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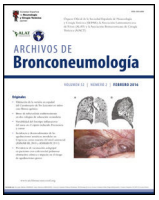

Scientific Letter

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

Factores de riesgo e impacto clínico de los cambios fibróticos y el patrón de neumonía organizada en los pacientes con síndrome de distrés respiratorio agudo producido o no por COVID-19

Dear Editor:

Patients with COVID-19-induced acute respiratory distress syndrome (ARDS) face high mortality due primarily to respiratory failure.[1–4] Diffuse alveolar damage (DAD)—the most common histological finding in these patients—can develop into a fibroproliferative phase and increase mortality risk.[5,6] In several COVID-19 autopsy reports, the presence of DAD and a pattern of acute fibrinous organizing pneumonia have been identified.[7] Organizing pneumonia is a manifestation of acute lung injury, which can be found in isolation or accompanying other lung diseases such as DAD. Organizing pneumonia is known to be able to develop into interstitial fibrosis and increase mortality risk as well, but it is often responsive to steroids.[8,9]

Currently, it remains unknown as to whether patients with COVID-19-induced ARDS, in comparison to those with non-COVID-19-induced ARDS, have slower or defective resolution of pulmonary inflammation characterized by interstitial abnormalities such as fibrotic-like changes and/or organizing pneumonia.

Therefore, we will evaluate the presence of persistent or new-onset diffuse pulmonary opacities in these patients, as well as fibrotic-like changes with or without an organizing pneumonia pattern within the first week of ARDS diagnosis. Finally, in patients with COVID-19, we will analyze risk factors associated with the presence of fibrotic-like changes, and determine any possible association between these findings and clinical outcomes.

We included all consecutive patients admitted to our institution for COVID-19- and non-COVID-19-induced ARDS[10] between June 15th, 2019 and March 28th, 2020. Patients who presented with one of the following criteria were excluded from the study: mechanical ventilation >72 h before inclusion; $PaO_2/FiO_2 > 300$ within 24 h of inclusion; expected decisions to have life-sustaining treatment withdrawn in <24 h; refusal of study participation on behalf of relatives; and the presence of previously known interstitial lung disease. Patients were divided into two groups according to the cause of ARDS (i.e., COVID-19 and non-COVID-19 cohorts).

We compared the presence of persistent or new-onset diffuse pulmonary opacities in chest X-rays (CXRs) beginning day 7 of ARDS diagnosis to death or intensive care unit (ICU) discharge. Furthermore, we assessed the presence and severity of pulmonary fibrotic-like changes and organizing pneumonia pattern in thoracic computed tomography (CT) scans during the same time frame. Patients with COVID-19-related ARDS were further divided into those who presented with fibrotic-like changes and those who did not. We analyzed risk factors for its development and compared clinical outcomes between both groups.

Attending doctors ordered thoracic CT scans without following any research protocol. Time (days) from ARDS diagnosis to CT scan was recorded. CXRs were performed every 24–48 h per protocol until ICU discharge. A pulmonologist and experienced thoracic radiologist independently and blindly assessed CT features to diagnose fibrotic-like changes and organizing pneumonia pattern. Additionally, two pulmonologists independently and blindly assessed CXRs to diagnose persistent or new-onset diffuse pulmonary opacities. Agreement between evaluators was assessed for CT scans and CXRs using Cohen's Kappa. After the first independent analysis, and without unblinding the cohort, evaluators met to discuss the radiological images on which there was a disagreement.

Persistent or new onset diffuse pulmonary opacities were defined as the presence of any of the following criteria between day 7 since ARDS diagnosis and death or ICU discharge: (1) persistence of ≥50% of radiological opacities found at ARDS diagnosis (2) an increase in or new-onset bilateral pulmonary opacities between day 7 since ARDS diagnosis and death or ICU discharge. An increase in radiological opacities had to be identified in both lungs. New-onset unilateral opacities did not meet this definition.

Fibrotic-like changes were defined as the presence of traction bronchiectasis, reticulation, parenchymal bands and/or honeycombing in thoracic CT scans performed between day 7 since ARDS diagnosis and death or ICU discharge.[11] Extension of fibrotic-like changes in thoracic CT scans was classified into one of three categories based on visual assessment and the percentage of bilateral lung involvement: mild (<25%), moderate (25%–50%) and severe (>50%).

An organizing pneumonia pattern was defined as peribronchovascular consolidations with perilobular distribution and/or the reverse halo sign between day 7 since ARDS diagnosis and death or ICU discharge.[11] Further, in the same manner, we assessed 30- and 90-day, hospital and ICU mortality, as well as ventilator- and ICU-free days, hospital and ICU length of stay, mechanical ventilation duration and other epidemiological variables (Supplementary Methods).

Abbreviations: ARDS, acute respiratory distress syndrome; DAD, diffuse alveolar damage; CXRs, chest X-rays; CT, computed tomography; ICU, intensive care unit; APACHE-II, acute physiology and chronic health evaluation II; ETI, endotracheal intubation; SOFA, sequential organ failure assessment; PaO_2, oxygen pressure; FiO_2, fraction of inspired oxygen; VILI, ventilator-induced lung injury; VAP, ventilator-associated pneumonia; VAT, ventilator-associated tracheobronchitis; VA-LRTI, ventilator-associated lower respiratory tract infection.

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Table 1
Epidemiology, Clinical Characteristics, Radiology and Microbiology 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
Sex, male/female, n (%)	26 (65)/14 (35)	42 (69)/19 (31)	.68
Age, years, median (Q1; Q3)	64 (50; 72)	65 (56; 74)	.45
Smoking, n (%)	10 (29)	5 (10)	.01
Alcohol use, n (%)	9 (28)	7 (17)	.23
Ischemic heart disease, n (%)	1 (3)	4 (7)	1
Congestive heart failure, n (%)	2 (5)	1 (2)	.56
Peripheral vascular disease, n (%)	0 (0)	1 (2)	1
Ischemic or hemorrhagic stroke, n (%)	1 (3)	4 (7)	.64
Chronic renal failure, n (%)	3 (8)	7 (12)	.73
COPD, n (%)	5 (13)	7 (12)	1
Liver disease, n (%)	12 (30)	2 (3)	.006
Diabetes mellitus, n (%)	7 (18)	11 (18)	.48
Solid neoplasm, n (%)	2 (5)	0 (0)	.008
Hematologic neoplasm, n (%)	2 (5)	2 (3)	.64
Solid metastases, n (%)	2 (5)	0 (0)	.15
AIDS, n (%)	0 (0)	2 (3)	.51
Dementia, n (%)	1 (3)	0 (0)	.39
Charlson Comorbidity Index, median (Q1; Q3)	4 (0; 5)	2 (1; 4)	.25
APACHE-II upon ICU admission, median (Q1; Q3)	26 (17; 29)	13 (11; 17)	<.001
SOFA upon ARDS diagnosis, median (Q1; Q3)	11 (8; 15)	7 (6; 9)	<.001
Prone position, n (%)	7 (18)	13 (23)	.56
Neuromuscular blockade, n (%)	10 (26)	27 (47)	.038
ECMO, n (%)	3 (8)	0 (0)	.062
Corticosteroid use upon ARDS diagnosis, n (%)	20 (56)	25 (43)	.24
Time from hospital to ICU admission days, median (Q1; Q3)	1 (0; 2)	1 (0; 2)	.20
Time from ICU admission to ETI, days, median (Q1; Q3)	2 (1; 3)	1 (0; 2)	.001
ARDS risk factor, n (%)			
Pulmonary sepsis	21 (54)	61 (100)	<.001
Bronchoaspiration	10 (26)	–	–
Extrapulmonary sepsis	5 (13)	–	–
Postoperative	1 (3)	–	–
Connective tissue disease	1 (3)	–	–
Trauma	1 (3)	–	–
Unknown	1 (3)	–	–
Radiology, n (%)[a,b]			
Persistent or new-onset diffuse opacities > 7 days[a]	8 (29)	25 (47)	.10
Fibrotic-like changes[b]	2 (12)	24 (71)	<.001
Mild[b]	1 (6)	3 (9)	.002
Moderate[b]	0 (0)	8 (24)	.002
Extensive[b]	1 (6)	12 (36)	.002
Organizing pneumonia pattern[b]	0 (0)	24 (71)	<.001
Time from ARDS to CT scan, days, median (Q1; Q3)	15 (11; 18)	24 (14; 36)	.054
Microbiology, n (%)			
VA-LTRI	9 (23)	25 (43)	.03
VAP	6 (15)	9 (15)	.97
VAT	5 (13)	18 (30)	.046
Candida spp. respiratory colonization	5 (13)	7 (12)	1
Gas exchange, respiratory mechanics and ventilatory parameters upon ARDS diagnosis, median (Q1; Q3)			
PaO_2/FiO_2	163 (120; 218)	175 (147; 232)	.14
Ventilatory ratio	1.83 (1.59; 2.21)	1.91 (1.57; 2.15)	.92
Tidal volume, mL/IBW	6.61 (6.15; 7.89)	6.80 (6.30; 7.45)	.67
PEEP, cmH_2O	9 (7; 10)	13 (11; 14)	<.001
Positive end-inspiratory pressure, cmH_2O	23 (22; 26)	24 (21; 26)	.95
Driving pressure, cmH_2O	14 (11; 18)	11 (9; 13)	<.001
Mechanical power, J/min	22 (17; 29)	23 (18; 28)	.58
Respiratory system compliance, $TV * cmH_2O^{-1}$	30 (26; 35)	39 (31; 50)	.002

[a] X-ray available for 81 patients from day 7 since ARDS diagnosis to ICU discharge. The remaining 20 patients either died or were discharged before reaching day 7 since ARDS diagnosis.

[b] Thoracic computed tomography scans available for 50 patients from day 7 since ARDS diagnosis to ICU discharge. The extension of fibrotic-like changes could not be assessed in one patient.

Abbreviations: APACHE-II: acute physiology and chronic health evaluation II; ARDS: acute respiratory distress syndrome; AIDS: acquired immune deficiency syndrome; COPD: chronic obstructive pulmonary disease; CT: computed tomography; ECMO: extracorporeal membrane oxygenation; ETI: endotracheal intubation; IBW: Ideal body weight; ICU: intensive care unit; mL: milliliters; PEEP: positive end-expiratory pressure; SOFA: sequential organ failure assessment; TV: tidal volume; VA-LTRI: ventilator-associated lower respiratory tract infection; VAP: ventilator-associated pneumonia; VAT: ventilator-associated tracheobronchitis.

The study was approved by the Institution's Internal Review Board (HCB/2018/0231). For additional details on the method, see the online supplement.

From June 15th, 2019 to March 28th, 2020, 122 patients with COVID-19- and non-COVID-19-induced ARDS were admitted to our interdepartmental ICUs. Twenty-one patients were excluded from

Table 2
Gas Exchange, Respiratory Mechanics and Ventilatory Parameters 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
Gas exchange, respiratory mechanics and ventilatory parameters upon ARDS diagnosis, median (Q1; Q3)					
PaO_2/FiO_2	177 (124; 232)	170 (111; 191)	183 (115; 237)	.34	.42
Ventilatory ratio	1.87 (1.68; 2.15)	1.81 (1.28; 2.19)	1.91 (1.70; 2.11)	.54	.79
Tidal volume, mL/IBW	7.13 (6.39; 7.59)	6.42 (5.71; 7.04)	6.84 (6.34; 7.65)	.042	.14
PEEP, cmH_2O	13 (12; 14)	12 (10; 13)	13 (12; 14)	.16	.28
Positive end-inspiratory pressure, cmH_2O	24 (21; 26)	23 (21;25)	25 (24; 27)	.19	.044
Driving pressure, cmH_2O	11 (9; 13)	11 (10; 13)	12 (11; 15)	.69	.25
Mechanical power, J/min	22 (18; 28)	22 (19; 33)	21 (17; 24)	.66	.36
Respiratory system compliance, $TV * cmH_2O^{-1}$	40 (30; 53)	39 (36; 45)	35 (24; 43)	.67	.23
Gas exchange, respiratory mechanics and ventilatory parameters on day 3 since ARDS diagnosis, median (Q1; Q3)					
PaO_2/FiO_2	220 (155; 253)	200 (157; 222)	209 (162; 260)	.58	.79
Ventilatory ratio	2.03 (1.79; 2.26)	1.56 (1.37; 1.94)	1.98 (1.80; 2.39)	.011	.015
Tidal volume, mL/IBW	7.50 (6.81; 7.92)	6.46 (5.71; 6.76)	7.51 (6.85; 7.82)	.005	.01
PEEP, cmH_2O	12 (10; 13)	12 (10;13)	12 (9; 13)	.82	.66
Positive end-inspiratory pressure, cmH_2O	23 (22; 26)	23 (16; 24)	24 (22; 27)	.11	.09
Driving pressure, cmH_2O	11 (10; 13)	10 (6; 11)	12 (11; 15)	.055	.059
Mechanical power, J/min	23.37 (21.1; 29.9)	26.38 (18.7; 34.1)	22.12 (16.7; 28.5)	.64	.46
Respiratory system compliance, $TV * cmH_2O^{-1}$	37 (31; 46)	50 (41; 70)	36 (27; 46)	.08	.11

Abbreviations: ARDS: acute respiratory distress syndrome; IBW: ideal body weight; mL: milliliters; PEEP: positive end-expiratory pressure; TV: tidal volume.

the study (Supplementary Fig. 1). Of the 101 patients included in the analysis, 81 had sequential CXRs beginning day 7 since ARDS diagnosis to death or ICU discharge. In addition, and within the same time frame, fifty patients underwent a thoracic CT scan. Table 1 shows the demographic and clinical characteristics of these patients. Patients with COVID-19-induced ARDS ($n=24$, 71%) presented with a higher incidence of fibrotic-like changes when compared to those with non-COVID-19-induced ARDS ($n=2$, 12%) ($P=.001$). All patients with COVID-19 and fibrotic-like changes also presented with an organizing pneumonia pattern in thoracic CT scans. With respect to assessments of CT scan features, agreement between the thoracic radiologist and pulmonologist was 0.64; regarding assessments of CXRs, agreement between pulmonologists was 0.73.

Table 2 and Supplementary Table 1 show the characteristics of patients with COVID-19-induced ARDS, presenting with or without fibrotic-like changes. Those patients who later developed fibrotic-like changes or an extensive manifestation of these changes had higher dead space (ventilatory ratio) on day 3 since the ARDS diagnosis. In addition, we more frequently identified ventilation with higher tidal volume and positive end-inspiratory pressure upon ARDS diagnosis in patients who later presented with fibrotic-like changes or its extensive manifestation, respectively. Likewise, administering mechanical ventilation with a higher tidal volume and driving pressure on day 3 since ARDS diagnosis was associated with the development of fibrotic-like changes and the extensive manifestation of such changes thereafter.

Clinical outcomes from COVID-19 and non-COVID-19-induced ARDS according to the presence or absence of fibrotic-like changes are shown in Supplementary Tables 2 and 3, as well as Supplementary Fig. 2.

The main findings of this study are the following: first, patients with COVID-19-induced ARDS more frequently presented with fibrotic-like changes and an organizing pneumonia pattern than those with non-COVID-19-induced ARDS. Second, higher dead space ventilation (i.e., ventilatory ratio), tidal volume, end-inspiratory pressure and driving pressure during the early course of ARDS were associated with the development of fibrotic-like changes in patients with COVID-19-induced ARDS. Finally, the manifestation of fibrotic-like changes in its extensive form occurred in 36% of patients, being associated with longer mechanical ventilation and ICU length of stay.

Pulmonary fibrotic-like changes are a radiological manifestation of a defective healing process of the lung, which is related to higher mortality.[12,13] As in ARDS caused by other risk factors, exudative or fibroproliferative DAD is already known to be the main histological pattern in COVID-19-induced ARDS.[14] In our study, we identified an organizing pneumonia pattern in all patients with COVID-19 who also presented with fibrotic-like changes. The fact that DAD can have regions with organizing pneumonia or acute fibrinous organizing pneumonia has been well-established.[14] However, it remains unknown as to whether COVID-19-induced ARDS includes larger lung areas of these two histological patterns (organizing pneumonia or acute fibrinous organizing pneumonia). Our findings raise concerns about whether SARS-CoV-2 more frequently elicits a transition from inflammation to an organizing process. Further, our findings invite the consideration of whether steroids would confer a benefit even if DAD is present as well.

We found that, during the early course of ARDS, several variables related to VILI (i.e., tidal volume, positive end-inspiratory pressure and driving pressure) were associated with the development of fibrotic-like changes. Interestingly, this association was identified even when all of these parameters were within the range that is currently believed to be *protective*.

The degree of impairment in oxygenation at days 1 and 3 since ARDS diagnosis was not related to the development of fibrotic-like changes. Conversely, on day 3, higher dead space ventilation was found in patients who developed extensive and non-extensive fibrotic-like changes. In comparison to oxygenation, dead space ventilation is a better marker of lung inhomogeneities and is strongly related to a higher mortality risk.[15]

This study has several limitations. First, due to the observational design of the study, there was no specific protocol to perform CT scans. A selection bias may therefore have overestimated the

presence of fibrotic-like changes in COVID-19-induced ARDS. Indeed, patients with COVID-19 underwent more thoracic CT scans and at a different time point than those without COVID-19. Second, as a result of the low sample size of patients with available CT scans, a large type II error may have occurred. Third, organizing pneumonia is a pathological diagnosis, and information provided by CT scans should be interpreted with caution.

Ethics Approval and Consent to Participate

The study was approved by the Institution's Internal Review Board (HCB/2018/0231)

Consent for Publication

Informed written consent was obtained from the patients for publication of this article.

Availability of Data and Material

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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Authors' Contribution

A.T. had full access to all of the data in the study and takes responsibility for the integrity of the data and accuracy of the data analysis. E.B., A.M., and A.T. provided the concept and design. All authors contributed to acquisition. E.B., A.M., A.T., A.C., M.F., L.B., R.M., R.L., CF., L.F-B., N.A., J.R.B., T.L., E.S., D.T., A.S. E.B., A.M., and A.T. drafted the manuscript. E.B. and A.M. provided statistical analysis. All authors contributed to the critical revision of the manuscript for important intellectual content.

Conflict of Interest

I declare no competing interests.

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Appendix A. Covid Clinic Critical Care Group

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Appendix B. Supplementary Data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.arbres.2021.05.023.

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