

COVID-19-related acute respiratory distress syndrome: lessons learned during the pandemic



In 2020 and 2021, SARS-CoV-2 put enormous pressure on our health-care systems. Countless patients with COVID-19 were admitted to hospitals for oxygen support, or to intensive care units (ICUs) when respiratory failure required a more intensive treatment. This hectic situation did not stop the ICU community from providing excellent care, even though most clinicians working in the early stages of the pandemic struggled with many uncertainties, including how best to provide respiratory support. Meanwhile, the critical care community was able to design and conduct a large volume of clinical studies, perhaps as much as we had seen in the two preceding decades combined. Now that the dust has started to settle, and as we look ahead to further surges of COVID-19 and to the potential emergence of new pandemics, it is worth considering what lessons we have learnt.

Individualisation of ventilation of patients with acute respiratory distress syndrome (ARDS) attracted much attention just before the COVID-19 pandemic.¹ With the exception of low-tidal-volume ventilation, restrictive fluid management, and prone positioning, the previous two decades of ARDS research had not yielded any effective treatment strategies. A reduction of clinical and biological heterogeneity through the identification of ARDS subphenotypes was recognised as a promising method to move towards a precision medicine approach in research and clinical practice.²

Early in the pandemic, it was suggested on the basis of small case series that in a subgroup of patients, the severity of hypoxaemia was disproportional to the reduction in lung volume and decreased mechanics of the respiratory system (ie, respiratory system compliance [C_{RS}]). In contrast to patients who had severe hypoxaemia with a decreased C_{RS} and consolidated lung, which is regarded as the classic combination in conventional ARDS, this subgroup of patients had severe hypoxaemia without major changes to aeration and respiratory system mechanics. If this suggestion proved to be true, it would have major implications for ventilatory management (eg, how to set positive end-expiratory pressure [PEEP]) in this patient subgroup. Despite debate within and criticism from some

members of the research and clinical communities, these findings influenced ventilatory management in many patients with COVID-19-related ARDS.

In this issue of *The Lancet Respiratory Medicine*, Mallikarjuna Ponnappa Reddy and colleagues report the results of a well performed systematic review and meta-analysis of 37 studies of COVID-19-related ARDS published between 2019 and 2022.³ In 11356 patients, mean reported C_{RS} was 35.8 mL/cm H₂O (95% CI 33.9–37.8). Mean reported C_{RS} was normally distributed and inversely related to ARDS severity (39.3 mL/cm H₂O [36.6–42.0] in mild ARDS, 34.9 mL/cm H₂O [32.8–36.9] in moderate ARDS, and 27.3 mL/cm H₂O [23.3–31.2] in severe ARDS). In other words, Reddy and colleagues could not confirm, on the basis of C_{RS} , the presence of two different subphenotypes in patients with COVID-19-related ARDS. Thus, the findings of this report argue strongly against the use of ventilatory strategies that differ from those used in patients with conventional ARDS.

We concur with Reddy and colleagues' hypothesis that the apparent presence of two subphenotypes of COVID-19-related ARDS might have resulted from the policy to intubate early (ie, at arrival in the ICU or on ICU admission) in patients with hypoxaemic COVID-19. This policy—which reflected the fact that less invasive respiratory support was scarce, if not unavailable, during the first weeks of the pandemic, and might also have been implemented to minimise the risk of infections in health-care workers—could have created a subgroup of patients with hypoxaemia who exhibited high C_{RS} . These patients could have received less invasive support later in the pandemic,⁴ and therefore might have disappeared from the cohorts described in the literature.

We have also searched for subphenotypes of COVID-19-related ARDS.⁵ We found no evidence for cross-sectional respiratory subphenotypes using unbiased data analysis. When considering longitudinal trends in measures of respiratory system mechanics or lung function, we identified subphenotypes with a worsening ventilatory ratio and mechanical power of ventilation. Upon external validation, the subphenotype with an upward ventilatory ratio trajectory was consistently associated with worse outcomes. Importantly, C_{RS} did not contribute



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substantially to the observed heterogeneity in these analyses.

These reported findings lead to one important question: is COVID-19-related ARDS really a new clinical entity? We believe that the ventilatory management of COVID-19-related ARDS should not be approached any differently from that of ARDS related to other causes. In our view, the most important factor driving our appreciation of subphenotypic differences was that we had never seen so many patients with ARDS in such a short period of time, which led us to observe all kinds of patterns in clinical presentation.

The reported findings also raise a practical problem: how should the ventilator be set in patients with COVID-19-related ARDS? Based on the evidence that COVID-19-related ARDS is not an atypical form of ARDS, the simple answer could be that the ventilator should be set in the same way as for conventional, albeit heterogeneous, ARDS related to other causes. The individualisation of ventilation management is receiving increasing attention; for example, in how we set PEEP. In this context, the ART (Alveolar Recruitment for Acute Respiratory Distress Syndrome Trial) study⁶ showed reduced overall survival in patients who received an optimal C_{RS} -targeted high-PEEP strategy with recruitment manoeuvres compared with those who received a lower-PEEP strategy without recruitment manoeuvres. This finding was nuanced by a Bayesian analysis in ART, which suggested that a high-PEEP strategy is especially detrimental in patients with ARDS caused by a pneumonia.⁷ The LIVE (Lung Imaging for Ventilator Setting in ARDS) study,⁸ however, suggested that patients with non-focal ARDS could benefit from high PEEP whereas patients with focal ARDS would not.

Considering that COVID-19-related ARDS could be classified as ARDS caused by a pneumonia, should it then be concluded that a high-PEEP strategy in these patients should be avoided? In line with this proposal, use of lower PEEP in patients with COVID-19 is supported by a 2021 analysis of a large cohort of patients with COVID-19, in which the use of high PEEP was associated with worse outcomes compared with the use of lower PEEP.⁹ However, if we consider COVID-19-related ARDS to be mainly a non-focal form of ARDS, and thus recruitable,¹⁰ benefit from higher levels of PEEP might be anticipated. Therefore, the optimal PEEP strategy for patients with COVID-19-related ARDS remains an open question.

The study by Reddy and colleagues has taught us one important, and overall, lesson: we should always take a cautious approach when interpreting small case series, and we should change practice only on the basis of firm evidence.

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- 1 Bos LDJ, Artigas A, Constantin JM, et al. Precision medicine in acute respiratory distress syndrome: workshop report and recommendations for future research. *Eur Respir Rev* 2021; **30**: 200317.
- 2 Bos LDJ, Ware LB. Acute respiratory distress syndrome: causes, pathophysiology, and phenotypes. *Lancet* 2022; published online Sept 2. [https://doi.org/10.1016/S0140-6736\(22\)01485-4](https://doi.org/10.1016/S0140-6736(22)01485-4).
- 3 Reddy MP, Subramaniam A, Chua C, et al. 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. *Lancet Respir Med* 2022; published online Nov 3. [https://doi.org/10.1016/S2213-2600\(22\)00393-9](https://doi.org/10.1016/S2213-2600(22)00393-9).
- 4 Doidge JC, Gould DW, Ferrando-Vivas P, et al. Trends in intensive care for patients with COVID-19 in England, Wales, and Northern Ireland. *Am J Respir Crit Care Med* 2021; **203**: 565-74.
- 5 Bos LDJ, Sjoding M, Sinha P, et al. Longitudinal respiratory subphenotypes in patients with COVID-19-related acute respiratory distress syndrome: results from three observational cohorts. *Lancet Respir Med* 2021; **9**: 1377-86.
- 6 Cavalcanti AB, Suzumura EA, Laranjeira LN, et al. Effect of lung recruitment and titrated positive end-expiratory pressure (PEEP) vs low PEEP on mortality in patients with acute respiratory distress syndrome: a randomized clinical trial. *JAMA* 2017; **318**: 1335-45.
- 7 Zampieri FG, Costa EL, Iwashyna TJ, et al. Heterogeneous effects of alveolar recruitment in acute respiratory distress syndrome: a machine learning reanalysis of the alveolar recruitment for acute respiratory distress syndrome trial. *Br J Anaesth* 2019; **123**: 88-95.
- 8 Constantin JM, Jabaudon M, Lefrant JY, et al. Personalised mechanical ventilation tailored to lung morphology versus low positive end-expiratory pressure for patients with acute respiratory distress syndrome in France (the LIVE study): a multicentre, single-blind, randomised controlled trial. *Lancet Respir Med* 2019; **7**: 870-80.
- 9 Valk CMA, Tsonas AM, Botta M, et al. Association of early positive end-expiratory pressure settings with ventilator-free days in patients with coronavirus disease 2019 acute respiratory distress syndrome: A secondary analysis of the Practice of VENTilation in COVID-19 study. *Eur J Anaesthesiol* 2021; **38**: 1274-83.
- 10 Smit MR, Beenen LFM, Valk CMA, et al. Assessment of lung re-aeration at 2 levels of positive end-expiratory pressure in patients with early and late COVID-19-related acute respiratory distress syndrome. *J Thorac Imaging* 2021; **36**: 286-93.