SUPPLEMENTAL MATERIAL

TITLE: SEVERITY OF RESPIRATORY FAILURE AT ADMISSION AND IN-HOSPITAL MORTALITY IN PATIENTS WITH COVID-19: A PROSPECTIVE OBSERVATIONAL MULTICENTRE STUDY.

Participating centers

1. Division of Respiratory Diseases, Ospedale L. Sacco, ASST Fatebenefratelli-Sacco, Via G.B. Grassi 74 – 20157, Milano, Italy.
2. Department of Medicine and Rehabilitation, Division of Emergency Medicine, Ospedale Fatebenefratelli - ASST Fatebenefratelli-Sacco, Piazzale Principessa Clotilde, 3 - 20121 Milano, Italy.
3. Division of Internal Medicine, Ospedale L. Sacco - ASST Fatebenefratelli-Sacco, Via G.B. Grassi 74 – 20157, Milano, Italy.
4. Department of Health Bioscience, Università degli Studi di Milano—Respiratory Unit, Policlinico di San Donato, IRCCS— Via Rodolfo Morandi, 30 - 20097, San Donato Milanese, Milano, Italy.

The study protocol is available at: ClinicalTrials.gov: NCT04307459

Definition of immunocompromission

Immunocompromission was defined as the presence of ≥1 of the following risk factors:[1]

1. Acquired Immuno-Deficiency Syndrome (AIDS), defined either as human immunodeficiency virus infection with CD4+ lymphocyte count <200/μL or by the occurrence of AIDS-defining conditions;
2. aplastic anemia;
3. asplenia;
4. hematological cancer, defined as lymphoma, acute or chronic leukemia, or multiple myeloma;
5. chemotherapy during the last 3 months;

6. neutropenia, defined as a neutrophil count <500/dL at complete blood cell count;
7. biological drug use (including trastuzumab and therapies for autoimmune diseases, e.g., anti–tumor necrosis factor α, prescribed during ≥6 months before hospital admission);
8. lung transplantation;
9. chronic steroid use (>10 mg/d of prednisone or equivalent ≥3 months before hospital admission);
10. lung cancer with either neutropenia or chemotherapy;
11. other solid tumor with either neutropenia or chemotherapy;
12. other immunocompromise (any immunocompromised state, including congenital/genetic immunocompromised and immunosuppressive therapy due to hematological cancer/solid organ transplantation other than lung).

Criteria for hospitalization

Hospitalization criteria were based on the standard operating procedures created for the management of patients with suspected Covid-19,[2, 3] and on the latest international recommendations.[4, 5] Criteria included any of the following: 1) the presence of respiratory failure at admission (a PaO2 <60 mmHg while breathing room air or a PaO2/FiO2 ratio <300 mmHg); 2) age >65 years old with one or more comorbidities, pulmonary infiltrates at the chest X-ray or Ct scan and respiratory distress (a respiratory rate ≥ 30 breaths/minute and dyspnea); 3) pulmonary infiltrates and persistence of respiratory symptoms (cough, chest tightness, dyspnea at rest or during effort, fever) for more than 10 days; 4) pulmonary infiltrates with evidence of oxygen desaturation (drop in SpO2 of more than 4 units from resting value) while walking for 3 minutes; 5) hemodynamic instability, sepsis or shock; 6) sepsis and septic shock; 7) pulmonary infiltrates associated with confusion or a Glasgow Coma Scale <15; 8) inability to cope with outpatient therapy due to psychosocial or such as inability to maintain oral intake, history of substance abuse, cognitive impairment, severe comorbid illnesses, and impaired functional status.[5]

References

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3. Radovanovic D, Rizzi M, Pini S, et al. Helmet CPAP to Treat Acute Hypoxemic Respiratory Failure in Patients with COVID-19: A Management Strategy Proposal. *J Clin Med* 2020;9:E1191. doi: 10.3390/jcm9041191
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5. Metlay JP, Waterer GW, Long AC, et al. Diagnosis and Treatment of Adults with Community-acquired Pneumonia. An Official Clinical Practice Guideline of the American Thoracic Society and Infectious Diseases Society of America. *Am J Respir Crit Care Med* 2019;200:e45–67. doi: 10.1164/rccm.201908-1581ST.

Supplemental Table 1. Complete list of comorbidities observed in the study sample.

COMORBIDITIES	
Hypertension, n (%)	160 (38.8)
Ischaemic heart disease, n (%)	43 (10.4)
Arrythmia, n (%)	49 (11.9)
Vasculopathy, n (%)	32 (7.8)
Valvulopathy, n (%)	15 (3.6)
Heart failure, n (%)	17 (4.1)
Cardiovascular disease*, n (%)	207 (50.2)
Diabetes mellitus, n (%)	69 (16.8)
Severe obesity, n (%)	26 (6.3)
COPD, n (%)	25 (6.1)
Obstructive sleep apnoea syndrome, n (%)	5 (1.2)
Asthma, n (%)	13 (3.2)
Interstitial lung disease, n (%)	1 (0.2)
Active solid cancer, n (%)	20 (4.9)
Active haematological tumour, n (%)	7 (1.7)
Previous cancer, n (%)	18 (4.4)
Anaemia, n (%)	8 (1.9)
Immune depression, n (%)	39 (9.5)
Psychiatric disease, n (%)	12 (2.9)
Endocrinology disease, n (%)	57 (13.9)
Neurological disease, n (%)	49 (11.9)
Kidney disease, n (%)	31 (7.5)
Gastrointestinal disease, n (%)	28 (6.8)
MRGE, n (%)	12 (2.9)
Rheumatology, n (%)	4 (1.0)
Orthopaedic disease, n (%)	31 (7.5)
BPH, n (%)	25 (6.1)
Infectious, n (%)	7 (1.7)
Eye disease, n (%)	9 (2.2)
ORL, n (%)	4 (1.0)
Haematological disease, n (%)	8 (1.9)
Gynaecological disease, n (%)	9 (2.2)
Depression, n (%)	9 (2.2)
Others psychiatric disease, n (%)	5 (1.2)
Hypothyroidism, n (%)	32 (7.8)
Hyperuricemia, n (%)	4 (1.0)
Osteoporosis, n (%)	7 (1.7)
Others endocrinological disease, n (%)	8 (1.9)
Stroke, n (%)	17 (4.1)
Mental disability, n (%)	5 (1.2)
Alzheimer, n (%)	5 (1.2)
Dementia, n (%)	7 (1.7)

Epilepsy, n (%)	8 (1.9)
Others neurological disease, n (%)	14 (3.4)
CKD, n (%)	25 (6.1)
Kidney stones, n (%)	7 (1.7)
Others renal disease, n (%)	7 (1.7)
Cholecystectomy, n (%)	9 (2.2)
Appendectomy, n (%)	9 (2.2)
Gastric/Duodenal ulcer, n (%)	6 (1.5)
Chronic Hepatitis-C, n (%)	6 (1.5)
Others gastro, n (%)	18 (4.4)
Prosthetics, n (%)	12 (2.9)
Hernia, n (%)	14 (3.4)
Others surgery, n (%)	8 (1.9)
Hysterectomy, n (%)	7 (1.7)
Others gynaecology, n (%)	0 (0.0)

BPH: benign prostate hypertrophy; COPD: chronic obstructive pulmonary disease; CKD: chronic kidney disease; CPAP: continuous positive airway pressure; LMWH: low molecular weight heparin; ORL: otolaryngology.

Supplemental Table 2. Respiratory failure and outcomes in patients exposed and not exposed to angiotensin converting enzyme inhibitors

	Not-exposure to ACE inhibitors (n= 353)	Exposure to ACE inhibitors (n= 59)	p-value
Median (IQR) PaO_2/FiO_2 ratio at admission, mmHg	273 (148.0-346.5)	223.5 (113-290)	0.004
Presence of respiratory failure at admission, n (%)	250 (70.8)	49 (83.1)	0.05
Need for CPAP at admission, n (%)	34 (9.6)	6 (10.2)	0.90
Need for CPAP during the hospital stay, n (%)	148 (41.9)	28 (47.5)	0.43
In-hospital mortality, n (%)	83 (23.5)	21 (35.6)	0.048
Need for intubation, n (%)	31 (8.8)	5 (8.5)	0.94

ACEi: angiotensin converting enzyme inhibitors; PaO_2: arterial partial pressure of oxygen; FiO_2: fraction of inhaled oxygen; CPAP: continuous positive airway pressure.

Supplemental table 3. Respiratory failure severity and outcomes in patients exposed and not exposed to angiotensin receptor blockers

	Non-exposure to ARBs (n = 351)	Exposure to ARBs (n= 61)	p-value
Median (IQR) PaO_2/FiO_2 ratio at admission, mmHg	262 (140-341)	289 (140-343)	0.98
Presence of respiratory failure at admission, n (%)	252 (71.8)	47 (77.1)	0.40
Need for CPAP at admission, n (%)	32 (9.1)	8 (13.1)	0.33
Need for CPAP during the hospital stay, n (%)	146 (41.6)	30 (49.2)	0.27
In-hospital mortality, n (%)	90 (25.6)	14 (23.0)	0.66
Need for intubation, n (%)	32 (9.1)	4 (6.6)	0.63

ARBs: angiotensin receptor blockers; PaO_2: arterial partial pressure of oxygen; FiO_2: fraction of inhaled oxygen; CPAP: continuous positive airway pressure.

Supplemental table 4. Severity of respiratory failure and outcomes in patients with hypertension compared with patients without hypertension.

	Hypertension (n = 160)	**No-hypertension (n= 252)**	**p-value**	**No-hypertension (n= 252)**			
				Without CVD (n=205)	**p-value***	**With CVD (n= 47)**	**p-value***
PaO_2/FiO_2 at admission, mmHg	214.5 (120.0-300.0)	291.5 (153.5-362.0)	<0.0001	307.5 (180-381)	<0.0001	184 (126-310)	0.65
Respiratory failure at admission, n (%)	135 (84.4)	164 (65.1)	<0.0001	125 (61.0)	<0.0001	39 (83.0)	0.82
CPAP at admission, n (%)	18 (11.3)	22 (8.7)	0.40	16 (7.8)	0.26	6 (18.8)	0.78
CPAP in-hospital, n (%)	76 (47.5)	100 (39.7)	0.12	76 (37.1)	0.045	24 (51.2)	0.67
In-hospital mortality, n (%)	53 (33.1)	51 (20.2)	0.003	32 (15.6)	<0.0001	19 (40.4)	0.36
Intubation, n (%)	10 (6.3)	26 (10.3)	0.15	23 (11.2)	0.10	3 (6.4)	0.97

A sensitivity analysis has been performed excluding patients with cardiovascular diseases from patients without hypertension**.** PaO_2: arterial partial pressure of oxygen; FiO_2: fraction of inhaled oxygen; CPAP: continuous positive airway pressure.

* VS. patients with hypertension