

SUPPLEMENT

Risk Factors and Clinical Impact of Fibrotic-Like Changes and the Organizing Pneumonia Pattern in Patients with COVID-19- and Non-COVID-19-induced Acute Respiratory Distress Syndrome.

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SUPPLEMENTARY METHODS

Participants

Patients admitted to the interdepartmental ICUs of our institution within the study period were assessed for eligibility if they presented with ARDS induced by COVID-19 or other causes. ARDS was defined according to the Berlin criteria.¹ COVID-19 pneumonia was defined as the presence of pulmonary opacities and a positive SARS-CoV-2 polymerase chain reaction of nasopharyngeal or invasive respiratory samples (i.e., bronchoalveolar lavage). Researchers performed a screening process during the daily ICU rounds (Supplementary Figure 1).

Variables

All relevant data was collected upon ICU admission and ARDS onset, as noted in medical records and bedside flow charts (e.g., clinical, laboratory and radiological) (supplement). Patient follow-up was extended to death, hospital discharge or up to 90 days since ARDS diagnosis.

Clinical and epidemiological characteristics

We assessed the following general epidemiological characteristics upon ICU admission, including the acute physiology and chronic health evaluation II (APACHE-II) score²; chronic comorbidities and Charlson Comorbidity Index³; time from hospital to ICU admission; time from ICU admission to endotracheal intubation (ETI); and risk factor(s) for ARDS. When criteria for ARDS diagnosis were met¹ and invasive mechanical ventilation was needed, we performed the following assessments: inflammatory biomarkers as described elsewhere⁴; sequential organ failure assessment score (SOFA)⁵; the partial pressure of oxygen (PaO₂) / fraction of inspired oxygen (FiO₂) ratio; and the ventilatory ratio (surrogate parameter of physiological dead space).⁶ In addition, we investigated adjunctive therapies and mechanical ventilation parameters related with ventilator-induced lung injury (VILI) described elsewhere.^{7,8} Finally, we evaluated the presence of ventilator-associated pneumonia (VAP) and/or tracheobronchitis (VAT) [e.g., ventilator-associated lower tract respiratory infections (VA-LTRI)] as well as respiratory pathogen colonization until death, ICU discharge and 90-day follow-up.⁹

Study size

We did not perform any formal sample size calculation.

Statistical methods

We reported number and percentage of patients as categorical variables, and median and first and third quartile (Q1;Q3) as continuous variables with non-normal distribution. Categorical variables were compared using the χ^2 test or Fisher's exact test. Continuous variables were compared using the t-test or nonparametric Mann-Whitney U test. Patient survival was analyzed with the use of the Kaplan–Meier method and the Gehan-Breslow-Wilcoxon test. The level of significance was set at 0.05 (two-tailed). All analyses were performed using IBM SPSS Statistics version 25.0 (Armonk, New York, USA).

SUPPLEMENTARY RESULTS

Supplementary Table 1. Epidemiology, clinical characteristics and microbiology of 34 patients with COVID-19-induced ARDS according to the presence or absence of pulmonary fibrotic-like changes and its extensive form.

	COVID-19-induced ARDS with fibrotic-like changes n = 24	COVID-19-induced ARDS without fibrotic-like changes n = 10	COVID-19-induced ARDS with extensive fibrotic-like changes n = 12	p-value Fibrotic-like changes vs. none	p-value Extensive fibrotic-like changes vs. none
Sex, male/female, n (%)	15(63)/9(38)	8(80)/2(20)	5 (42)/7(58)	0.43	0.099
Age, years, median (Q1; Q3)	67 (56; 75)	65 (58; 76)	69 (65; 75)	0.92	0.488
Smoking, n (%)	1 (5)	1 (11)	0(0)	0.83	0.54
Alcohol Use, n (%)	4 (22)	0 (0)	1 (13)	0.29	1
Charlson Comorbidity Index, median (Q1; Q3)	3 (1; 3)	2 (1;3)	3 (2; 4)	0.52	0.25
APACHE-II upon ICU admission, median (Q1; Q3)	12 (10; 17)	13 (11; 18)	12 (11; 18)	0.50	0.48
SOFA upon ARDS diagnosis, median (Q1; Q3)	7 (6; 9)	7 (7; 8)	9 (6; 9)	0.93	0.54
Prone Position, n (%)	4 (18)	1 (10)	1 (9)	1	1
Neuromuscular Blockade, n (%)	10 (44)	3 (30)	4 (33)	0.70	1
Corticosteroid Use upon ARDS Diagnosis, n (%)	12 (52)	5 (50)	7 (58)	1	1
Persistent or New-onset Diffuse	18 (75)	3 (30)	11 (92)	0.02	0.006

Opacities >7 Days, n (%)					
C-Reactive Protein, mg/dL, median (Q1; Q3)	17 (6; 28)	14 (10; 25)	10 (2; 32)	0.90	0.77
D-dimer, ng/mL, median (Q1; Q3)	1150 (850; 2000)	1200 (1000; 2800)	1300 (900; 1750)	0.63	0.83
Lymphocyte Count x 10⁹/L, median (Q1; Q3)	0.6 (0.40; 0.70)	0.50 (0.40; 0.70)	0.50 (0.30; 0.65)	0.80	0.57
LDH, U/L, median (Q1; Q3)	408 (386; 544)	453 (369; 519)	470 (420; 529)	0.93	0.61
Microbiology, n (%)					
VA-LTRI	12 (50)	4 (40)	8 (67)	0.71	0.39
VAP	4 (17)	1 (10)	3 (25)	1	0.59
VAT	8 (33)	3 (30)	5 (42)	1	0.67
<i>Candida</i> spp. respiratory colonization	6 (25)	0 (0)	5 (42)	0.14	0.04

Abbreviations: APACHE-II: Acute physiology and chronic health evaluation II; ARDS: Acute respiratory distress syndrome; LDH: Lactate dehydrogenase; SOFA: Sequential organ failure assessment; VA-LTRI: Ventilator-associated lower respiratory tract infection; VAP: Ventilator-associated pneumonia; VAT: Ventilator-associated tracheobronchitis.

Supplementary Table 2. Clinical outcomes of 101 patients with ARDS presenting with or without COVID-19.

	Non-COVID-19- induced ARDS n = 40	COVID-19-induced ARDS n = 61	p-value
ICU Mortality, n (%)	23 (58)	19 (31)	0.009
Hospital Mortality, n (%)	25 (63)	19 (31)	0.002
30-day Mortality, n (%)	17 (43)	13 (21)	0.023
90-day Mortality, n (%)	23 (58)	18 (30)	0.005
ICU-free Days (days), median (Q1; Q3)	0 (0; 13)	0 (0; 7)	0.74
Ventilation-free Days (days), median (Q1; Q3)	2 (0; 20)	9 (0; 19)	0.62
Mechanical Ventilation Duration (days), median (Q1; Q3)	9 (5; 14)	15 (7; 22)	0.050
Mechanical Ventilation Duration (days), median (Q1; Q3)*	8 (5; 12)	14 (6; 22)	0.08
Length of ICU Stay (days), median (Q1; Q3)	14 (5; 29)	26 (9; 41)	0.022
Length of ICU Stay (days), median (Q1; Q3) †	15 (10; 29)	29 (17; 42)	0.049
Length of Hospital Stay (days), median (Q1; Q3)	23 (13; 46)	35 (16; 45)	0.18
Length of Hospital Stay (days), median (Q1; Q3) ‡	29 (15; 47)	36 (21; 47)	0.25

Abbreviations: ARDS: Acute respiratory distress syndrome; ICU: Intensive care unit.

* , † , ‡ Analyses restricted to patients who survived.

Supplementary Table 3. Clinical outcomes of 34 patients with COVID-19-induced ARDS according to the presence or absence of pulmonary fibrotic-like changes and its extensive form.

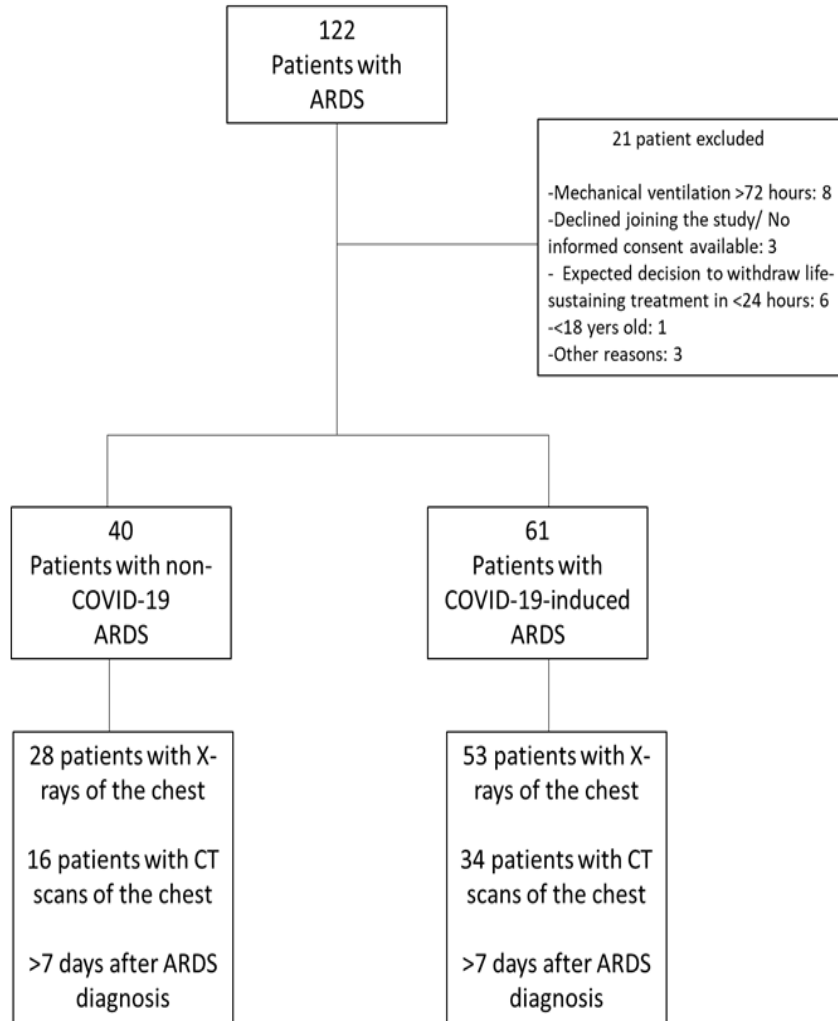
	COVID-19-induced ARDS with fibrotic-like changes n = 24	COVID-19-induced ARDS without fibrotic-like changes n = 10	COVID-19-induced ARDS with extensive fibrotic-like changes n = 12	p-value Fibrotic-like changes vs. none	p-value Extensive fibrotic-like changes vs. none
ICU Mortality, n (%)	5 (21)	1 (10)	5 (42)	0.64	0.16
Hospital Mortality, n (%)	5 (21)	1 (10)	5 (42)	0.64	0.16
30-day Mortality, n (%)	1 (4)	1 (10)	1 (8)	0.51	1
90-day Mortality, n (%)	4 (17)	1 (10)	4 (33)	1	0.32
ICU-free Days (days), median (Q1; Q3)	0 (0; 5)	0 (0; 0)	0 (0; 0)	0.77	0.11
Ventilation-free Days (days), median (Q1; Q3)	10 (1; 20)	9 (3; 16)	1 (0; 7)	0.84	0.16
Mechanical Ventilation Duration (days), median (Q1; Q3)	19 (8; 28)	19 (7; 22)	29 (22; 35)	0.78	0.049

Mechanical Ventilation Duration (days), median (Q1; Q3)*	18 (6; 27)	19 (7; 22)	27 (21; 33)	0.93	0.08
Length of ICU Stay (days), median (Q1; Q3)	41 (24; 52)	37 (15; 45)	51 (45; 64)	0.60	0.047
Length of ICU Stay (days), median (Q1; Q3) †	31 (20; 52)	38 (32; 45)	52 (50; 69)	0.82	0.1
Length of Hospital Stay (days), median (Q1; Q3)	43 (33; 62)	46 (31; 66)	48 (38; 70)	0.64	0.53
Length of Hospital Stay (days), median (Q1; Q3) ‡	39 (30; 68)	47 (45; 66)	68 (36; 70)	0.32	0.59

Abbreviations: ARDS: Acute respiratory distress syndrome; ICU: Intensive Care Unit.

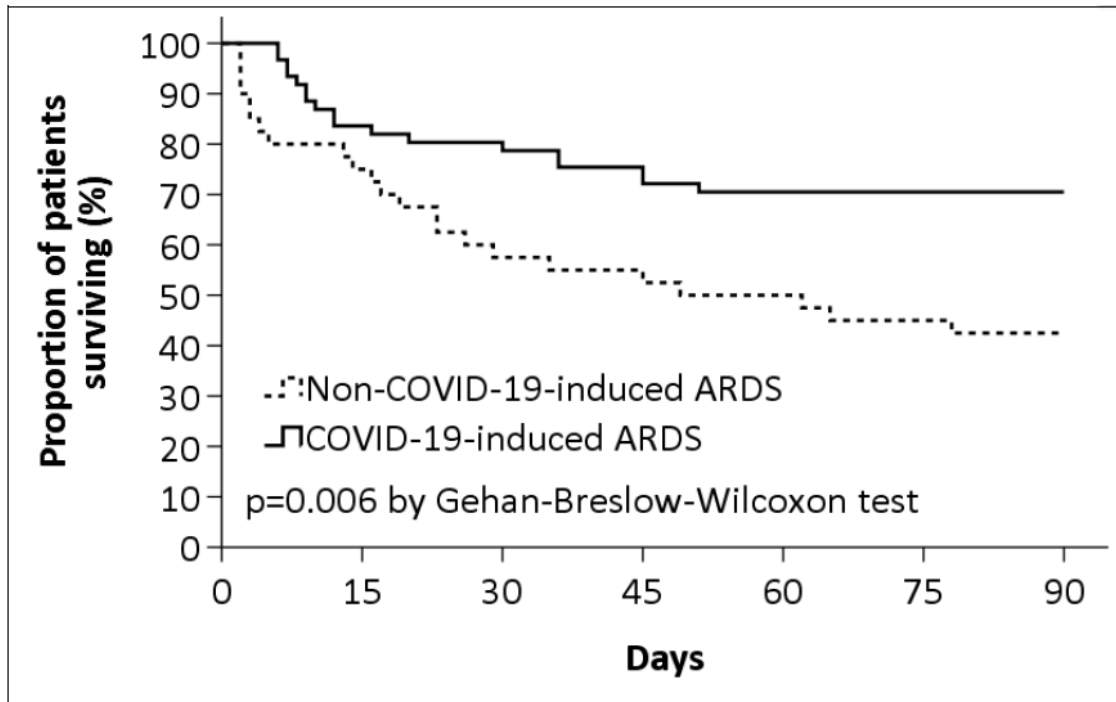
*, †, ‡ Analyses restricted to patients who survived.

Supplementary Figure 1. Study flowchart.



Abbreviations: ARDS: Acute respiratory distress syndrome; CT: Computed tomography.

Supplementary Figure 2. Kaplan-Meier survival curve.



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