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

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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}. Ascertaining 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 11356 patients in 37 studies, mean reported C_{RS}, measured close to the time of endotracheal intubation, was $35\cdot8$ mL/cm H_2O (95% CI $33\cdot9$–$37\cdot8$; $I^2=96\cdot9\%$, $\tau^2=32\cdot6$). Pooled mean C_{RS} was normally distributed. Increasing ARDS severity (assessed by PaO_2/FiO_2 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 [PaO_2] to fractional inspired oxygen [FiO_2] 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.[1] ARDS severity is classified on the basis of the PaO_2/FiO_2 ratio as mild (>200 to 300 mm Hg), moderate (>100 to 200 mm Hg), or severe (≤100 mm Hg).[1] 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.[1]

The current protocolised approach to treating ARDS has attracted much scrutiny, especially during the COVID-19 pandemic, with calls being made for a more personalised approach.[2] 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.[3,4] Despite meeting the criteria for moderate-to-severe ARDS, these patients were found to have relatively normal respiratory system compliance, and shunt fraction—ie, 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.[3,5,6] However, these early observations have been challenged by several researchers and commentators.[4,7–9]

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})—ie, respiratory system compliance when there is no airflow—could mediate ARDS progression via patient self-inflicted lung injury (P-SILI).[2,10] 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.[8,11,12] 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

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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 sheer 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

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See **Online** for appendix

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.[13] 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.[9,11] 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 epidemic[15] 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.

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).[18,19] The

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.[20] Furthermore, the popular two-step arc-sine transformation described by Freeman and Tukey[21] 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.[22]

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 (R_0 estimator) 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 (PaO_2/FiO_2 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 [$PaCO_2$] >45 mm Hg vs ≤45 mm Hg) and value of positive end-expiratory pressure (PEEP; >15 cm H_2O vs ≤15 cm H_2O). The random-effects χ^2 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 C_{RS}. 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 PaO_2/FiO_2 ratio and $PaCO_2$), and intervention factors (PEEP, plateau pressure, driving pressure, and tidal volume [V_T]). 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[23] and Wan and colleagues.[24] Because statistical

heterogeneity can be overestimated by I^2 statistics in observational studies, we assessed interstudy variability as part of the assessment of the certainty of evidence outlined by the GRADE approach.[25,26] 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.
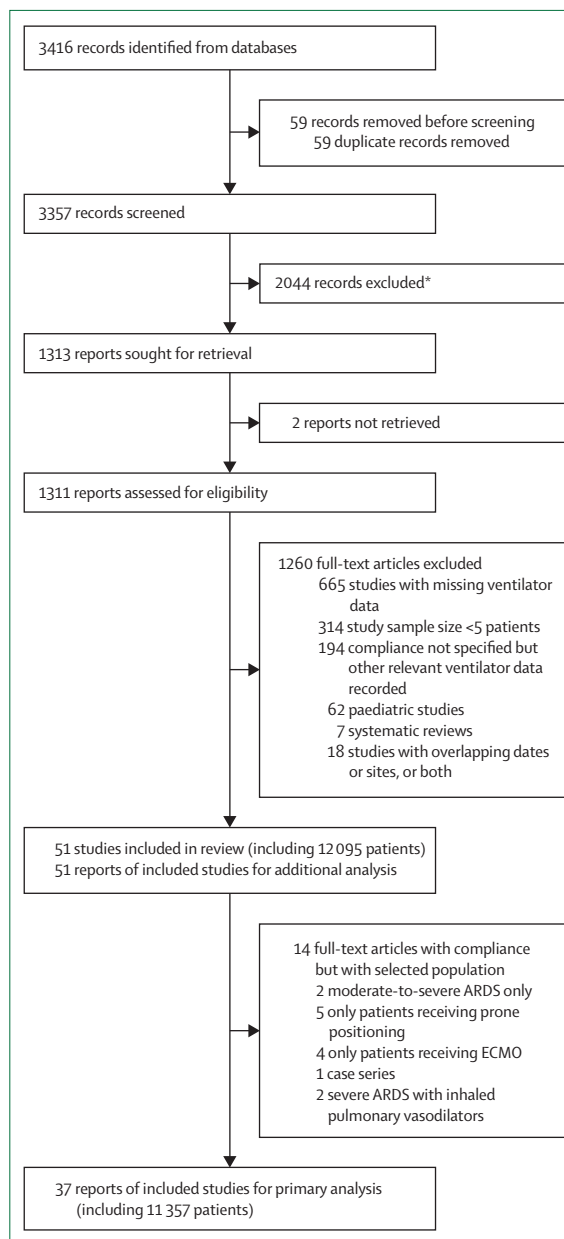

Figure 1: Study selection
ARDS=acute respiratory distress syndrome. ECMO=extracorporeal membrane oxygenation. *Studies were excluded because they were not about patients with COVID-19.
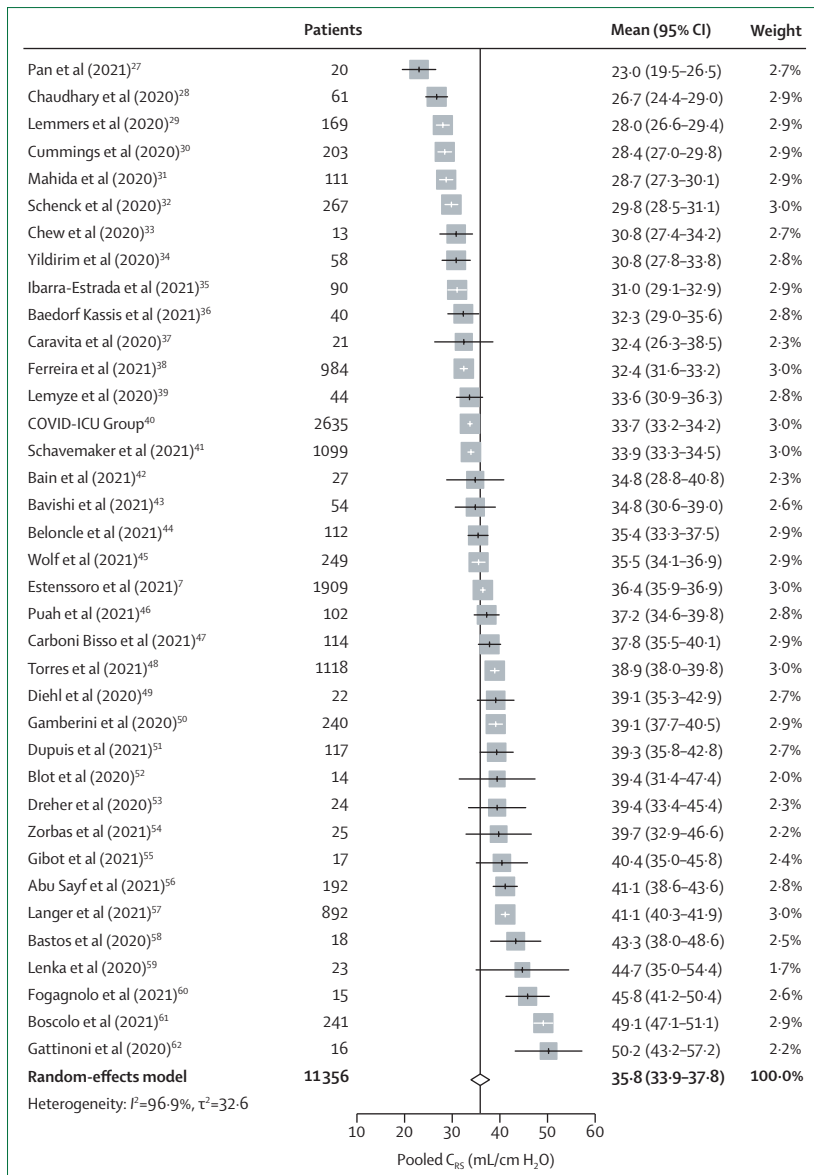
	Patients		Mean (95% CI)	Weight
Pan et al (2021)[27]	20		23·0 (19·5–26·5)	2·7%
Chaudhary et al (2020)[28]	61		26·7 (24·4–29·0)	2·9%
Lemmers et al (2020)[29]	169		28·0 (26·6–29·4)	2·9%
Cummings et al (2020)[30]	203		28·4 (27·0–29·8)	2·9%
Mahida et al (2020)[31]	111		28·7 (27·3–30·1)	2·9%
Schenck et al (2020)[32]	267		29·8 (28·5–31·1)	3·0%
Chew et al (2020)[33]	13		30·8 (27·4–34·2)	2·7%
Yildirim et al (2020)[34]	58		30·8 (27·8–33·8)	2·8%
Ibarra-Estrada et al (2021)[35]	90		31·0 (29·1–32·9)	2·9%
Baedorf Kassis et al (2021)[36]	40		32·3 (29·0–35·6)	2·8%
Caravita et al (2020)[37]	21		32·4 (26·3–38·5)	2·3%
Ferreira et al (2021)[38]	984		32·4 (31·6–33·2)	3·0%
Lemyze et al (2020)[39]	44		33·6 (30·9–36·3)	2·8%
COVID-ICU Group[40]	2635		33·7 (33·2–34·2)	3·0%
Schavemaker et al (2021)[41]	1099		33·9 (33·3–34·5)	3·0%
Bain et al (2021)[42]	27		34·8 (28·8–40·8)	2·3%
Bavishi et al (2021)[43]	54		34·8 (30·6–39·0)	2·6%
Beloncle et al (2021)[44]	112		35·4 (33·3–37·5)	2·9%
Wolf et al (2021)[45]	249		35·5 (34·1–36·9)	2·9%
Estenssoro et al (2021)[7]	1909		36·4 (35·9–36·9)	3·0%
Puah et al (2021)[46]	102		37·2 (34·6–39·8)	2·8%
Carboni Bisso et al (2021)[47]	114		37·8 (35·5–40·1)	2·9%
Torres et al (2021)[48]	1118		38·9 (38·0–39·8)	3·0%
Diehl et al (2020)[49]	22		39·1 (35·3–42·9)	2·7%
Gamberini et al (2020)[50]	240		39·1 (37·7–40·5)	2·9%
Dupuis et al (2021)[51]	117		39·3 (35·8–42·8)	2·7%
Blot et al (2020)[52]	14		39·4 (31·4–47·4)	2·0%
Dreher et al (2020)[53]	24		39·4 (33·4–45·4)	2·3%
Zorbas et al (2021)[54]	25		39·7 (32·9–46·6)	2·2%
Gibot et al (2021)[55]	17		40·4 (35·0–45·8)	2·4%
Abu Sayf et al (2021)[56]	192		41·1 (38·6–43·6)	2·8%
Langer et al (2021)[57]	892		41·1 (40·3–41·9)	3·0%
Bastos et al (2020)[58]	18		43·3 (38·0–48·6)	2·5%
Lenka et al (2020)[59]	23		44·7 (35·0–54·4)	1·7%
Fogagnolo et al (2021)[60]	15		45·8 (41·2–50·4)	2·6%
Boscolo et al (2021)[61]	241		49·1 (47·1–51·1)	2·9%
Gattinoni et al (2020)[62]	16		50·2 (43·2–57·2)	2·2%
Random-effects model	**11356**		**35·8 (33·9–37·8)**	**100·0%**
Heterogeneity: I^2=96·9%, τ^2=32·6				

Pooled C_{RS} (mL/cm H_2O)

10 20 30 40 50 60

Figure 2: Forest plot showing pooled C_{RS} from studies of unselected patients with COVID-19-related ARDS
Data from 37 unselected ARDS studies, with a total of 11 356 patients, are shown. ARDS=acute respiratory distress syndrome. C_{RS}=respiratory system static compliance.

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 mean 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 C_{RS}, $PaCO_2$, V_T, and PEEP are also shown in the appendix (p 9).

The pooled reported C_{RS} in patients from studies of unselected COVID-19-related ARDS was 35·8 mL/cm H_2O (95% CI 33·9–37·8; I^2=96·9%, τ^2=32·6; high certainty; figure 2).[27–62] In these studies, C_{RS} dispersion was not significantly different from a normal distribution (Shapiro-Wilk test p=0·92; figure 3). The pooled reported C_{RS} in all patients from studies of selected and unselected COVID-19-related ARDS was 34·7 mL/cm H_2O (32·8–36·6; 97·2%, 43·6; high certainty; appendix p 5). C_{RS} of patients remained similar (33·9 mL/cm H_2O, 32·0–35·9; 98·0%, 37·1) after excluding nine studies with mNOS scores of less than 3. Visual inspection did not reveal any significant asymmetry of the funnel plot (Egger's test p=0·95; appendix p 6). Furthermore, correction of small-study effects using the R_0 estimator procedure did not change the pooled estimate of C_{RS} (34·7 mL/cm H_2O, 32·8–36·6).

The overall pooled mean PaO_2/FiO_2 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 PaO_2/FiO_2, was associated with reduced C_{RS} ($p_{interaction}$<0·0001): C_{RS} progressively decreased from 39·3 mL/cm H_2O (95% CI 36·6–42·0) in patients with mild ARDS, to 34·9 mL/cm H_2O (32·8–36·9) in patients with moderate ARDS, and 27·3 mL/cm H_2O (23·3–31·2) in patients with severe ARDS (table 1, figure 4).[63–75] There was no significant association between C_{RS} and $PaCO_2$ (31·5 [95% CI 27·7–35·4] in patients with $PaCO_2$ >45 mm Hg vs 36·5 [33·3–39·6] in those with $PaCO_2$ ≤45 mm Hg; $p_{interaction}$=0·052; table 1) or between C_{RS} and PEEP (35·2 [95% CI 27·6–42·8] in patients with PEEP >15 cm H_2O vs 34·2 [32·3–36·2] in those with PEEP ≤15 cm H_2O; $p_{interaction}$=0·80; table 1). Further details of the association between C_{RS} and PEEP are provided in the appendix (pp 8–9).

The complex interactions of C_{RS} with PaO_2/FiO_2 ratio and PEEP are shown in figure 5A; the interactions of C_{RS} with V_T and PEEP are shown in figure 5B. In patients with moderate-to-severe ARDS (PaO_2/FiO_2 ratio ≤200 mm Hg), increased PEEP was associated with higher compliance than in patients with mild ARDS (PaO_2/FiO_2 ratio >200 to 300 mm Hg).

In univariable meta-regression analyses, there was a statistically significant positive correlation between C_{RS} (the dependent variable) and PaO_2/FiO_2 ratio (β=0·06, 95% CI 0·02 to 0·11), between C_{RS} and PEEP (0·88, 0·07 to 1·68), and between C_{RS} and V_T (6·28, 3·37 to 9·19). C_{RS}

had a statistically significant negative correlation with 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%, $τ^2$=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). 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_2O [95% CI 31·8–37·3; I^2=91·9%, $τ^2$=55·5] for sample ≤100 vs 35·0 mL/cm H_2O [32·4–37·5; 98·5%, 32·5] 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_2O, 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 11356 patients in 37 unselected 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_2O (95% CI 33·9–37·8) across 37 unselected studies and the reported mean C_{RS} across the 51 studies ranged from 22·7 to 54·3 mL/cm H_2O. In comparison, the reported mean C_{RS} in landmark ARDS
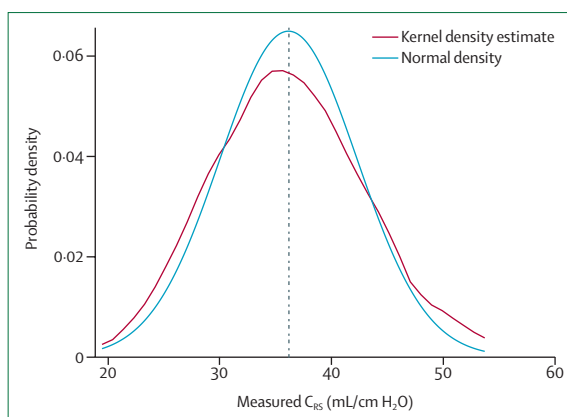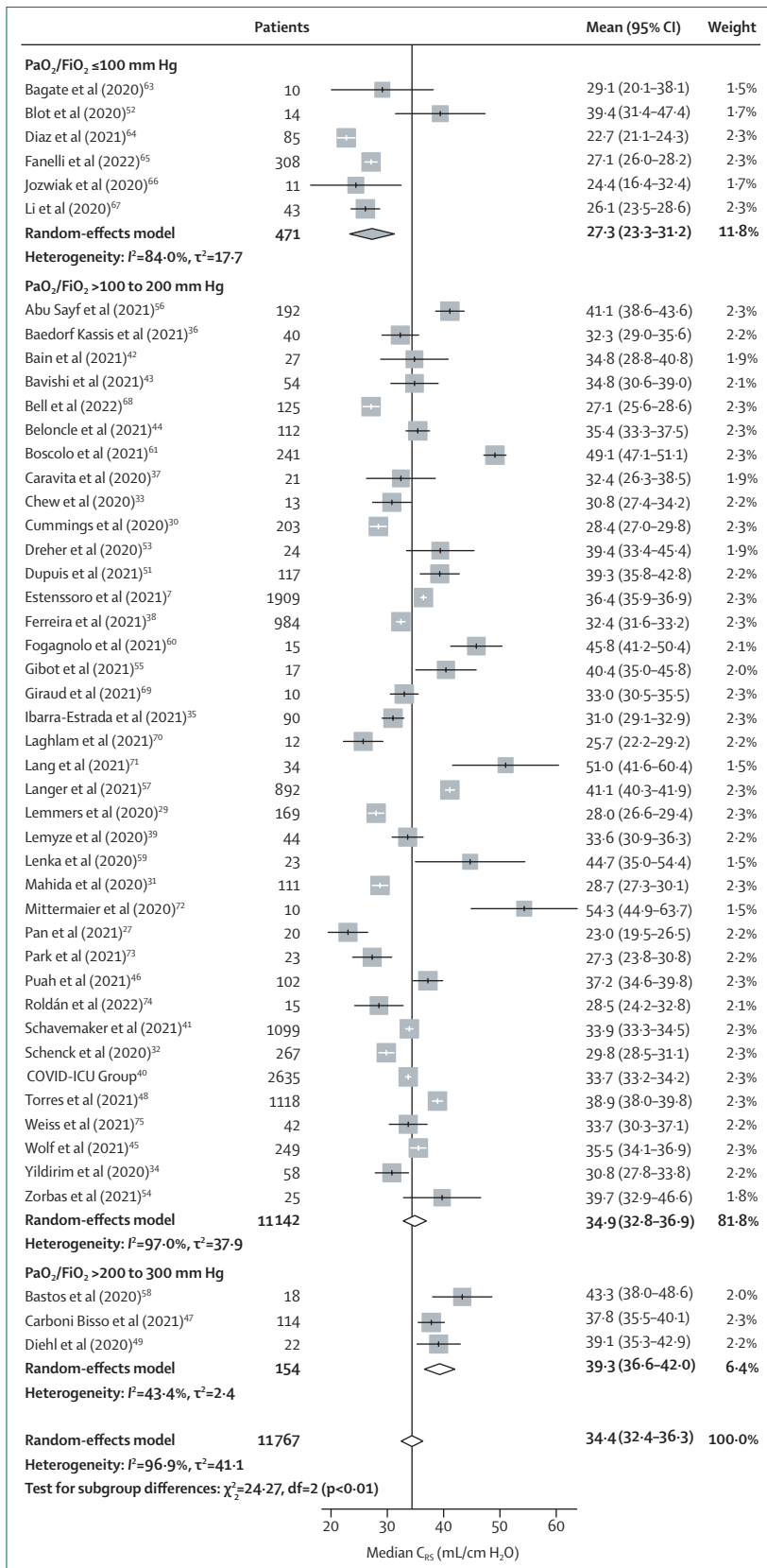

Figure 3: **Kernel density plot showing the distribution of C_{RS} means**
C_{RS} means in 37 unselected ARDS studies were normally distributed (Shapiro-Wilk test p=0·92). Pooled mean C_{RS} was 35·8 mL/cm H_2O (vertical dashed line). ARDS=acute respiratory distress syndrome. C_{RS}=respiratory system static compliance.

	Number of studies	Number of patients	Pooled estimate of C_{RS}, mL/cm H_2O (95% CI)	Heterogeneity and between-studies variance
PaO_2/FiO_2 ratio ($p_{interaction}$<0·0001)				
>200 to 300 mm Hg	3	154	39·3 (36·6–42·0)	I^2=43·4%, $τ^2$=2·4
>100 to 200 mm Hg	38	11142	34·9 (32·8–36·9)	I^2=97·0%, $τ^2$=37·9
≤100 mm Hg	6	471	27·3 (23·3–31·2)	I^2=84·3%, $τ^2$=17·7
$PaCO_2$ ($p_{interaction}$=0·052)				
>45 mm Hg	16	2814	31·5 (27·7–35·4)	I^2=98·2%, $τ^2$=56·6
≤45 mm Hg	13	7738	36·5 (33·3–39·6)	I^2=97·8%, $τ^2$=31·7
PEEP ($p_{interaction}$=0·80)				
>15 cm H_2O	7	410	35·2 (27·6–42·8)	I^2=92·3%, $τ^2$=95·5
≤15 cm H_2O	41	11685	34·2 (32·3–36·2)	I^2=97·6%, $τ^2$=37·9

Severity of ARDS was assessed using the PaO_2/FiO_2 ratio (mild, >200 to 300 mm Hg; moderate, >100 to 200 mm Hg; or severe, ≤100 mm Hg). The presence of hypercarbia was assessed using $PaCO_2$ (>45 mm Hg vs ≤45 mm Hg). PEEP values were high or low (>15 cm H_2O vs ≤15 cm H_2O) compared with patients with mild ARDS (PaO_2/FiO_2 ratio >200 to 300 mm Hg). C_{RS}=respiratory system static compliance. FiO_2=fractional inspired oxygen. $PaCO_2$=partial pressure of carbon dioxide in arterial blood. PaO_2=partial pressure of oxygen in arterial blood. PEEP=positive end-expiratory pressure.

Table 1: **Interaction of C_{RS} with the severity of ARDS, the presence of hypercarbia, and the value of PEEP**

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_2O.[76–84] 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

Patients		Mean (95% CI)	Weight
PaO$_2$/FiO$_2$ ≤100 mm Hg			
Bagate et al (2020)[63]	10	29·1 (20·1–38·1)	1·5%
Blot et al (2020)[52]	14	39·4 (31·4–47·4)	1·7%
Diaz et al (2021)[64]	85	22·7 (21·1–24·3)	2·3%
Fanelli et al (2022)[65]	308	27·1 (26·0–28·2)	2·3%
Jozwiak et al (2020)[66]	11	24·4 (16·4–32·4)	1·7%
Li et al (2020)[67]	43	26·1 (23·5–28·6)	2·3%
Random-effects model	**471**	**27·3 (23·3–31·2)**	**11·8%**
Heterogeneity: I^2=84·0%, τ^2=17·7			
PaO$_2$/FiO$_2$ >100 to 200 mm Hg			
Abu Sayf et al (2021)[56]	192	41·1 (38·6–43·6)	2·3%
Baedorf Kassis et al (2021)[36]	40	32·3 (29·0–35·6)	2·2%
Bain et al (2021)[42]	27	34·8 (28·8–40·8)	1·9%
Bavishi et al (2021)[43]	54	34·8 (30·6–39·0)	2·1%
Bell et al (2022)[68]	125	27·1 (25·6–28·6)	2·3%
Beloncle et al (2021)[44]	112	35·4 (33·3–37·5)	2·3%
Boscolo et al (2021)[61]	241	49·1 (47·1–51·1)	2·3%
Caravita et al (2020)[37]	21	32·4 (26·3–38·5)	1·9%
Chew et al (2020)[33]	13	30·8 (27·4–34·2)	2·2%
Cummings et al (2020)[30]	203	28·4 (27·0–29·8)	2·3%
Dreher et al (2020)[53]	24	39·4 (33·4–45·4)	1·9%
Dupuis et al (2021)[51]	117	39·3 (35·8–42·8)	2·2%
Estenssoro et al (2021)[7]	1909	36·4 (35·9–36·9)	2·3%
Ferreira et al (2021)[38]	984	32·4 (31·6–33·2)	2·3%
Fogagnolo et al (2021)[60]	15	45·8 (41·2–50·4)	2·1%
Gibot et al (2021)[55]	17	40·4 (35·0–45·8)	2·0%
Giraud et al (2021)[69]	10	33·0 (30·5–35·5)	2·2%
Ibarra-Estrada et al (2021)[35]	90	31·0 (29·1–32·9)	2·3%
Laghlam et al (2021)[70]	12	25·7 (22·2–29·2)	2·2%
Lang et al (2021)[71]	34	51·0 (41·6–60·4)	1·5%
Langer et al (2021)[57]	892	41·1 (40·3–41·9)	2·3%
Lemmers et al (2020)[29]	169	28·0 (26·6–29·4)	2·3%
Lemyze et al (2020)[39]	44	33·6 (30·9–36·3)	2·2%
Lenka et al (2020)[59]	23	44·7 (35·0–54·4)	1·5%
Mahida et al (2020)[31]	111	28·7 (27·3–30·1)	2·3%
Mittermaier et al (2020)[72]	10	54·3 (44·9–63·7)	1·5%
Pan et al (2021)[27]	20	23·0 (19·5–26·5)	2·2%
Park et al (2021)[73]	23	27·3 (23·8–30·8)	2·2%
Puah et al (2021)[46]	102	37·2 (34·6–39·8)	2·3%
Roldán et al (2022)[74]	15	28·5 (24·2–32·8)	2·1%
Schavemaker et al (2021)[41]	1099	33·9 (33·3–34·5)	2·3%
Schenck et al (2020)[32]	267	29·8 (28·5–31·1)	2·3%
COVID-ICU Group[40]	2635	33·7 (33·2–34·2)	2·3%
Torres et al (2021)[48]	1118	38·9 (38·0–39·8)	2·3%
Weiss et al (2021)[75]	42	33·7 (30·3–37·1)	2·2%
Wolf et al (2021)[45]	249	35·5 (34·1–36·9)	2·3%
Yildirim et al (2020)[34]	58	30·8 (27·8–33·8)	2·2%
Zorbas et al (2021)[54]	25	39·7 (32·9–46·6)	1·8%
Random-effects model	**11142**	**34·9 (32·8–36·9)**	**81·8%**
Heterogeneity: I^2=97·0%, τ^2=37·9			
PaO$_2$/FiO$_2$ >200 to 300 mm Hg			
Bastos et al (2020)[58]	18	43·3 (38·0–48·6)	2·0%
Carboni Bisso et al (2021)[47]	114	37·8 (35·5–40·1)	2·3%
Diehl et al (2020)[49]	22	39·1 (35·3–42·9)	2·2%
Random-effects model	**154**	**39·3 (36·6–42·0)**	**6·4%**
Heterogeneity: I^2=43·4%, τ^2=2·4			
Random-effects model	**11767**	**34·4 (32·4–36·3)**	**100·0%**
Heterogeneity: I^2=96·9%, τ^2=41·1			
Test for subgroup differences: χ^2_2=24·27, df=2 (p<0·01)			

20 30 40 50 60

Median C$_{RS}$ (mL/cm H$_2$O)

***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.

aerosolisation and resultant safety concerns for 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.[76–84] 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.[76–84] 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.[85,86] 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 C_{RS} 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 V_T found in patients with greater C_{RS} might indicate that clinicians applied both V_T and PEEP—based on an assessment of respiratory mechanics—to maintain safe driving and plateau pressures, instead of undertaking a routine low-V_T, 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 C_{RS}, 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 V_T 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 C_{RS}, 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 C_{RS}[5,62,87] or very low C_{RS}.[88] Subsequent studies addressed the existence of these COVID-19-related ARDS phenotypes, but the studies were limited by relatively small sample sizes.[8,9,12] Early in the pandemic, many guidelines across the globe recommended early intubation to minimise the risk of SARS-CoV-2 infection among healthcare workers.[89–92] 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.[93] 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
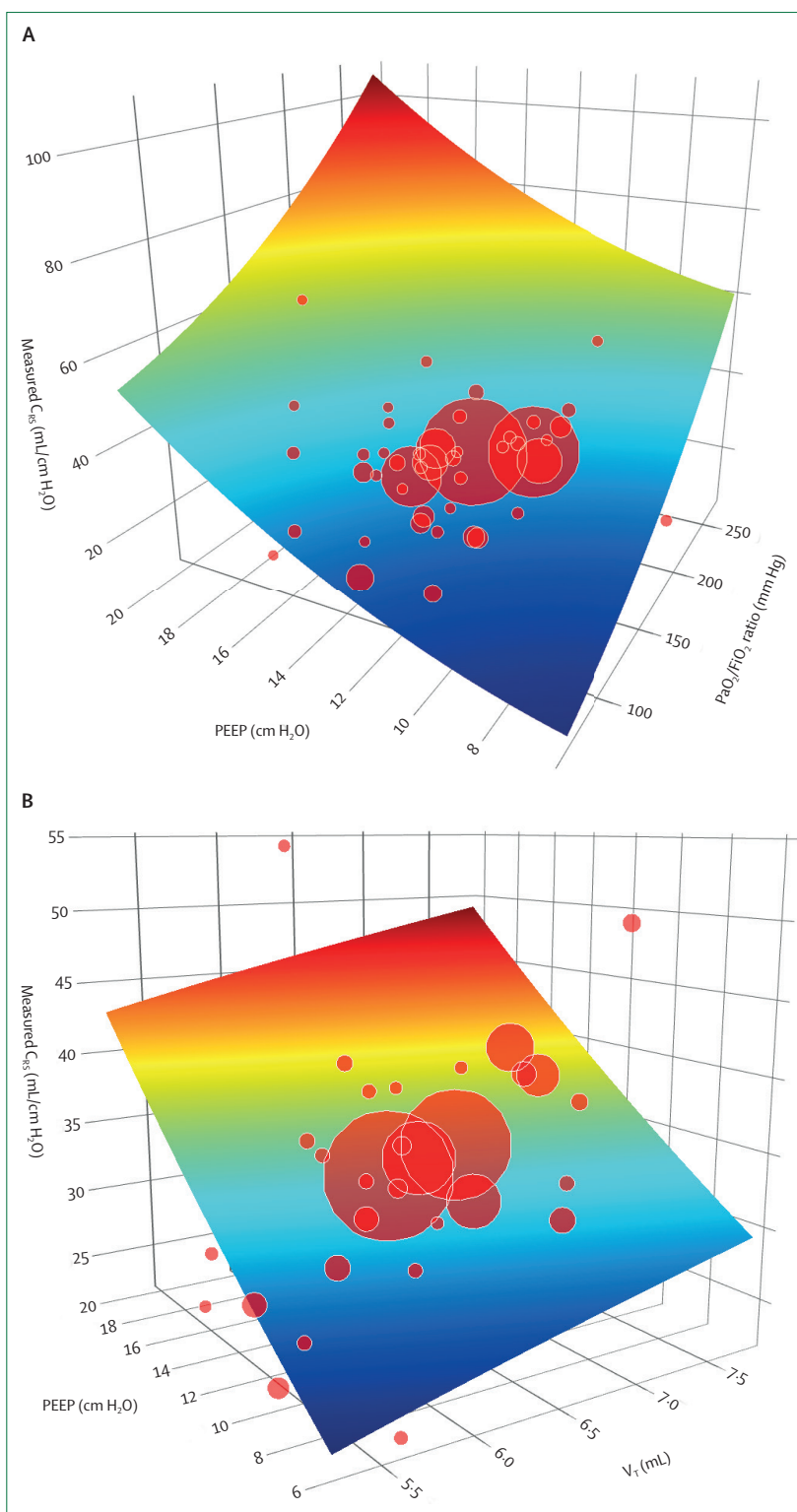

Figure 5: **Three-dimensional plots showing the complex interactions between C_{RS} and related variables**
(A) Interactions between C_{RS}, PaO_2/FiO_2 ratio, and PEEP. As oxygenation worsened (ie, PaO_2/FiO_2 ratio decreased), C_{RS} also decreased. As PEEP increased, C_{RS} also increased. (B) Interactions between C_{RS}, V_T, and PEEP. C_{RS} increased with an increase in V_T or PEEP. C_{RS}=respiratory system static compliance. FiO_2=fractional inspired oxygen. PaO_2=partial pressure of oxygen in arterial blood. PEEP=positive end-expiratory pressure. V_T=tidal volume.

	Number of studies	Regression coefficient, β (95% CI)	p value
PaO_2/FiO_2 ratio (mm Hg)	47	0·06 (0·02 to 0·11)	0·0070
$PaCO_2$ (mm Hg)	29	–0·39 (–0·71 to –0·07)	0·018
PEEP (cm H_2O)	48	0·88 (0·07 to 1·68)	0·033
V_T (mL)	31	6·28 (3·37 to 9·19)	<0·0001
Driving pressure (cm H_2O)	36	–2·49 (–3·12 to –1·86)	<0·0001
Plateau pressure (cm H_2O)	36	–0·77 (–1·53 to –0·02)	0·045
BMI (kg/m²)	30	–0·02 (–1·09 to 1·05)	0·97
Average date of patient enrolment (days from Jan 1, 2020)*	47	–0·005 (–0·04 to 0·03)	0·76

*Average date of patient enrolment was calculated by taking the midpoint of the first and final dates of patient enrolment. ARDS=acute respiratory distress syndrome. C_{RS}=respiratory system static compliance. FiO_2=fractional inspired oxygen. $PaCO_2$=partial pressure of carbon dioxide in arterial blood. PaO_2=partial pressure of oxygen in arterial blood. PEEP=positive end-expiratory pressure. V_T=tidal volume.

Table 2: Univariable meta-regression analysis with C_{RS} as the dependent variable

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, PaO_2/FiO_2 ratio, PEEP, $PaCO_2$, 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.[94,95] However, our sensitivity analysis showed that the study sample size and fixed-effects model did not affect the derived mean C_{RS}. Third, deriving the mean (SD) C_{RS} from studies that reported C_{RS} as median (IQR) using validated methods, despite being a well described practice, might have influenced the distribution pattern of C_{RS}. Fourth, we did not have individual patient data, which would have provided us with a richer analysis, allowing us to investigate patient-level variability and possible factors related to mean C_{RS}. In addition, the absence of individual patient data meant that we could not precisely delineate the association of an individual patient's mechanics with their clinical and functional outcomes. We performed subgroup and meta-regression analyses to look for potential sources of heterogeneity and prognostically relevant study-level covariates. Finally, we did not have large datasets with approximate physiology to comment on phenotypes. Despite these limitations, our analysis was a comprehensive analysis of large sample size and provided an estimate of C_{RS} with a relatively narrow confidence interval.

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 greater 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.

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