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.

Authors' full names: Enric Barbeta[1,2,3,4,5], Mariana Benegas[6], Marcelo Sánchez[6], Anna Motos[2,3,5], Miquel Ferrer[1,2,3,5] Adrián Ceccato[2,3,4,5], Rubén Lopez[2,3,5], Leticia Bueno[2,3,5], Ricard Mellado -Artigas[7], Carlos Ferrando[7], Laia Fernández-Barat[2,3,5], Nuria Albacar[1,5], Joan Ramon Badia[1,3,5], Teresa López[8], Elena Sandoval[9], David Toapanta[10], Pedro Castro[2,5,11], Alex Soriano[12], Antoni Torres[1,2,3,5,] The Covid Clinic Critical Care Group*.

Authors' affiliation(s):

1) Pulmonology and Respiratory Intensive Care Unit. Respiratory Institute. Hospital Clinic of Barcelona. Barcelona, Spain.

2) Institut d'Investigacions Biomèdiques August Pi i Sunyer. Barcelona, Spain.

3) Centro de Investigación Biomédica en Red–Enfermedades Respiratorias.

4) Intensive Care Unit. Sagrat Cor University Hospital. Barcelona, Spain.

5) University of Barcelona. Barcelona, Spain

6) Radiology Department. Centre de Diagnòstic per la Imatge Clínic. Hospital Clinic of Barcelona. Barcelona, Spain

7) Anesthesiology and Surgical Intensive Care Unit. Hospital Clinic of Barcelona. Barcelona, Spain.

8) Cardiac Intensive Care Unit, Cardiology. Cardiovascular Institute. Hospital Clinic of Barcelona. Barcelona, Spain.

9) Cardiac Surgery Intensive Care Unit. Cardiovascular Institute. Hospital Clinic of Barcelona. Barcelona, Spain.

10) Liver Intensive Care Unit. Metabolic and Digestive Disease Institute. Hospital Clinic of Barcelona. Barcelona, Spain.

11) Medical Intensive Care Unit. Internal Medicine and Dermatology Institute. Hospital Clinic of Barcelona. Barcelona, Spain.

12) Department of Infectious Diseases. Internal Medicine and Dermatology Institute. Hospital Clinic of Barcelona. Barcelona, Spain.

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) score[2]; chronic comorbidities and Charlson Comorbidity Index[3]; 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 met[1] and invasive mechanical ventilation was needed, we performed the following assessments: inflammatory biomarkers as described elsewhere[4]; 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 $\chi 2$ 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 10^9/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
***Candida* 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.

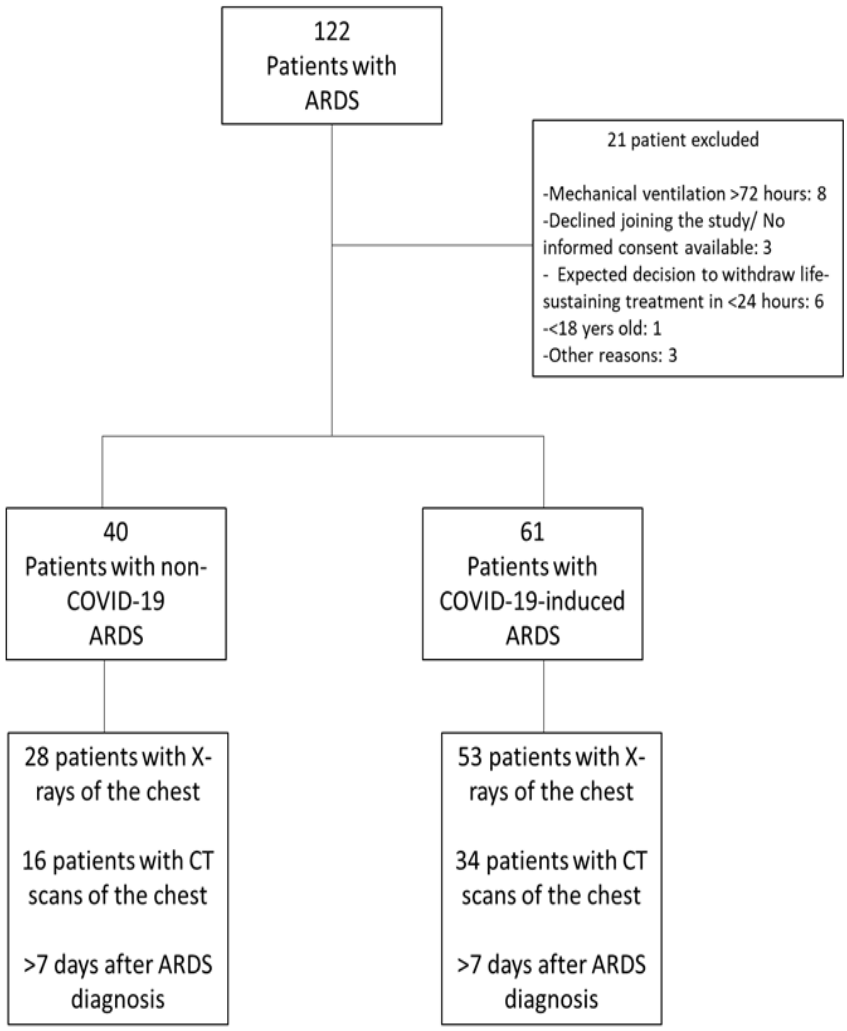
Supplementary Table 3. Clinical outcomes of 34 patients with COVID-19-induced ARDS according to the presence or absence of pulmonary fibrotic-like changes and its extensive form.

	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

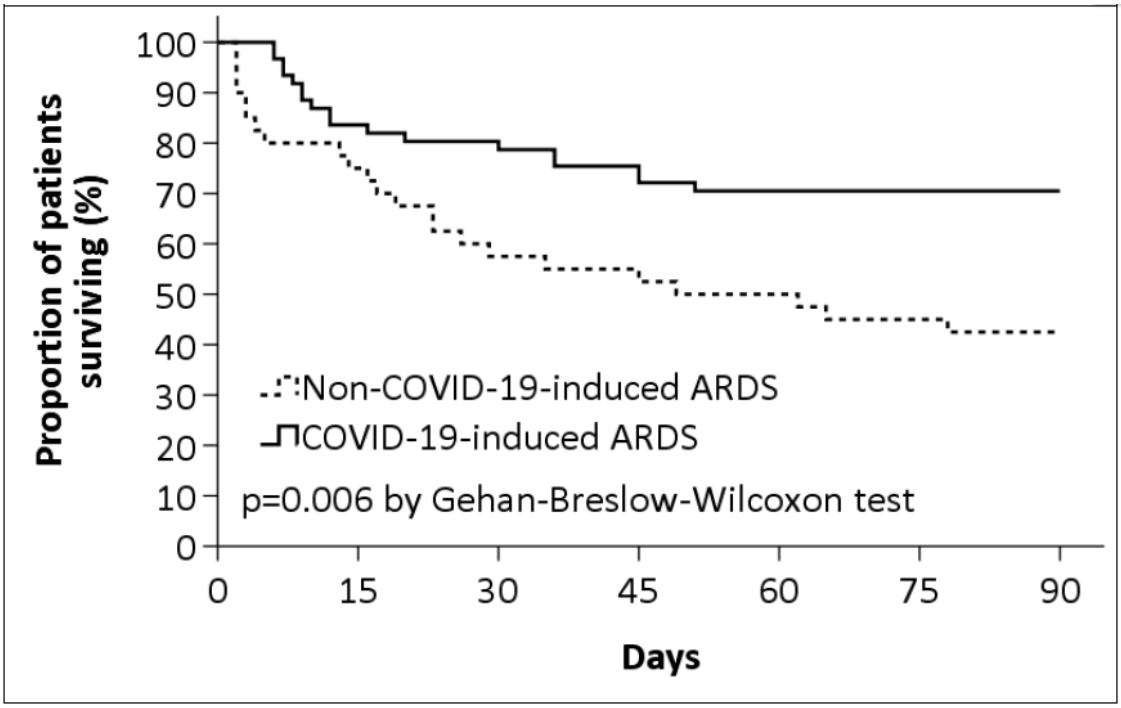
Abbreviations: ARDS: Acute respiratory distress syndrome; ICU: Intensive Care Unit.
*,†, ‡ Analyses restricted to patients who survived.

Supplementary Figure 1. Study flowchart.



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

Supplementary Figure 2. Kaplan-Meier survival curve.



References Supplement:

1. ARDS Definition Task Force; Ranieri VM, Rubenfeld GD, Thompson BT, Ferguson ND, Caldwell E, Fan E, Camporota L, Slutsky AS. Acute respiratory distress syndrome: the Berlin Definition. JAMA. 2012 Jun 20;307(23):2526-33.

2. Knaus WA, Draper EA, Wagner DP, Zimmerman JE. APACHE II: a severity of disease classification system. Crit Care Med. 1985 Oct;13(10):818-29.

3. Charlson M, Szatrowski TP, Peterson J, Gold J. Validation of a combined comorbidity index. J Clin Epidemiol. 1994 Nov;47(11):1245-51.

4. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, Xiang J, Wang Y, Song B, Gu X, Guan L, Wei Y, Li H, Wu X, Xu J, Tu S, Zhang Y, Chen H, Cao B. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet. 2020 Mar 28;395(10229):1054-1062.

5. Vincent JL, Moreno R, Takala J, Willatts S, De Mendonça A, Bruining H, Reinhart CK, Suter PM, Thijs LG. The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. On behalf of the Working Group on Sepsis-Related Problems of the European Society of Intensive Care Medicine. Intensive Care Med. 1996, 22, 707–710.

6. Sinha P, Calfee CS, Beitler JR, Soni N, Ho K, Matthay M, Kallet RH. Physiologic analysis and clinical performance of the ventilatory ratio in acute respiratory distress syndrome. Am J Respir Crit Care Med 2019;199:333–341.

7. Cressoni M, Gotti M, Chiurazzi C, Massari D, Algieri I, Amini M, Cammaroto A, Brioni M, Montaruli C, Nikolla K, Guanziroli M, Dondossola D, Gatti S, Valerio V, Vergani GL, Pugni P, Cadringher P, Gagliano N, Gattinoni L. Mechanical power and development of ventilator-induced lung injury. Anesthesiology 2016;124:1100–1108.

8. Amato MB, Meade MO, Slutsky AS, Brochard L, Costa ELV, Schoenfeld DA, Stewart TE, Briel M, Talmor D, Mercat A, Richard JCM, Carvalho CRR, Brower RG. Driving pressure and survival in the acute respiratory distress syndrome. N Engl J Med 2015;372:747–755.

9. Torres A, Niederman MS, Chastre J, Ewig S, Fernandez-Vandellos P, Hanberger H, Kollef M, Li Bassi G, Luna CM, Martin-Loeches I, Paiva JA, Read RC, Rigau D, Timsit JF, Welte T, Wunderink R. International ERS/ESICM/ESCMID/ALAT guidelines for the management of hospital-acquired pneumonia and ventilator-associated pneumonia: Guidelines for the management of hospital-acquired pneumonia (HAP)/ventilator-associated pneumonia (VAP) of the European Respiratory Society (ERS), European Society of Intensive Care Medicine (ESICM), European Society of Clinical Microbiology and Infectious Diseases (ESCMID) and Asociación Latinoamericana del Tórax (ALAT). Eur Respir J. 2017 Sep 10;50(3):1700582.