# Pathophysiology of COVID-19-associated acute respiratory distress syndrome: a multicentre prospective observational study

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## Summary

**Background** Patients with COVID-19 can develop acute respiratory distress syndrome (ARDS), which is associated with high mortality. The aim of this study was to examine the functional and morphological features of COVID-19-associated ARDS and to compare these with the characteristics of ARDS unrelated to COVID-19.

**Methods** This prospective observational study was done at seven hospitals in Italy. We enrolled consecutive, mechanically ventilated patients with laboratory-confirmed COVID-19 and who met Berlin criteria for ARDS, who were admitted to the intensive care unit (ICU) between March 9 and March 22, 2020. All patients were sedated, paralysed, and ventilated in volume-control mode with standard ICU ventilators. Static respiratory system compliance, the ratio of partial pressure of arterial oxygen to fractional concentration of oxygen in inspired air, ventilatory ratio (a surrogate of dead space), and D-dimer concentrations were measured within 24 h of ICU admission. Lung CT scans and CT angiograms were done when clinically indicated. A dataset for ARDS unrelated to COVID-19 was created from previous ARDS studies. Survival to day 28 was assessed.

**Findings** Between March 9 and March 22, 2020, 301 patients with COVID-19 met the Berlin criteria for ARDS at participating hospitals. Median static compliance was 41 mL/cm $H_2O$ (33–52), which was 28% higher than in the cohort of patients with ARDS unrelated to COVID-19 (32 mL/cm $H_2O$ [25–43]; p<0·0001). 17 (6%) of 297 patients with COVID-19-associated ARDS had compliances greater than the 95th percentile of the classical ARDS cohort. Total lung weight did not differ between the two cohorts. CT pulmonary angiograms (obtained in 23 [8%] patients with COVID-19-related ARDS) showed that 15 (94%) of 16 patients with D-dimer concentrations greater than the median had bilateral areas of hypoperfusion, consistent with thromboembolic disease. Patients with D-dimer concentrations equal to or less than the median had ventilatory ratios lower than those of patients with D-dimer concentrations greater than the median (1·66 [1·32–1·95] *vs* 1·90 [1·50–2·33]; p=0·0001). Patients with static compliance equal to or less than the median and D-dimer concentrations greater than the median had markedly increased 28-day mortality compared with other patient subgroups (40 [56%] of 71 with high D-dimers and low compliance *vs* 18 [27%] of 67 with low D-dimers and high compliance, 13 [22%] of 60 with low D-dimers and low compliance, and 22 [35%] of 63 with high D-dimers and high compliance, all p=0·0001).

**Interpretation** Patients with COVID-19-associated ARDS have a form of injury that, in many aspects, is similar to that of those with ARDS unrelated to COVID-19. Notably, patients with COVID-19-related ARDS who have a reduction in respiratory system compliance together with increased D-dimer concentrations have high mortality rates.

**Funding** None.



## Introduction

The COVID-19 pandemic has affected millions of people and caused hundreds of thousands of deaths worldwide. Although most patients have a favourable prognosis, pneumonia and severe hypoxaemia associated with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection can lead to acute respiratory distress syndrome (ARDS), which is associated with a high mortality rate.[1]

The proportion of patients with COVID-19 who are diagnosed with ARDS on the basis of oxygenation criteria ranges between 20%[2] and 67%[1] in patients admitted to hospital and is 100% in mechanically ventilated patients.[3] However, few data are available that link the physiological, laboratory, and imaging features of these patients. This information is important because several studies have suggested that patients with COVID-19-associated ARDS have markedly higher lung compliances than do patients with ARDS unrelated to COVID-19 (so-called classical ARDS), so typical protective ventilatory settings might not be indicated in patients with COVID-19-related

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## Research in context

### Evidence before this study

We searched PubMed on July 8, 2020, with the search terms "COVID-19" and "ARDS", for research published in English between March 1 and July 1, 2020. Our search found 457 PubMed-indexed articles. Limitations of these studies included small sample size; retrospective design; and single-centre observation. Nevertheless, despite these limitations, highly cited studies have spread the knowledge that patients with COVID-19 that are diagnosed with ARDS might not have what we think of as classical ARDS, because they have significant hypoxaemia but relatively normal respiratory system compliance. These findings resulted in the clinical recommendation that suggested abandoning the previously proven best practices for lung protection.

### Added value of this study

We completed a systematic analysis of clinical and laboratory features in patients with COVID-19-associated ARDS in a large (301 patients), unbiased (all consecutive patients prospectively enrolled in seven Italian hospitals) series, and compared the pathophysiology of COVID-19-related ARDS with that of classical ARDS using two large historical datasets. We present evidence that patients with COVID-19-associated ARDS have a form of injury that is similar to that of classical ARDS, characterised by decreased compliance and increased lung weight. In many patients, this injury is complicated by increased dead space, which is probably related to diffuse microthrombi or emboli of the pulmonary vascular bed. When pulmonary damage occured together with high D-dimer concentrations in our cohort, mortality was extremely high.

### Implications of all the available evidence

The proposal that evidence-based lung-protective ventilatory strategies might not be recommended for some patients with COVID-19-associated ARDS is not backed up by our data, since the morphological hallmark of ARDS was essentially similar in COVID-19-related and classical ARDS. In view of these data, limitation of tidal volume to 6 mL/kg and plateau pressure to 30 cm $H_2O$ is still recommended. The observation of higher values of dead space might suggest the use of lower levels of positive end-expiratory pressure, especially in patients in the higher range of compliance. Our results also have implications for the design of clinical trials, because patients with the phenotype characterised by low respiratory system compliance and high D-dimers have an extremely high 28-day mortality rate.

ARDS.[4–6] Additionally, patients with COVID-19-associated ARDS are thought to have substantial pulmonary thrombotic injury,[7] associated with increased D-dimer levels.[8] If confirmed, these findings could have major implications in terms of treatment strategies and prognosis.

The objective of this study was to examine the functional and morphological features of invasively ventilated patients with COVID-19-related ARDS and to assess whether the physiological and biological characteristics in patients with COVID-19 are similar to those previously described for classical ARDS.

## Methods

### Study design and participants

This prospective observational study was done at seven Italian hospitals (Policlinico di Sant'Orsola, Bologna; Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan; University Hospital of Modena, Modena; Grande Ospedale Metropolitano Niguarda, Milan; Ospedale San Gerardo, Monza; Humanitas Clinical and Research Center—IRCCS, Milan; and Fondazione Policlinico Universitario A Gemelli IRCCS, Rome).

Institutional review boards at each hospital approved the study protocol and decided that consent could be waived in the context of the COVID-19 pandemic. We enrolled all consecutive patients older than 18 years with confirmed COVID-19[9] who were admitted to intensive care units (ICUs) of participating hospitals between March 9 and March 22, 2020, with the following inclusion criteria in the first 24 h after admission: (1) presence of all Berlin definition criteria for ARDS;[5] and (2) receiving invasive mechanical ventilation.

### Procedures

All patients were sedated, paralysed,[10,11] and ventilated in volume-control mode with standard ICU ventilators. Positive end-expiratory pressure (PEEP) selection was not protocolised. Tidal volume, respiratory rate, and airway pressures were recorded from the ventilator monitors. End-inspiratory and end-expiratory occlusions were performed using ventilator functions. End-inspiratory plateau pressure and total PEEP were measured as previously described.[12,13] The most representative set of measurements of ventilatory and physiological variables was collected within the first 24 h of ICU admission on the basis of the senior attending physician's assessment.

Static compliance of the respiratory system was calculated as tidal volume/(end-inspiratory plateau pressure–total PEEP), with a normal mean value being 67 mL/cm $H_2O$ (SD 4).[12,14] Chest CT scans and CT-pulmonary angiograms were obtained when clinically indicated and technically feasible.[15] Total lung weight was estimated from standard non-contrast chest CT scans (done at clinical levels of PEEP) with a dedicated medical imaging software equipped with a semi-automated segmentation algorithm (3D Slicer).[16] Presence of pulmonary intravascular clots was assessed by analysing CT-pulmonary angiograms using software

installed on the IntelliSpace Portal release 11. The application uses an advanced automatic computer-aided design algorithm for detecting filling defects.[17,18] In addition, to estimate the hypoperfused areas of the lung parenchyma, the application provides a Hounsfield unit-based colour map of the lungs as an experimental feature.

Oxygenation was quantified as the ratio of partial pressure of arterial oxygen to fractional concentration of oxygen in inspired air ($PaO_2/FiO_2$). Ventilatory ratio was calculated and used as a surrogate of dead space. Ventilatory ratio=measured minute ventilation×measured $PaCO_2$/(predicted minute ventilation×predicted $PaCO_2$), where minute ventilation=tidal volume×respiratory rate; predicted minute ventilation is calculated as predicted bodyweight in kg×100 (mL/min); predicted $PaCO_2$ is the expected $PaCO_2$ (37·5 mm Hg) if the patient is ventilated with the predicted minute ventilation. Ventilatory ratio is unitless; values greater than 1 suggest increased dead space.[19]

Clinical and physiological variables and D-dimer concentrations were collected within 24 h of study admission. Values of static compliance and results of pulmonary CT scans in patients with COVID-19-related ARDS were compared with a dataset of non-COVID-19-related classical ARDS obtained from the physiological database (n=269) used in the creation of the Berlin definition,[5] and the database of the LUNG-SAFE study (n=3022).[20] To minimise the potential effects of confounding variables in such comparisons, we first performed a stratified analysis for gender, body-mass index (BMI), ARDS severity ($PaO_2/FiO_2$ criteria[5]), and presence of pneumonia as the underlying disease causing ARDS and then built a multivariable linear model that used COVID-19 ARDS versus classical ARDS, gender, age, BMI, and $PaO_2/FiO_2$ as independent variables, and static compliance or lung weight as the dependent variable.

### Statistical analysis

Continuous variables were expressed as medians and IQRs. Categorical variables were summarised as numbers and percentages. Comparison of continuous data between groups was done using Wilcoxon-Mann-Whitney or Kruskal Wallis test and comparison of categorical data was done using $\chi^2$ or Fisher's exact test. We used the Kaplan-Meier method to estimate survival to day 28 from ICU admission and we assessed differences in survival curves using the log-rank test. A Cox proportional hazard model was used to estimate adjusted hazard ratios (HRs) with 95% CIs and to assess the influence of D-dimer and static compliance on survival. The relevant available clinical variables in the adjusted model were sequential organ failure assessment score at ICU admission, sex, age, and $PaO_2/FiO_2$ ratio.

All statistical tests were two sided. $p<0·05$ was considered statistically significant and analyses were done without any imputation for missing data. Analyses were done using SAS version 9.4, R version 3.4.0, and Graphpad Prism version 8.4.3 software packages.

### Role of the funding source

There was no funding source for this study. ASS, APe, and VMR had full access to all the data in the study and had final responsibility for the decision to submit for publication.

## Results

During the study period of March 9–22, 2020, 301 patients fulfilled all Berlin criteria for ARDS and were recruited to the study.[5] Median time from hospital admission to intubation was 2 days (IQR 0–4). Median age was 63 years (55–70), 232 (77%) were men and 69 (23%) were women, and all were ventilated according to a conventional protective ventilatory strategy.[13] D-dimer concentrations in the first 24 h from ICU admission were available for 261 (87%) patients (appendix p 2).

See Online for appendix

Chest CT scans were obtained for 43 (14%) patients; median time from ICU admission to CT scan was 0·5 days (IQR 0–6). Quantitative analysis of lung CT scans was done in 20 (7%) patients. Analysis of pulmonary CT angiograms was done in 23 (8%) patients.

Baseline characteristics of COVID-19 ARDS compared with classical ARDS[5,20] were significantly different with regards to sex, BMI, incidence of mild and severe ARDS, and incidence of pneumonia (table 1).

Median static compliance of the respiratory system was 28% higher in patients with COVID-19 (n=297; 41 mL/cm $H_2O$ [IQR 33–52]) than in those with classical ARDS (n=960; 32 mL/cm $H_2O$ [25–43], $p<0·0001$). The distribution of static compliance was unimodal in the two groups, with a slight shift to the right (ie, towards higher values) in the COVID-19 group (appendix p 12). Only 17 (6%) of 297 of patients with COVID-19-related ARDS had compliances greater than the 95th percentile of the patients with classical ARDS. Static compliance decreased as $PaO_2/FiO_2$ decreased in patients with classical ARDS and in a pneumonia subset of patients with ARDS, while it remained unchanged in patients with COVID-19 ARDS (appendix p 3). Total lung weight did not differ between patients with COVID-19 ARDS and classical ARDS (figure 1).

The stratified analysis showed that differences in static compliance between COVID-19 ARDS and classical ARDS tended to become smaller (at least in some subgroups) after controlling for gender, BMI, severity of ARDS, and pneumonia (appendix p 4). Application of the multivariable linear model showed that static compliance was dependent on cause of ARDS, sex, and $PaO_2/FiO_2$ (appendix p 4), while lung weight was dependent on sex and $PaO_2/FiO_2$ but independent of cause of ARDS (appendix p 4).

Quartile analysis of D-dimer concentrations (n=261; normal range <500 ng/mL) and compliance (n=297) in

| | COVID-19 ARDS | Classical ARDS | p value |
|---|---|---|---|
| Sex | | | |
| Men | 232/301 (77·1%) | 1580/2548 (62·0%) | <0·0001 |
| Women | 69/301 (22·9%) | 968/2548 (38·0%) | .. |
| Age, years* | 63 (55–70) | 63 (49–73) | 0·943 |
| Body-mass index, kg/m²† | 27·8 (25·3–31·1) | 26·0 (22·9–30·4) | <0·0001 |
| ARDS severity | | | |
| Mild | 33/300 (11·0%) | 772/2634 (29·3%) | <0·0001 |
| Moderate | 163/300 (54·3%) | 1263/2634 (47·9%) | 0·2254 |
| Severe | 104/300 (34·7%) | 599/2634 (22·7%) | 0·0005 |
| Underlying disease | | | |
| Pneumonia | 301/301 (100·0%) | 1523/2643 (57·6%) | <0·0001 |
| Non-pneumonia | 0 | 1120/2643 (42·4%) | .. |

Data are n/N (%) or median (IQR). ARDS=acute respiratory distress syndrome. *n=301 for COVID-19 ARDS and n=2643 for classical ARDS. †n=294 for COVID-19 ARDS and n=2186 for classical ARDS.

***Table 1:*** **Baseline characteristics of patients with COVID-19 and classical ARDS[5,20]**

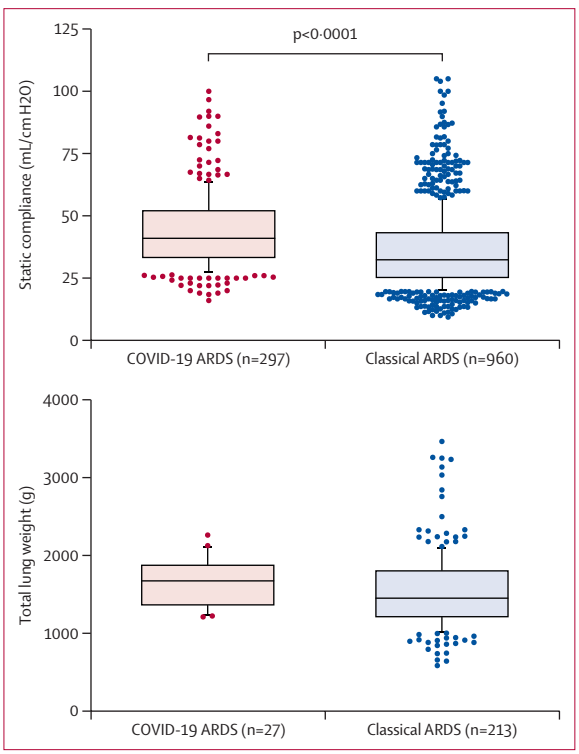


***Figure 1:*** **Static compliance of the respiratory system and total lung weight of patients with COVID-19-associated ARDS or classical ARDS[5,20]**
Boxes show medians and IQRs; whiskers show the tenth to 90th percentiles. ARDS=acute respiratory distress syndrome.

patients with COVID-19 is shown in the appendix (pp 6–7). Patients with D-dimers equal to or less than the median (ie, 1880 ng/mL [IQR 820–6243]; n=131) had ventilatory ratios lower than those observed in patients with D-dimer concentrations greater than the median (n=130; 1·66 [1·32–1·95] *vs* 1·90 [1·50–2·33], p=0·0001; appendix p 6). Distributions of hyperinflated, normally inflated, poorly aerated, and non-aerated lung tissue in patients with static compliance either greater than or equal to or less than the median are shown in the appendix (p 14). Patients with static compliance greater than median (n=8) tended to have more hyperinflated and normally inflated lung tissue and less poorly aerated and non-aerated lung tissue than patients with static compliance equal to or less than the median (n=9), but none of these differences was statistically significant.

Based on quartiles of D-dimer concentrations and static compliance, patients were classified into four groups. The high D-dimers, low compliance (HDLC) group was patients with D-dimer concentrations greater than the median in COVID-19 ARDS (1880 ng/mL) and static compliance equal to or less than the median (41 mL/cm $H_2O$; 71 [27%] patients). The low D-dimers, high compliance (LDHC) group was patients with D-dimer concentrations equal to or less than the median and static compliance greater than the median (67 patients [26%]). The low D-dimers, low compliance (LDLC) group was patients with D-dimer concentrations and static compliance equal to or less than the medians (60 [23%] patients). The high D-dimers, high compliance (HDHC) group was patients with D-dimer concentrations and static compliance greater than the medians (63 [24%] patients; appendix p 8).

Patients with D-dimer concentrations equal to or less than median had normal perfusion scans regardless of compliance (figure 2). 15 (94%) of 16 patients with D-dimer concentrations greater than the median had bilateral, diffuse areas of hypoperfusion, consistent with the presence of thrombi or emboli (appendix p 9); this was the case in patients with both high and low static compliance.

28-day mortality was 36% (93 of 261 patients). The HDLC group had significantly higher 28-day mortality than the other three groups (40 [56%] of 71 in the HDLC group *vs* 18 [27%] of 67 in the LDHC group, 13 [22%] of 60 in the LDLC group, and 22 [35%] of 63 in the HDHC group, all p=0·0001). Kaplan-Meier analysis of survival for the four groups is shown in figure 3. In the Cox model with HDLC as the reference group, the adjusted HRs for 28-day mortality were 0·420 (95% CI 0·215–0·818) for the LDHC group, 0·386 (0·152–0·985) for the LDLC group, and 0·448 (0·230–0·873) for the HDHC group (table 2). Biological sex does not appear to be a risk factor for 28-day mortality.

## Discussion

Our study provides two major findings. First, patients with COVID-19-related ARDS have lung morphology and respiratory mechanics that largely match those of classical ARDS. Second, there is a subgroup of patients with COVID-19-related ARDS who have disease characterised by low static compliance of the respiratory system and high D-dimer concentration and have a markedly increased mortality compared with other patients.

ARDS is a form of lung injury that occurs in response to various predisposing events and is characterised by inflammation, increased pulmonary vascular permeability, and loss of aerated lung tissue. The diagnosis of ARDS is based on severe hypoxaemia and bilateral radiographic opacities occurring within 7 days of exposure to known predisposing factors.[5] Central to the pathophysiology of ARDS is the presence of fibrin-rich exudates (hyaline membranes) due to activation of coagulation and inhibition of fibrinolysis.[21] Upregulation of procoagulant activity in the alveolar compartment has been proposed as the driving force for intra-alveolar fibrin deposition and has been implicated in the development of ARDS.[22] Concentrations of D-dimer, a proteic fragment present in the blood resulting from clot degradation commonly found in patients with suspected thrombotic disorders, are significantly increased in the oedema fluid of patients with ARDS.[23] Early studies proposed that widespread pulmonary vascular thrombosis was a consistent feature of ARDS,[24–26] and increased serum levels of D-dimers[7] and pulmonary vascular endothelialitis, thrombosis, and angiogenesis[27] have been observed in patients with COVID-19. Furthermore, dysregulation of other factors related to coagulation (eg, low vitamin K-dependent protein C and increased plasminogen activator inhibitor 1) has been associated with very high mortality in ARDS.[28]

Although unsupported by large studies, several authors have concluded that patients with COVID-19 who are diagnosed with ARDS might actually not have what we think of as classical ARDS because of the fact that they have significant hypoxaemia but quite compliant lungs.[6,29,30] Mean static compliance of 50·2 mL/cm $H_2O$ (SD 14·3) was reported for 16 patients mechanically ventilated for COVID-19.[4]

To answer the question of whether patients with COVID-19-related ARDS have characteristics found in classical ARDS, we selected reference values from the dataset of 269 patients used to empirically assess the Berlin definition of ARDS[5] and from the 3022 patients included in the LUNG-SAFE database.[20] Patients with COVID-19-related ARDS have a median compliance 28% higher than the median in classical ARDS cohorts. Regardless, only 5·7% of patients with COVID-19 related ARDS had static compliance greater than the 95th percentile of those with classical ARDS. Notably, other published case series of critically ill patients with COVID-19 have reported median static compliance of 20–43 mL/cm $H_2O$,[31,32] similar to those in classical ARDS. In the three most recent and largest studies, median static compliance was 27 mL/cm $H_2O$ (IQR 22–36; n=257), 28 mL/cm $H_2O$ (IQR 23–38; n=267), and 35 mL/cm $H_2O$ (IQR 27–45; n=296).[33–35] Furthermore, by quantitative analysis of lung CT scans, we found that total lung weight was similar to that in classical ARDS and was virtually identical to classical ARDS, when normalised to ARDS severity (appendix p 4). Together, these data strongly suggest that patients with COVID-19-related ARDS have values of static compliance that overlap those in classical ARDS.

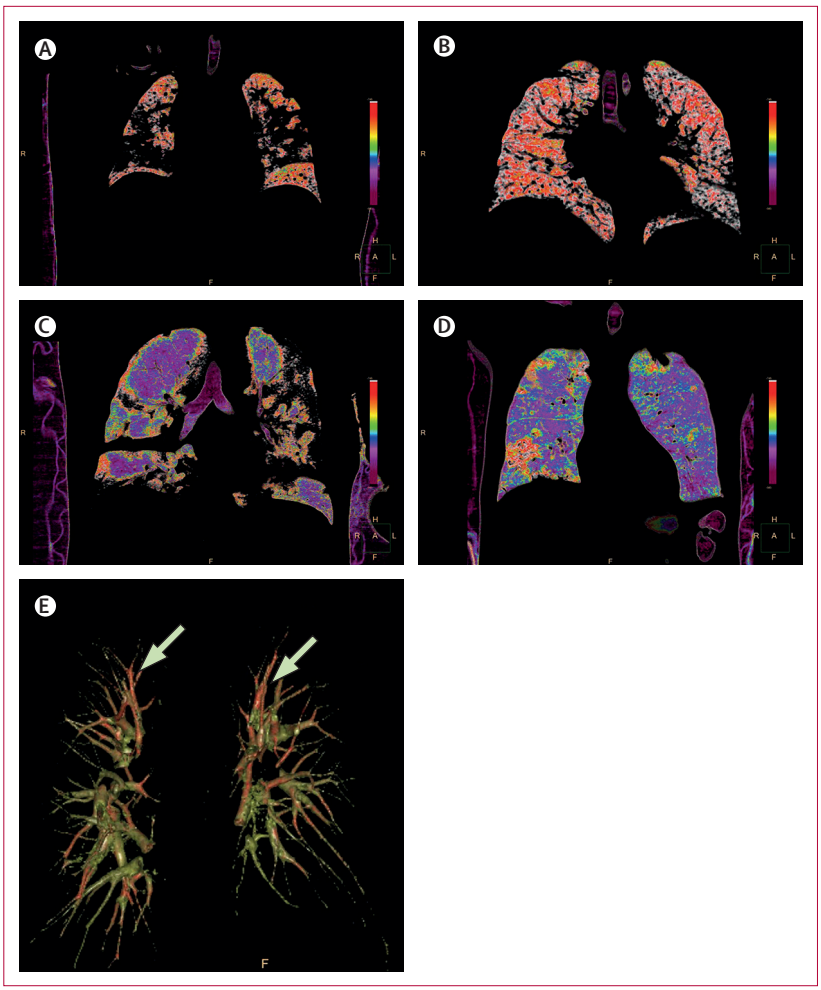


*Figure 2:* **Distribution of perfusion through CT angiogram coronal slices of patients representative of each D-dimer and compliance subgroup**
(A–D) CT angiogram in patients with COVID-19. (A) A 42-year-old man from the LDLC group (static compliance 38 mL/cm $H_2O$; D-dimer 1260 ng/mL; $PaO_2/FiO_2$ 144). (B) A 70-year-old man from the LDHC group (static compliance 46 mL/cm $H_2O$; D-dimer 587 ng/mL; $PaO_2/FiO_2$ 114). (C) A 62-year-old man from the HDLC group (static compliance 32 mL/cm $H_2O$; D-dimer 15 430 ng/mL; $PaO_2/FiO_2$ 52). (D) A 75-year-old man from the HDHC group (static compliance 50 mL/cm $H_2O$; D-dimer 21 010 ng/mL; $PaO_2/FiO_2$ 76). Purple-blue colouring indicates hypoperfusion. (E) Three-dimensional reconstruction of the pulmonary vascular arterial tree from the patient in panel D. Red (arrows) shows thromboembolic lesions. HDHC=high D-dimers, high compliance. HDLC=high D-dimers, low compliance. LDHC=low D-dimers, high compliance. LDLC=low D-dimers, low compliance. $PaO_2/FiO_2$=ratio of partial pressure of arterial oxygen to fractional concentration of oxygen in inspired air.

Similarly to a previous study,[8] we found that most of our patients had markedly increased D-dimer concentrations (median 1880 ng/mL [IQR 820–6243]), a biomarker linked to increased inflammation, fibrin degradation, and possibly to vascular endothelial injury. Although we cannot demonstrate a direct link between D-dimer concentrations and thrombotic burden, we found that the ventilatory ratio, a marker of dead space, was higher in patients with COVID-19-related ARDS who had very high D-dimer concentrations irrespective of the patients' static compliance. Moreover, we showed

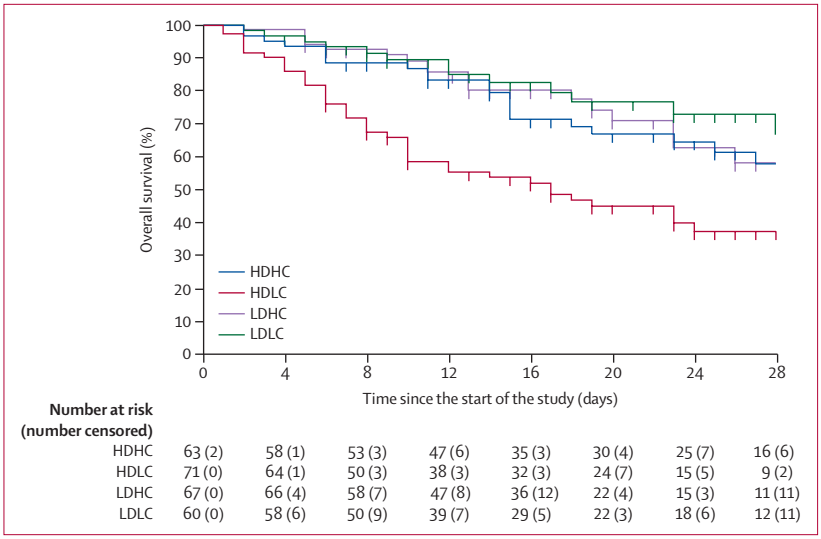


***Figure 3:*** **Kaplan-Meier analysis of 28-day survival in the four D-dimer and static compliance subgroups**
HDHC=high D-dimers, high compliance. HDLC=high D-dimers, low compliance. LDHC=low D-dimers, high compliance. LDLC=low D-dimers, low compliance.

| | Hazard ratio (95% CI) |
|---|---|
| Class | |
| High D-dimers, low compliance | 1 (ref) |
| High D-dimers, high compliance | 0·448 (0·230–0·873) |
| Low D-dimers, high compliance | 0·420 (0·215–0·818) |
| Low D-dimers, low compliance | 0·386 (0·152–0·985) |
| Sex | |
| Female | 1 (ref) |
| Male | 1·803 (0·679–4·788) |
| Age | 1·048 (1·002–1·095)* |
| $PaO_2/FiO_2$ | 0·996 (0·992–1·000)* |

$PaO_2/FiO_2$=ratio of partial pressure of arterial oxygen to fractional concentration of oxygen in inspired air. *Change in risk of death per one unit increase (years for age and mm Hg for $PaO_2/FiO_2$).

***Table 2:*** **Cox proportional risk analysis for mortality**

a dose–response association with higher values of ventilatory ratio at higher D-dimer concentrations (appendix p 6).

CT angiogram studies showed filling defects or occlusions of the pulmonary vasculature that were more prominent in patients with high D-dimer concentrations. Although limited by the experimental algorithm used to identify clots, this finding is similar to that observed in patients with H1N1-associated ARDS who had a significantly higher incidence of pulmonary embolism than patients with ARDS of different causes.[36] Although increased D-dimer concentrations might be driven by inflammatory mechanisms and dead-space ventilation might be due to mechanisms other than microclots, our study suggests that intravascular pathology plays a major role increasing dead space and causing hypoxaemia in COVID-19-related ARDS. This role could explain the observation that static compliance and $PaO_2/FiO_2$ were not correlated in COVID-19-related ARDS, but were correlated in classical ARDS (appendix p 3).

We also found a dramatic increase in mortality in a subgroup of patients that had a combination of very high D-dimer concentrations and low static compliance. The 28-day mortality in this group was more than two times higher than in patients who had increases of either D-dimer concentration or static compliance individually. These data suggest that patients have poor prognosis if SARS-CoV-2 attacks both the pulmonary cells and vascular system; although we cannot distinguish between injury in the pulmonary or systemic vasculature. Our findings are consistent with data showing that the lungs of patients with COVID-19 display distinctive vascular features, consisting of severe endothelial injury associated with the presence of intracellular virus and disrupted cell membranes.[25]

The observational nature of this study is its major weakness and affected several aspects of the study. First, the decision to use the physiological or ventilatory variables judged as most representative of the patient's status by the senior attending physician might have introduced inconsistencies because different selection criteria were used in the two historical comparators (ie, temporal criteria for the LUNG-SAFE[20] and protocol-driven criteria for the Berlin definition[5]). Second, since the number of CT scans and CT angiograms was limited by the risk of contagion[15] and since the angiograms might have been ordered in response to high D-dimer concentrations, we cannot exclude a selection bias in the subset of patients in whom CT scans were done, and they might not have been representative of the entire population. However, although quantitative CT scan analysis was done in a subset of patients with more severe ARDS (appendix p 11), stratified analysis showed that lung weight in severe COVID-19-related ARDS was essentially identical to the lung weight in severe classical ARDS (appendix p 4). Third, PEEP levels during CT scans in COVID-19-related ARDS (clinically set) and in classical ARDS (protocolised in an experimental settings)[5] were different, thus adding an element of heterogeneity in the comparisons; however, this should not have affected measurements of total lung weight. Fourth, although we did a stratified analysis and built a multivariable model to account for a number of potential confounding factors, the differences between COVID-19-related ARDS and classical ARDS could be influenced by many other factors not captured by our analysis—eg, comorbidities and onset of complications during ICU stay. Moreover, by definition, all patients with COVID-19-related ARDS had a viral origin for their ARDS, whereas classical ARDS can have various causes. However, our stratified analysis examining a subgroup of patients with classical ARDS caused by pneumonia yielded similar results. Fifth, physiological values obtained from previous studies were probably not taken at the same

timepoints as values obtained from our patients with COVID-19-related ARDS. In fact, this issue might partially explain the great heterogeneity in classical ARDS. Also, not all patients with COVID-19-related ARDS had all ventilatory and laboratory variables assessed.

The major strength of this study is the systematic analysis of physiological, laboratory, and clinical features obtained from a large, unbiased, multicentre series of patients. As such, it might have important implications for the clinical management of patients with COVID-19-related ARDS. The statement that classical protective ventilatory strategies[13] might not be recommended for some[4,36] patients with COVID-19-related ARDS is not backed up by our data. Under these circumstances, protective ventilatory strategies[13] are still recommended. The observation of higher values of ventilatory ratios (a marker of dead space) in patients with very high D-dimer concentrations might suggest that lower levels of PEEP should be used, especially in patients in the higher range of static compliance.[37] Furthermore, a meta-analysis of the use of PEEP in ARDS found that higher PEEP was associated with decreased mortality in patients with a $PaO_2/FiO_2$ less than 200, possibly related to lower static compliance.[38] The absence of correlation between $PaO_2/FiO_2$ and static compliance in patients with COVID-19 (appendix p 7) suggests that this conclusion will have to be reassessed in these patients.

Our results also have implications for the design of clinical trials. When SARS-CoV-2 affects both the pulmonary parenchyma and the coagulation or vasculature system, the 28-day mortality rate is extremely high. Identification of this phenotype is important for ongoing trials of anticoagulants or thrombolytics.

In conclusion, this study provides evidence confirming that patients with COVID-19-related ARDS have a form of injury similar to classical ARDS. When an easily identified phenotype of increased parenchymal damage (low static compliance) and increased D-dimer concentrations occurs together, mortality is extremely high.

#### Contributors

GG, TT, JL, CF, FL, MC, RF, SN, J-LV, MA, ASS, APe, and VMR were responsible for study design, data analysis, data interpretation, and preparing the first draft of the manuscript. All authors were responsible for data acquisition and data interpretation. CF did the statistical analysis. GG, TT, ASS, APe, and VMR finalised the manuscript. ASS, APe, and VMR are responsible for study data integrity. All authors reviewed the manuscript and approved the final submitted version.

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#### Declaration of interests

GG reports personal fees and non-financial support from Getinge and Biotest; personal fees from ThermoFisher Scientific; grants and personal fees from Fisher & Paykel; and personal fees from Draeger Medical, outside the submitted work. AZ has patent ES2732104 licensed to AW Technologies and patents US2017348472 and US2017224898 licensed to Fresenius. MC reports personal fees from Edwards Lifesciences, Directed Systems, and Cheetah Medical, outside the submitted work. ASS reports personal fees from Baxter and Novalung/Xenios. APe reports personal fees from Maquet, Novalung/Xenios, Baxter, and Boehringer Ingelheim, outside the submitted work. All other authors declare no competing interests.

#### Data sharing

Deidentified individual participant data that underlie results reported in this Article will be available. Applicants must provide (1) a methodologically sound approach to achieve scientific aims and (2) formal documents of approval from the ethics committee of the applicant's institution. Data will be made available pending authorisation of the Policlinico di Sant'Orsola ethics committee, which will review applicants' requests, and after signing an appropriate data sharing agreement. Proposals should be directed to the corresponding author. Data will be available immediately after publication with no end date.

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