertension had significantly lower PaO2/FiO2 at admission (both p<0.0001), a higher proportion of respiratory failure (both p<0.0001) and an increased need for CPAP during the hospital stay (p=0.02 and 0.003, respectively) (table 4 of the online supplemental file and table 3).

In-hospital mortality and respiratory failure

In-hospital mortality was 25.5%. It proportionally increased with lower PaO2/FiO2 values, being highest in the severe group (55.6%) and lowest in patients with PaO2/FiO2 >300 mm Hg (6.5%; p<0.0001). The number of days from admission to death was lowest in the severe group and highest in patients with normal PaO2/FiO2 at admission (p=0.0001) (table 2). Age >65 years, male sex, exposure to ACEi, having a CVD, presence of respiratory failure at admission, a PaO2/FiO2 ≤200 mm Hg and need for CPAP at admission were significantly associated with an increased mortality at the univariate analysis (table 4); however, the multivariate analysis showed that the only independent risk factors were age >65 years (HR 3.41; 95% CI 2.00 to 5.78, p<0.0001), a PaO2/FiO2 ≤200 mm Hg (HR 3.57; 95% CI 2.20 to 5.77, p<0.0001) and the presence of respiratory failure at admission (HR 3.58; 95% CI 1.05 to 12.18, p=0.04) (figure 2). Fifteen days postadmission, patients with moderate-to severe respiratory failure had a survival rate of 56% (figure 2).

Table 3 Respiratory failure and outcomes in patients with cardiovascular disease, depending on ACEi and ARBs exposure

	Patients with COVID-19 (n=412)			CVD yes (n=207)				
	CVD no (n=205)	CVD yes (n=207)	P value	ACEi no (n=154)	ACEi yes (n=53)	P value	ARBs no (n=147)	ARBs yes (n=60)	P value
PaO2/FiO2 at admission	307.5 (180–381)	206.5 (123–305)	<0.0001	203 (127–319)	228 (113–290)	0.62	201.5 (118.0–285.5)	285.5 (135–343)	0.01
RF at admission, n (%)	125 (61.0)	174 (84.1)	<0.0001	129 (83.8)	45 (84.9)	0.85	128 (87.1)	46 (76.7)	0.06
CPAP at admission, n (%)	16 (7.8)	24 (11.6)	0.19	20 (13.0)	4 (7.6)	0.29	17 (11.6)	7 (11.7)	0.98
CPAP in-hospital, n (%)	76 (37.1)	100 (48.3)	0.02	75 (48.7)	25 (47.2)	0.85	71 (48.3)	29 (48.3)	1.00
In-hospital mortality, n (%)	32 (15.6)	72 (34.8)	<0.0001	53 (34.4)	19 (35.9)	0.85	58 (39.5)	14 (23.3)	0.03
Intubation, n (%)	23 (11.2)	13 (6.3)	0.08	9 (5.8)	4 (7.6)	0.74	9 (6.1)	4 (6.7)	1.00

Data are reported as frequencies or medians (IQR).
ACEi, ACE inhibitor; ARB, angiotensin receptor blocker; CPAP, continuous positive airway pressure; CVD, cardiovascular disease; FiO2, fraction of inhaled oxygen; PaO2, arterial partial pressure of oxygen.

Table 4 Risk factors for in-hospital mortality

	Univariate analysis		Multivariate analysis	
	HR (95% CI)	P value	HR (95% CI)	P value
Age >65 years	5.76 (3.46 to 9.60)	<0.0001	3.41 (2.00 to 5.78)	<0.0001
Males	1.58 (1.00 to 2.50)	0.049	1.17 (0.73 to 1.86)	0.52
Exposure to ACE inhibitors	1.68 (1.03 to 2.74)	0.04	1.28 (0.77 to 2.13)	0.34
Exposure to sartan	0.91 (0.52 to 1.61)	0.76		
Exposure to ACE inhibitors or sartan	1.33 (0.88 to 2.02)	0.17		
Cardiovascular disease	2.49 (1.63 to 3.79)	<0.0001	1.37 (0.88 to 2.13)	0.16
PaO2/FiO2 ≤200 mm Hg	6.68 (4.25 to 10.52)	<0.0001	3.57 (2.20 to 5.77)	<0.0001
Presence of hARF at admission	15.08 (4.78 to 47.59)	<0.001	3.58 (1.05 to 12.18)	0.04
CPAP at admission	2.20 (1.32 to 3.67)	0.002	1.62 (0.96 to 2.72)	0.07

Multivariate Cox regression analysis that identifies risk factors for in-hospital mortality. Data are reported as HR and 95% CIs.
ACEi, ACE inhibitor; CPAP, continuous positive airway pressure; FiO2, fraction of inhaled oxygen; PaO2, arterial partial pressure of oxygen.

DISCUSSION

To the best of our knowledge, the results of the present study demonstrated for the first time the independent relationship between impaired gas exchange and clinical outcomes (mortality, intubation and need for respiratory support).

We showed that age >65 years, presence of respiratory failure and a PaO2/FiO2 ≤200 mm Hg at admission were independently associated with a higher mortality rate. In fact, the mortality risk for patient without respiratory failure at admission was of 1% after 15 days from hospital admission. Conversely, survival in patients with a moderate-to-severe respiratory failure (PaO2/FiO2 ≤200 mm Hg) at admission was only 56% at 15 days. The overall mortality rate in our cohort is comparable to previous reports.[5 24] However, it is higher if compared with the mortality described in other observational studies.[25 26] Richardson *et al* reported a prevalence of respiratory failure (SpO2 <90%) of 20.4%,[25] whereas it was 72.6% in our cohort. Cheng *et al* reported an in-hospital mortality as low as 11% in Wuhan, China. However, 58% of enrolled patients were not discharged from hospital at the time of the report,[26] whereas only 12% of our cohort was hospitalised at the time of writing.

Hypoxaemia has been rarely considered as a risk factor for patients with COVID-19. Xie *et al* showed that patients with SpO2 <90% had 47 times more probability to die when compared with patients with SpO2 >90%.[27] However, in patients with COVID-19-associated pneumonia, low PaO2 values can be associated with satisfactory SpO2, hiding hypoxia, which might lead to an underestimation of the severity of the disease and in a treatment delay.[28] On this basis, clinicians should not rely solely on SpO2 values, especially when evaluating patients in which symptoms had lasted for 10–12 days before their presentation to the emergency department.[29] The ratio between PaO2 and FiO2 has been demonstrated to be a reliable tool to assess severity and stratify mortality risk.[17] When compared with the ARDS Berlin's definition, our respiratory failure classes had a slightly higher mortality with PaO2/FiO2 <200 mm Hg (severe 55% vs 45% and moderate 48% vs 35%). This should probably depend on the cohort heterogeneity and in, in our case, the absence of 5 cmH_2O of PEEP used in the Berlin definition to grade severity of ARDS. Another issue is the low number of patients with severe respiratory failure at admission who underwent intubation (n=11). This finding can be justified by the higher chance of DNI orders in patients with severe respiratory failure, secondary to the median age and to the higher prevalence of CVD.[5] However, the absence of respiratory failure at admission or a mild hypoxia did not preclude the chance of in-hospital death or intubation. Sign of respiratory distress and worsening gas exchange should be closely monitored, as a sudden and rapidly evolving disease can involve patients in stable conditions.[29 30]

CVD and hypertension are the most frequently observed comorbidities in patients with COVID-19 and are associated with severe disease.[31 32] A debate was focused on the negative effects of ACEi and ARBs due to the role of the ACE2 receptor in viral-host dynamics.[32] However, several studies ruled out the increased risk of COVID-19 infection and the link between disease severity and antihypertensive treatment.[28 31 33] Our cohort was characterised by a high prevalence of CVD (50.2%), which was associated with a significantly higher mortality compared with patients without CVD. However, mortality did not change in patients chronically exposed to ACEi and ARBs. ACEi was associated with a significantly higher mortality, potentially explained by the higher disease severity of at admission of patients taking ACEi. Indeed, neither CVD, nor hypertension, nor the exposure to antihypertensive medications were independently associated with decreased survival.

STUDY LIMITATIONS

The initial gas exchange assessment was not homogeneously conducted in all patients at admission (only 30.3% of patients were in room air conditions). This might have underestimated the severity of respiratory failure, especially in patients

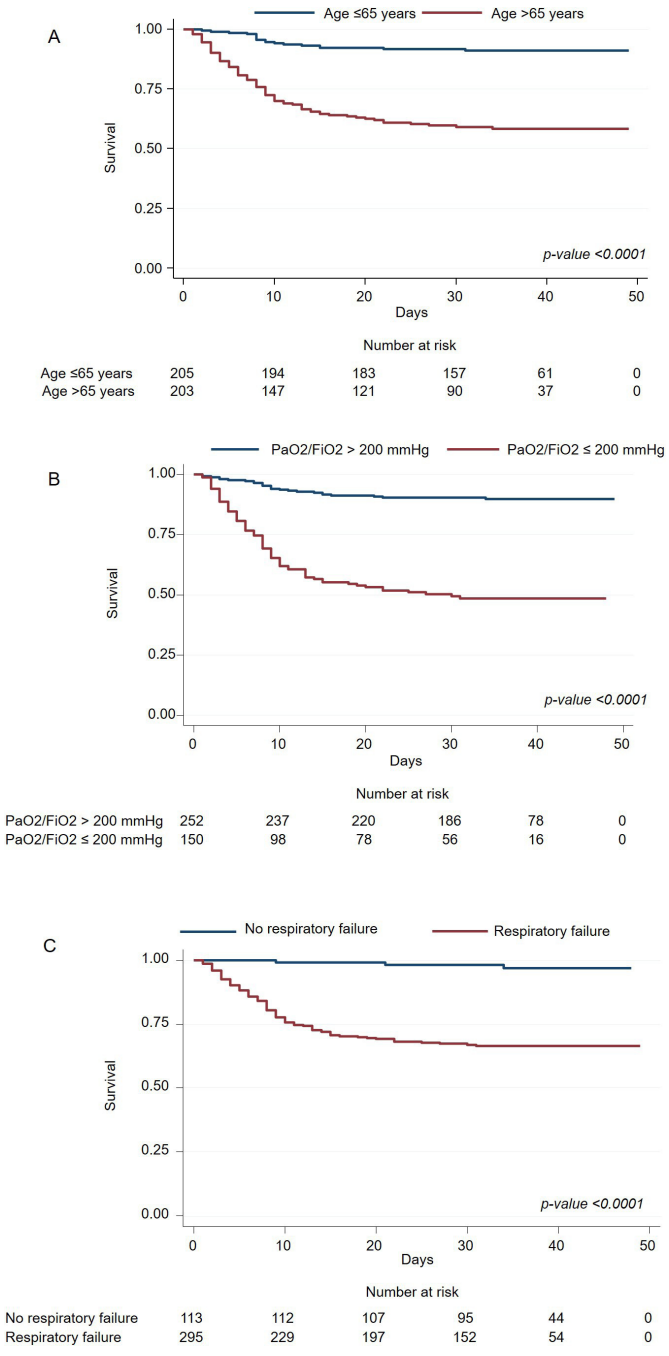

Figure 2 Survival in patients hospitalised for COVID-19 based on age and severity of respiratory failure. HR for survival in patients hospitalised with COVID-19 pneumonia stratified by age (> or ≤ 65 years, panel A), severity of respiratory failure at admission (PaO2/FiO2 ratio ≤200 mm Hg and >200 mm Hg, panel B) and presence of respiratory failure at admission (panel C). Note that 15 days postadmission, patients with moderate-to-severe respiratory failure had a survival rate of about 56%, while patients without respiratory failure (panel C) had a survival rate of 99%. PaO2/FiO2, partial pressure of oxygen to fraction of inspired oxygen ratio.

treated with CPAP at admission. At the time of writing, 12% of patients were still hospitalised, biasing mortality and length of stay estimates. Furthermore, a selection bias could be hypothesised, being the participating centres hub for severe patients transferred from peripheral hospitals. The local standard operating procedures, criteria for ICU admittance or management with CPAP/NIV implemented in Italy could differ in other settings, limiting the inference of our findings.

CONCLUSIONS

The severity of respiratory failure assessed with the PaO2/FiO2 ratio is significantly associated with intubation rate, need for respiratory support and in-hospital mortality. Age, respiratory failure and PaO2/FiO2 value at admission are independently associated with in-hospital mortality. Although the findings of the present study need to be confirmed in larger cohorts, they suggest that severity of hypoxaemia can be useful to triage patients with COVID-19 pneumonia and identify patients at higher risk of unfavourable outcomes.

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Data availability statement PS and DR had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis and had final responsibility for the decision to submit for publication. The datasets used and analysed during the current study are available from the corresponding author on reasonable request.

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