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Respiratory system mechanics, gas exchange, and outcomes in mechanically ventilated patients with COVID-19-related acute respiratory distress syndrome: a systematic review and meta-analysis

Malikkarjuna Ponnapa Reddy, Ashwin Subramanium, Clara Chua, Ryan Ruiyang Ling, Christopher Anstey, Kollengode Ramanathan, Arthur S Slutsky, Kiran Shekar

The association of respiratory mechanics, particularly respiratory system static compliance ($C_{RS}$), with severity of hypoxaemia in patients with COVID-19-related acute respiratory distress syndrome (ARDS) has been widely debated, with some studies reporting distinct ARDS phenotypes based on $C_{RS}$. Ascertainment whether such phenotypes exist is important, because they might indicate the need for ventilation strategies that differ from those used in patients with ARDS due to other causes. In a systematic review and meta-analysis of studies published between Dec 1, 2019, and March 14, 2022, we evaluated respiratory system mechanics, ventilator parameters, gas exchange parameters, and clinical outcomes in patients with COVID-19-related ARDS. Among 11,356 patients in 37 studies, mean reported $C_{RS}$ measured close to the time of endotracheal intubation, was 35·8 mL/cm H2O (95% CI 33·9–37·8; $P=0·96$; $I^2=32·6$). Pooled mean $C_{RS}$ was normally distributed. Increasing ARDS severity (assessed by PaO2/FiO2 ratio as mild, moderate, or severe) was associated with decreasing $C_{RS}$. We found no evidence for distinct $C_{RS}$-based clinical phenotypes in patients with COVID-19-related ARDS, and we therefore conclude that no change in conventional lung-protective ventilation strategies is warranted. Future studies should explore the personalisation of mechanical ventilation strategies according to factors including respiratory system mechanics and haemodynamic status in patients with ARDS.

Introduction

Acute respiratory distress syndrome (ARDS) is a complex clinical syndrome with a variety of aetiologies, including infectious and non-infectious precipitating factors. ARDS is characterised by a combination of acute onset, hypoxaemia (ratio of partial pressure of oxygen in arterial blood [PaO2] to fractional inspired oxygen [FiO2] of ≥300 mm Hg), and bilateral pulmonary opacities on chest x-ray or CT that are not fully explained by cardiac failure or volume overload. ARDS severity is classified on the basis of the PaO2/FiO2 ratio as mild (>200 to 300 mm Hg), moderate (>200 to 200 mm Hg), or severe (≤200 mm Hg). Patients with ARDS usually have low respiratory system compliance, but this factor was excluded from the Berlin definition of ARDS because respiratory mechanics added little predictive value.

The current protocolised approach to treating ARDS has attracted much scrutiny, especially during the COVID-19 pandemic, when calls being made for a more personalised approach. There was an initial suggestion, on the basis of small observational studies of patients with COVID-19-related ARDS, that the severity of hypoxaemia was out of proportion to impairment in respiratory system mechanics. Despite meeting the criteria for moderate-to-severe ARDS, these patients were found to have relatively normal respiratory system compliance, and shunt fraction—i.e., the percentage of cardiac output circulating through the lungs that is not completely oxygenated—that was out of proportion to non-aerated lung fraction. If this finding proved to be generalisable to the large population of patients with COVID-19-related ARDS, it could have implications for ventilation management, as suggested by others.

However, these early observations have been challenged by several researchers and commentators.

It has also been proposed that severe hypoxaemia and high respiratory drive in patients with COVID-19-related and non-COVID-19-related ARDS with otherwise preserved respiratory system static compliance ($C_{RS}$)—i.e., respiratory system compliance when there is no airflow—could mediate ARDS progression via patient self-inflicted lung injury (P-SILI). P-SILI refers to the lung injury that can develop from intense inspiratory effort. Although the existence of different phenotypes in patients with COVID-19-related ARDS based on $C_{RS}$ values seems plausible, measured $C_{RS}$ is intricately linked to extent of the aerated lung at the time of measurement, which depends on the timing of endotracheal intubation and invasive mechanical ventilation. Multiple small observational studies have not been able to identify such distinct phenotypes of $C_{RS}$ and reported a unimodal distribution of $C_{RS}$ in COVID-19-related ARDS.

It is possible that patients with hypoxaemia who were intubated early and placed on mechanical ventilation during the first months of the pandemic, when less invasive respiratory supports were discouraged, could have exhibited high $C_{RS}$. Subsequently, greater uptake of less invasive supports, less proactive endotracheal intubation, and the advent of disease-modifying therapies, such as corticosteroids, might all have affected the occurrence of the high-$C_{RS}$ phenotype.

A 2021 study that used dual-energy CT showed that, in critically ill patients with severe COVID-19-related ARDS, oxygenation impairment and the need for invasive
mechanical ventilation were associated with a loss of lung aeration, greater shunt fraction, and the extent of ventilation–perfusion mismatch, which indicates a potential loss of hypoxic vasoconstriction.11 Patients with COVID-19-related ARDS could have varying degrees of $C_{rs}$, recruitability, and hypoxaemia depending on the extent of ventilation–perfusion mismatch.

In view of uncertainty about respiratory system mechanics and phenotypes of $C_{rs}$ in patients with COVID-19-related ARDS—and their potential implications for ventilation management and outcomes—we aimed to characterise and evaluate basic respiratory system mechanics, ventilator parameters, gas exchange parameters, and clinical outcomes in a systematic review and meta-analysis of studies of patients with COVID-19-related ARDS. We used the earliest measures of respiratory variables taken (hours to days) after the initiation of invasive mechanical ventilation, because delayed findings would be influenced by disease progression and interventions or therapies administered to patients.13 We discuss the implications of our findings for the management of individuals with COVID-19-related ARDS.

Methods

The study was conducted and the findings reported in adherence to the Preferred Reporting Items for Systematic Reviews and Meta-analyses statement (appendix pp 2–3).14

Study selection

We carried out a literature search of MEDLINE through PubMed, Embase via Ovid, and the COVID-19 living systematic review on March 14, 2022. Living systematic reviews have been used during the Zika virus epidemic15 and during the COVID-19 pandemic.16 The key search terms “acute respiratory distress syndrome”; “intubate” or “mechanical ventilation”; and “coronavirus” were combined using the Boolean operators “OR” within search strings and using “AND” across search strings (appendix p 11).

We included several study types published during the COVID-19 pandemic period (from Dec 1, 2019, to March 14, 2022), including prospective cohort studies, case series with at least five patients, and studies of unspecified design. Studies were included if they involved adult patients (≥18 years) who received mechanical ventilation and if ventilator parameters were reported soon (hours to days) after the initiation of invasive mechanical ventilation. Studies were excluded if they did not present $C_{rs}$ data. Studies with a selected group of patients (eg, patients with moderate or severe ARDS or patients with obesity) or with patients who required special interventions (eg, prone positioning or inhaled nitric oxide) were excluded from the primary analysis. In the case of overlapping patient data (eg, overlapping enrolment period or same hospital) across two or more studies, we included the study with the largest sample size.

Key messages

- Acute respiratory distress syndrome (ARDS) is typically associated with reduced respiratory system compliance due to loss of surfactant, flooded alveoli, and compressive atelectasis
- Reduced lung compliance in ARDS is usually a marker of decreased lung volume, and hence an indication that tidal volume should be reduced to prevent over-distension of healthy lung units; substantially reduced compliance in ARDS is associated with a high risk of lung injury from shear strain, barotrauma, or volutrauma; lung-protective ventilation with high positive end-expiratory pressure and low tidal volume in patients with poor lung compliance has been shown to decrease lung injury
- In the first months of the pandemic, when less invasive strategies for respiratory support were discouraged and disease-modifying therapies such as corticosteroids were not in use, some reports suggested that patients with COVID-19–related ARDS had higher respiratory system static compliance ($C_{rs}$) measured soon after intubation than that reported for ARDS due to other causes, with potential implications for ventilation management
- The suggestion that severity of hypoxaemia is out of proportion to impairment in respiratory system mechanics in patients with COVID-19-related ARDS was not borne out in our systematic review and meta-analysis, in which $C_{rs}$ measured soon after the initiation of invasive mechanical ventilation in patients with COVID-19-related ARDS was normally distributed and similar to $C_{rs}$ reported in clinical trials that recruited patients with conventional ARDS; we did not find evidence for distinct $C_{rs}$–based clinical phenotypes in patients with COVID-19-related ARDS
- Reported $C_{rs}$ in patients with COVID-19–related ARDS decreased as the severity of ARDS increased (assessed by PaO$_2$/FiO$_2$ ratio); positive end-expiratory pressure and tidal volume showed a positive association with $C_{rs}$, whereas plateau pressure was negatively associated with $C_{rs}$
- Our study suggests that ventilatory strategies used in patients with non-COVID-19–related ARDS should be used in patients with COVID-19-related ARDS until there is evidence to the contrary; future research should focus on how best to individualise ventilatory strategy to the patient’s specific respiratory mechanics and haemodynamic status

Data extraction and quality assessment

We extracted data for the included studies using a pre-specified datasheet (appendix p 12). Variables in the pre-specified datasheet included study characteristics, demographic data, clinical characteristics, interventions, and outcomes. For each selected observational study, the risk of bias was evaluated by two authors (MPR and CC) independently, using the five domains (selection, sample size, comparability, compliance reporting method, and quality of statistics; appendix p 13) of the modified Newcastle-Ottawa Scale (mNOS), which has a range of scores from 2 to 5.17 The mNOS was used because there were no control groups in the included studies. Certainty of evidence was assessed by four main factors (risk of bias, inconsistency, indirectness, and imprecision)18 using the Grading of Recommendations Assessment, Development and Evaluations (GRADE) approach. The certainty of the evidence was rated from high (ie, we are very confident that the true effect lies close to that of the effect estimate) to very low (ie, we have very little confidence in the effect estimate: the true effect is likely to be substantially different; appendix pp 14–15).19–21
screening of studies, data collection, and risk-of-bias assessment were conducted independently and in duplicate by MPR and CC. Conflicts were resolved by consensus or by ASu.

**Data synthesis**

Given the substantial heterogeneity in patient demographics and treatment modalities for COVID-19, an inverse-variance random-effects meta-analysis was conducted. When pooling studies for meta-analysis of proportions, a distribution-free random-effects model was applied, using the standard method proposed by DerSimonian and Laird. Furthermore, the popular two-step arc-sine transformation described by Freeman and Tukey was applied to yield better final approximations of the normal distribution. We assessed the normal distribution of studies using a Shapiro-Wilk test. 95% CIs were computed using the Clopper-Pearson method.

We assessed the possibility of publication bias via visual inspection of the funnel plot and Egger’s test, and corrected for small-study effects using the random-effects trim-and-fill procedure. We performed two sensitivity analyses. Firstly, we excluded studies with higher risks of bias (defined as an mNOS score of <3). Secondly, we repeated the primary meta-analysis using the fixed-effects model. Survival outcomes are presented as pooled proportions, and continuous outcomes are presented as pooled means, each with their respective 95% CI.

To explore potential sources of heterogeneity and to examine potential prognostically relevant covariates, we conducted subgroup analyses on the basis of ARDS severity (PaO2/FiO2 ratio of >200–300 mm Hg, >100 to 200 mm Hg, or ≤100 mm Hg), presence of hypercarbia (partial pressure of carbon dioxide in arterial blood [PaCO2] >45 mm Hg vs ≤45 mm Hg) and value of positive end-expiratory pressure (PEEP; >15 cm H2O vs ≤15 cm H2O). The random-effects χ² test was used to assess differences between subgroups. We also conducted a summary-level meta-regression to investigate the effect of demographic factors, disease factors, and intervention factors on CRS. Demographic factors included mean BMI, average date of patient enrolment (defined as the midpoint between the first and last dates of patient enrolment in the study), disease factors (assessed by PaO2/FiO2 ratio and PaCO2), and intervention factors (PEEP, plateau pressure, driving pressure, and tidal volume [VT]). Subsequent regression results were reported as regression slopes (β) and 95% CIs.

We then pooled the following mortality rates: 28-day mortality, intensive care unit [ICU] mortality, in-hospital mortality, and cumulative mortality (defined as mortality at the latest point of recording). We also pooled the ICU length of stay, the hospital length of stay, and ventilator-free days. For continuous variables, means and SDs were derived from the aggregate data as per Luo and colleagues and Wan and colleagues. Because statistical heterogeneity can be overestimated by I² statistics in observational studies, we assessed interstudy variability as part of the assessment of the certainty of evidence outlined by the GRADE approach. A post-hoc sensitivity analysis was done on the basis of individual study sample size (≤100 vs >100). All statistical analyses were done with R (version 4.0.2). A nominal p value of less than 0.05 was considered to be statistically significant in our study. The study protocol is registered with PROSPERO, CRD42020226124.

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**Figure 1: Study selection**

ARDS=acute respiratory distress syndrome. ECMO=extracorporeal membrane oxygenation. *Studies were excluded because they were not about patients with COVID-19.
Results

Of the 3416 references published until March 14, 2022, we assessed 1311 full-text articles for eligibility. We identified 12 095 patients receiving invasive ventilation for COVID-19-related ARDS from 51 observational studies that met our inclusion criteria. Of these studies, 37 unselected ARDS studies, involving a total of 11 356 patients (8861 male patients and 2495 female patients), were used for the primary analysis (figure 1).

Among 51 studies of COVID-19-related ARDS, only nine had an mNOS score of less than 3; the others had an mNOS score that was 3 or more (23 studies had scores of 3, 11 studies had scores of 4, and eight studies had scores of 5; appendix p 13). The population was predominantly male (9268 [78·9%] of 11742 patients; 45 studies).

The pooled BMI of patients was 25·9 kg/m² (SD 2·45, range 25·3–34·7 kg/m²; appendix pp 18–20). GRADE assessments are illustrated in the appendix (pp 14–15). Ventilator parameters and respiratory variables are shown in the appendix (pp 21–23). Variations in Crs, PaCO₂, Vt, and PEEP are also shown in the appendix (p 9).

The pooled reported Crs in patients from studies of unselected COVID-19-related ARDS was 35·8 mL/cm H₂O (95% CI 33·9–37·8; I²=96·9%, τ²=32·6; high certainty; figure 2). In these studies, Crs dispersion was not significantly different from a normal distribution (Shapiro–Wilk test p=0·95; figure 3). The pooled reported Crs in all patients from studies of selected and unselected COVID-19-related ARDS was 35·8 mL/cm H₂O (95% CI 33·9–37·8; I²=96·9%, τ²=32·6; high certainty; figure 3). The complex interactions of Crs with PaO₂/FiO₂ ratio and PaCO₂ and PEEP are shown in figure 5A; the interactions of Crs and PaCO₂ (31·5 [95% CI 27·7–35·4] in patients with PaCO₂ >45 mm Hg vs 36·5 [33·3–39·6] in those with PaCO₂ ≤45 mm Hg; pinteraction=0·052; table 1) or between Crs and PEEP (35·2 [95% CI 27·6–42·8] in patients PEEP >15 cm H₂O vs 34·0 [32·3–36·2] in those with PEEP ≤15 cm H₂O; pinteraction=0·80; table 1). Further details of the association between Crs and PEEP are provided in the appendix (pp 8–9).

The overall pooled mean PaO₂/FiO₂ ratio of patients in unselected studies was 149·1 mm Hg (95% CI 135·4–162·9; 34 studies). Increasing severity of COVID-19-related ARDS, assessed by PaO₂/FiO₂, was associated with reduced Crs (pinteraction<0·0001); Crs progressively decreased from 39·3 mL/cm H₂O (95% CI 36·6–42·0) in patients with mild ARDS, to 34·9 mL/cm H₂O (32·8–36·9) in patients with moderate ARDS, and 27·3 mL/cm H₂O (23·3–31·2) in patients with severe ARDS (table 1, figure 4). There was no significant association between Crs and PaCO₂ (31·5 [95% CI 27·7–35·4] in patients with PaCO₂ >45 mm Hg vs 36·5 [33·3–39·6] in those with PaCO₂ ≤45 mm Hg; pinteraction=0·052; table 1) or between Crs and PEEP (35·2 [95% CI 27·6–42·8] in patients PEEP >15 cm H₂O vs 34·0 [32·3–36·2] in those with PEEP ≤15 cm H₂O; pinteraction=0·80; table 1). Further details of the association between Crs and PEEP are provided in the appendix (pp 8–9).

The complex interactions of Crs with PaO₂/FiO₂ ratio and PEEP are shown in figure 5A; the interactions of Crs with PaCO₂ and PEEP are shown in figure 5B. In patients with moderate-to-severe ARDS (PaO₂/FiO₂ ratio ≤200 mm Hg), increased PEEP was associated with higher compliance than in patients with mild ARDS (PaO₂/FiO₂ ratio >200 to 300 mm Hg).

In univariable meta-regression analyses, there was a statistically significant positive correlation between Crs (the dependent variable) and PaO₂/FiO₂ ratio (β=0·06, 95% CI 0·02 to 0·11), between Crs and PEEP (0·88, 0·07 to 1·68), and between Crs, PaCO₂, Vt, and PaO₂/FiO₂ ratio >200 to 300 mm Hg.

Crs had a statistically significant negative correlation with
The pooled mean ICU length of stay was 19 days (95% CI 15–22; high certainty; 25 studies), whereas the pooled mean hospital length of stay was 28 days (23–34; high certainty; 13 studies). The pooled mean ventilator-free days (up to day 28) was 5·2 days (2·9–7·6; high certainty; seven studies). The appendix shows the results for secondary outcomes (p 24).

Post-hoc sensitivity analysis conducted on the basis of the individual study sample size (≤100 patients in 31 studies vs >100 patients in 20 studies) found no difference in $C_{rs}$ (34·6 mL/cm H$_2$O [95% CI 31·8–37·3; $I^2$=91·9%, $t^2$=55·5] for sample ≤100 vs 35·0 mL/cm H$_2$O [32·4–37·5; 98·5%, $t^2$=52·5] for sample >100; appendix p 29).

Another post-hoc sensitivity analysis using the fixed-effects model yielded a value that was similar to that of the random-effects model ($C_{rs}$ 34·1 mL/cm H$_2$O, 33·9–34·3; 97·0%, 43·6; appendix p 10).

### Discussion

In this systematic review and meta-analysis, we evaluated respiratory mechanics, gas exchange, and outcomes in a very large group of mechanically ventilated patients with COVID-19-related ARDS. Our main findings, based on data from 11 356 patients in 37 unsellected studies, were as follows: pooled mean $C_{rs}$ measured close to the time of endotracheal intubation, was normally distributed; $C_{rs}$ decreased progressively with increasing severity of ARDS (assessed by decreasing PaO$_2$/FiO$_2$ ratio); higher PEEP and higher $V_t$ were associated with greater $C_{rs}$; and higher plateau pressure and driving pressure were associated with lower $C_{rs}$.

#### Respiratory system mechanics in COVID-19-related ARDS

We found that pooled mean $C_{rs}$, measured close to the time of the initiation of invasive mechanical ventilation, was 35·8 mL/cm H$_2$O (95% CI 33·9–37·8) across 37 unsellected studies and the reported mean $C_{rs}$ across the 51 studies ranged from 22·7 to 54·3 mL/cm H$_2$O. In comparison, the reported mean $C_{rs}$ in landmark ARDS clinical trials published between 2004 and 2017 that included patients with all severities of ARDS, or moderate-to-severe ARDS, ranged from 23·2 to 41·0 mL/cm H$_2$O. These ARDS trials are useful comparators because they applied lung-protective ventilation strategies (ie, low $V_t$ and moderate-to-high PEEP) similar to those applied in COVID-19 studies, given that such a strategy is now standard practice. In this setting, studies of patients with COVID-19-related ARDS that reported higher $C_{rs}$ than is typically seen in patients with ARDS due to other causes might have included patients who were treated with an early intubation strategy at the beginning of the COVID-19 pandemic. Non-invasive ventilation and high-flow oxygen ventilation were not preferentially used during the first months of the pandemic due to concerns of viral aerosolisation and resultant safety concerns for driving pressure (−2·49, −3·12 to −1·86), with plateau pressure (−0·77, −1·53 to −0·02), and with PaCO$_2$ (−0·39, −0·71 to −0·07). There was no significant correlation between $C_{rs}$ and BMI (−0·02, −1·09 to 1·05) or between $C_{rs}$ and average date of patient enrolment (−0·005, −0·04 to 0·03). The results of the meta-regression analyses are presented in table 2 and in the appendix (p 9).

The pooled mean reported ICU mortality was 35·7% (95% CI 29·4–42·2; $I^2$=97·6%, $t^2$=41·1; moderate certainty; 27 studies), whereas the pooled in-hospital mortality was 39·1% (32·6–45·8; moderate certainty; 14 studies). The overall pooled 28-day mortality was 43·2% (32·6–54·1; moderate certainty; 13 studies). Pooled cumulative mortality was 40·3% (35·1–45·6; moderate certainty; 43 studies). $C_{rs}$ had no significant correlation with cumulative morality ($β$=−0·005, 95% CI −0·01 to 0·002).
health-care workers. As such, patients were intubated at the early stages of the disease process, when $C_{rs}$ was still preserved.

In addition, we found that the mean $Pao_2$/$FiO_{2}$ ratio of patients from unselected COVID-19-related ARDS studies, obtained at the time of $C_{rs}$ measurements, was 149·1 mm Hg (95% CI 135·4–162·9; range 95·3–271·8). In comparison, the range of mean $Pao_2$/$FiO_{2}$ ratios in non-COVID-19-related ARDS clinical trials was 100–200 mm Hg.\textsuperscript{5–6} The range of mean $V_t$ values in COVID-19-related ARDS studies was 5–6·6–4 mL/kg, compared with a mean $V_t$ range of 5·8–8·6 mL/kg in ARDS clinical trials (appendix pp 31–33). The mean PEEP range in COVID-19 ARDS studies was 6–0–20–1 cm H$_2$O, compared with a range of 7·5–16·1 cm H$_2$O in ARDS clinical trials.\textsuperscript{7–8} These data indicate that the suggested existence of distinct $C_{rs}$-based phenotypes in patients with COVID-19-related ARDS could simply have been based on observations from small datasets during an early phase of the pandemic. Reduction in lung compliance in ARDS is attributed to a decrease in aerated lung volume due to fluid-filled alveoli from inflammatory oedema, decreased surfactant function, and atelectasis. We believe that patients with COVID-19 also have similar pathophysiological changes. However, in addition to the timing of intubation, ARDS severity, and the ventilation strategy applied, factors such as viral mutations, vaccination uptake, and increased use of disease-modifying drugs as the pandemic progressed could all contribute to the measures obtained and could not be controlled for in our analysis.

The association of higher PEEP with greater $C_{rs}$ might be related to lung recruitment. There is an ongoing debate about optimal PEEP and lung tissue available for recruitment in COVID-19-related ARDS, and about the routine application of low $V_t$, in all patients with ARDS, regardless of respiratory mechanics. Many have argued that the routine application of higher PEEP and low $V_t$ in all patients with COVID-19-related ARDS, regardless of their respiratory mechanics, could be detrimental.\textsuperscript{1,6,5} Greater $C_{rs}$ was seen in patients who received higher PEEP, higher $V_t$, or a combination of both. Application of higher PEEP in patients with relatively high $C_{rs}$ might have been driven partly by the severity of hypoxaemia, which suggests a possible dissociation between gas exchange and mechanics. These observations, in a small group of patients, might have led to the $C_{rs}$-based phenotype hypothesis. It is possible that hypoxaemia and

**Figure 4:** Forest plot comparing mean $C_{rs}$ of each study with the severity of ARDS

Data from 47 of the 51 studies of patients with COVID-19-related ARDS are shown, with severity of ARDS assessed by the mean $Pao_2$/$FiO_{2}$ ratio of each study ARDS-acute respiratory distress syndrome, $C_{rs}$-respiratory system static compliance, $FiO_{2}$-fractional inspired oxygen, $Pao_2$-partial pressure of oxygen in arterial blood.
CRS could at times be decoupled, albeit transiently, in patients with ARDS, and this observation might not be specific to COVID-19-related ARDS. Similarly, the higher VT found in patients with greater CRS might indicate that clinicians applied both VT and PEEP—based on an assessment of respiratory mechanics—to maintain safe driving and plateau pressures, instead of undertaking a routine low-VT, high-PEEP approach. Establishing whether either of these approaches was independently detrimental is beyond the scope of our analysis given the scarcity of individual patient data. Higher driving pressures seen in patients with lower CRS, although expected, are challenging to decipher further in the absence of individual patient data and measurements over time. Clinicians might have further optimised PEEP and VT to reduce driving pressure in the patients most severely affected by COVID-19-related ARDS.

Personalised ventilation management in ARDS
The COVID-19 pandemic has re-kindled the concept that mechanical ventilation should be personalised for every patient according to several factors, including a patient’s CRS, PEEP, overall respiratory system mechanics, acid-base balance, and haemodynamic status. Studies during the initial stages of the COVID-19 pandemic suggested the existence of different ARDS phenotypes with either normal CRS or very low CRS. Subsequent studies addressed the existence of these COVID-19-related ARDS phenotypes, but the studies were limited by relatively small sample sizes. Early in the pandemic, many guidelines across the globe recommended early intubation to minimise the risk of SARS-CoV-2 infection among healthcare workers. As such, many patients might have been intubated and mechanically ventilated early; alternatively,
they might have faced unnecessary delays owing to resource constraints. Either of these scenarios could have influenced measurements of $C_{rs}$ and might have led to potential artifactual clinical phenotypes.

Mechanical ventilation supports should be tailored to patient physiology rather than to a pathological condition. Making changes to conventional ventilatory strategies or adopting newer strategies on the basis of scarce evidence in emerging infectious respiratory pathologies can be deleterious to patients. Future studies should explore personalised strategies, which might be informed by multivariable in silico modelling of the dynamic variables related to respiratory mechanics and gas exchange. These strategies could be augmented by cardiopulmonary computational models and artificial intelligence, which might provide safer ventilatory approaches in patients with ARDS of any aetiology. Ideally, these approaches would be tested in clinical trials prior to widespread use.

Study strengths and limitations
Our systematic review and meta-analysis had many strengths. To our knowledge, this is the first systematic review evaluating respiratory characteristics and mechanics of patients with COVID-19-related ARDS. Rigorous search criteria were used, and appropriate statistical analyses were done to evaluate the outcomes. Of note, 42 of 51 COVID-19-related ARDS studies were of acceptable quality, with an mNOS score that was greater than 3. In addition, our meta-analysis summarised data from more than 2 years across the COVID-19 pandemic. Through this analysis, we can derive a broader, longitudinal view of how respiratory mechanics change in patients who receive mechanical ventilation for COVID-19, which other studies have not been able to investigate. Furthermore, appropriate sensitivity analyses were conducted, and the GRADE approach was used to rate the certainty of the evidence, allowing us to communicate our findings in an efficient and standardised manner.

However, some limitations of our study need to be acknowledged. First, there was substantial heterogeneity, not only in patient management with regard to mechanical ventilation, but also in the way and time of reporting of the analysed variables in the included studies. Variable effects of the pandemic on different countries, and variable resource availability during the COVID-19 era, might understandably have further influenced the timing of commencement of invasive mechanical ventilation and, therefore, might have affected measured $C_{rs}$. Nonetheless, the subgroup and meta-regression analyses were able to identify several covariates (eg, $P_P$, ratio, PEEP, $P_aCO_2$, $V_t$, plateau pressure, and driving pressure) that might have influenced $C_{rs}$, explaining the possible sources of heterogeneity in our analysis. Second, there was wide variation in sample size among studies, ranging from 11 to 2635 patients. This heterogeneity, especially in small studies, could lead to selection bias and could increase the risk of random error.

Conclusions and future directions
In this large systematic review and meta-analysis, the pooled $C_{rs}$ in patients with COVID-19-related ARDS, measured close to the time of the initiation of invasive mechanical ventilation, was normally distributed. We did not observe any distinct $C_{rs}$-based clinical phenotypes in patients with COVID-19-related ARDS. Furthermore, the association of higher $C_{rs}$ with higher PEEP or $V_t$, or both, indicates that clinicians might have applied either of these ventilator settings on the basis of respiratory mechanics, instead of using a routine low-$V_t$, high-PEEP approach. Similarly, the association of higher plateau pressure with lower $C_{rs}$ also supports the utility of plateau pressure as a guide to PEEP and $V_t$ optimisation in patients with COVID-19-related ARDS. Future studies that use patient-level data should explore the complex inter-relationship and trajectory of respiratory system mechanics, gas exchange, and control of breathing to assess the effect of these factors on clinical outcomes in patients with COVID-19-related ARDS, with a view to developing a personalised and safe approach to ventilation management.

Contributors
MPR, ASu, and KS designed the study. MPR, CC, and ASu contributed to the search strategy, screening of articles, data collection, and risk-of-bias assessment. RRL, CA, MPR, CC, ASu, KR, ASS, and KS contributed to the data analysis and interpretation. RRL, CA, MPR, and CC created the tables and figures. MPR drafted the manuscript. ASu, CC, RRL, CA, KR, ASS, and KS contributed to the critical revision of the manuscript for intellectually important content. All authors provided critical conceptual input, interpreted results of the data analysis, and read and approved the final draft of the manuscript. MPR and CC accessed and verified the data. All authors were responsible for the decision to submit the manuscript for publication.

Declaration of interests
We declare no competing interests.

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