Conservative management of COVID-19 associated hypoxaemia

To the Editor:

With great interest we read the article by Voshaar *et al.* [1] reporting data from a retrospective analysis of 78 coronavirus disease 2019 (COVID-19) patients treated with or without invasive mechanical ventilation. The authors conclude that avoiding invasive mechanical ventilation by allowing permissive hypoxaemia was superior to current treatment standards and guidelines. Overall mortality in this cohort was 7.7% (six out of 78), but 50% (four out of eight) of the patients supported with invasive mechanical ventilation eventually died [1].

We congratulate the authors on this remarkably low mortality of COVID-19 patients treated on an intensive care unit (ICU). We agree that the indication for invasive mechanical ventilation must be made after critical evaluation of treatment alternatives, both in COVID-19 and in other forms of severe respiratory failure. While welcoming additional data that could assist in guiding clinicians in difficult treatment decisions for or against invasive mechanical ventilation at a specific point in time, we are concerned that methodological limitations of this study limit its generalisability. We doubt that the data presented support the authors' conclusions on invasive mechanical ventilation and prognosis in severe COVID-19. In the following, we will address several concerns about both the study design and data analysis.

First, the study cohort is ill-defined. Basic information describing the patients' clinical condition and severity of disease (*e.g.* clinical scores, such as Sequential Organ Failure Assessment (SOFA), Acute Physiology and Chronic Health Evaluation (APACHE) or Simplified Acute Physiology Score (SAPS) II) is missing. This limits the possibility to compare findings from this cohort with data from other studies. Most of the patients included in this retrospective observation only required oxygen support without nasal high-flow oxygen therapy or mechanical ventilation (53 (68%) out of 78), which suggests that these patients were not as severely sick as patients from other ICU cohorts [2, 3]. From the data presented, it remains unclear why most of these patients were treated on an ICU at all.

Second, the authors did not appropriately describe their algorithm for initiation of different respiratory support strategies. The presented "escalation sequence" from "room air" to "invasive mechanical ventilation" does not sufficiently explain triggers or parameters for when to progress from one step to another. Most of the patients were treated with oxygen support, but without any type of additional respiratory support. Moreover, patients receiving nasal high-flow oxygen therapy were grouped together with noninvasively ventilated patients, without comprehensive description of the distribution between these treatment strategies. As it does not correspond to the established standard of care, the concept of permissive hypoxaemia and the rationale for applying it in this context should be explained and justified in more detail [4].

Third, evaluating hypoxaemia alone is insufficient for the description of severe COVID-19 related respiratory failure. Additional data on partial pressure of carbon dioxide and arterial blood pH could help to characterise the type and degree of respiratory failure in these patients. Furthermore, the authors argue for blood oxygen content to assess tissue hypoxaemia. However, in this context, oxygen delivery, considering cardiac output as an additional relevant parameter, would give a better impression of oxygen supply to the tissue and should therefore be reported instead.

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This correspondence argues that data presented previously cannot justify a novel approach for treating hypoxic patients with severe #COVID19 https://bit.ly/3dLaPlk

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Fourth, the authors did not report basic cardiocirculatory parameters, such as vasopressor dosage, nor did they report data on oxygen consumption, such as lactate or central venous saturation, that would further help to better understand severity of disease and discriminate patients. Also, general treatment targets, such as mean arterial pressure and urinary output, should be defined and reported.

Fifth, additional important treatment information is missing. The authors mentioned that prone positioning was applied, however, they did not report information on frequency and duration thereof. Likewise, all patients were treated with a "pneumococcal active antibiotic (ampicillin/sulbactam) in combination with a macrolide", but no information on potential bacterial super-infection was presented.

Sixth, patients that received invasive mechanical ventilation had seriously elevated troponin and brain natriuretic peptide (BNP) levels suggesting cardiac involvement and global stress, respectively [5]. This finding needs to be explained in order to better understand clinical deterioration and death of these patients. In COVID-19 patients, elevations of troponin and BNP are known to be a strong independent predictor for all-cause mortality [6, 7].

Finally, the sub-group of patients receiving invasive mechanical ventilation (n=8) is too small to allow meaningful inferences and conclusions. Instead, it would have been helpful if the authors related their results and conclusions to relevant findings from thorough assessments of noninvasive mechanical ventilation in much larger cohorts of COVID-19 patients [8, 9].

The authors conclude, that their "data suggest that the lungs recover well from COVID-19 if they are denied the stress of invasive ventilation and over-oxygenation." Considering the concerns discussed above, this conclusion is not supported by the presented data. In addition, it must be noted that ventilator-induced lung injury and hyperoxaemia can occur even with noninvasive mechanical ventilation.

As with all retrospective observational data, causal relationships cannot be assumed, and the results should be interpreted with caution and in context. Observational data is helpful to generate hypotheses and inform prospective study designs, but changing clinical practice needs to be supported by multiple lines of robust evidence. We believe the data presented here cannot justify a novel approach for treating fragile patients with severe COVID-19.

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References

1 Voshaar T, Stais P, Köhler D, *et al.* Conservative management of COVID-19 associated hypoxaemia. *ERJ Open Res* 2021; 7: 00026-2021.
2 Cummings MJ, Baldwin MR, Abrams D, *et al.* Epidemiology, clinical course, and outcomes of critically ill adults with COVID-19 in New York City: a prospective cohort study. *Lancet* 2020; 395: 1763–1770.
3 Grasselli G, Zangrillo A, Zanella A, *et al.* Baseline Characteristics and Outcomes of 1591 Patients Infected With SARS-CoV-2 Admitted to ICUs of the Lombardy Region, Italy. *JAMA* 2020; 323: 1574–1581.
4 Gilbert-Kawai ET, Mitchell K, Martin D, *et al.* Permissive hypoxaemia *versus* normoxaemia for mechanically ventilated critically ill patients. *Cochrane Database Syst Rev* 2014; 2014: CD009931.
5 Demir OM, Ryan M, Cirillo C, *et al.* Impact and determinants of high-sensitivity cardiac troponin-T concentration in patients with COVID-19 admitted to critical care. *Am J Cardiol* 2021; 147: 129–136.
6 Stefanini GG, Chiarito M, Ferrante G, *et al.* Early detection of elevated cardiac biomarkers to optimise risk stratification in patients with COVID-19. *Heart* 2020; 106: 1512–1518.
7 Kotecha T, Knight DS, Razvi Y, *et al.* Patterns of myocardial injury in recovered troponin-positive COVID-19 patients assessed by cardiovascular magnetic resonance. *Eur Heart J* 2021; 42: 1866–1878.
8 Bellani G, Grasselli G, Cecconi M, *et al.* Noninvasive Ventilatory Support of COVID-19 Patients Outside the Intensive Care Units (WARd-COVID). *Ann Am Thorac Soc* 2021; 18: 1020–1026.
9 Coppadoro A, Benini A, Fruscio R, *et al.* Helmet CPAP to treat hypoxic pneumonia outside the ICU: an observational study during the COVID-19 outbreak. *Crit Care* 2021: 25: 80.