Critical Care

LETTER

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Longitudinal ventilatory ratio monitoring for COVID-19: its potential in predicting severity and assessing treatment response

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To the Editor:

We read with great interest the recent research article, published in *Critical Care*: "Longitudinal changes in compliance, oxygenation and ventilatory ratio in COVID-19 versus non-COVID-19 pulmonary acute respiratory distress syndrome", by Beloncle and collaborators [1]. We agree with their conclusion that increase in ventilatory ratio (VR) during the first week of illness is characteristic to COVID-19 ARDS and reflects its uniqueness in pathophysiology. In addition, we herein wish to propose that VR in COVID-19 ARDS may serve as a potential bedside marker reflecting clinical severity and that its longitudinal monitoring may harbor prognostic value.

In our 28-day observational study including 39 patients with critically ill COVID-19 [2], longitudinal increase in VR values were associated with failure in discontinuing respiratory support (Fig. 1). Upon predicting failure, a VR threshold of 1.56 achieved the highest predictivity with a sensitivity of 0.667 and a specificity of 0.762 on day 5 of respiratory support. Of 21 patients with a VR value lower than 1.56 on day 5, 17 had successfully extubated within 28 days from respiratory support, suggesting that longitudinal VR monitoring could predict better outcome in COVID-19. Similar findings were obtained in another research applying VR changes from day 0 to 3 of respiratory support as a prognostic indicator [3]. Although statistically insignificant, Beloncle and collaborators have also shown an apparent trend towards better prognosis for a lower VR (Table S3; mortality in "VR < 2" versus "VR $\geq$ 2" were 15.5% versus 30%). It would be of great interest to validate our observations in their cohort as well, by assessing longitudinally the prognostic value of VR, if sufficient data were provided. The wide variety of VR values observed along the chronological course of COVID-19 ARDS, shown in Fig. 1D, may indicate the variable responses following therapeutic interventions. The expanding but yet investigatory list of therapeutics against COVID-19 warrants a deeper description of the therapeutic interventions received within the cohort.

Elevation in VR, a surrogate marker of the increasing dead space fraction, is attributed to the progressive exudative damage affecting the alveoli, as well as the development of micro-embolism in the pulmonary circulation [4, 5], both known histopathological determinants of COVID-19 clinical severity. In addition to the here proposed prognostic value of VR monitoring in predicting natural history of COVID-19, future interest resides in whether longitudinal evaluation of VR may further reflect clinical response to treatment.

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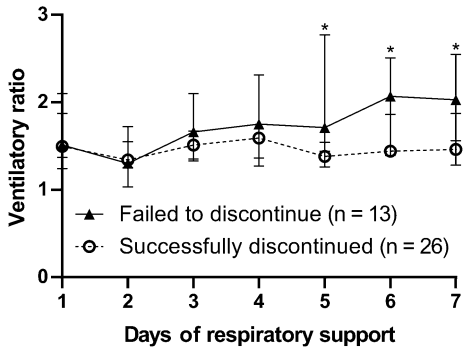

Fig. 1 Longitudinal VR values after initiation of respiratory support. Longitudinal daily values of VR during the first week after initiation of respiratory support. The failed to discontinue group presented as the solid triangles and solid lines, and the successfully discontinued group presented as the opened circles and the dashed lines. Each marker placed on the median value, and each error bar meant the 95% confidential interval. Statistical analysis determined the differences between the failed to discontinue and successfully discontinued groups on each day by Mann–Whitney test. **p*-value < 0.05

Authors' response letter

François Beloncle, Antoine Studer, Valérie Seegers, Jean-Christophe Richard, Christophe Desprez, Nicolas Fage Hamid Merdji, Bertrand Pavlovsky, Julie Helms, Sibylle Cunat, Satar Mortaza, Julien Demiselle, Laurent Brochard, Alain Alain Mercat and Ferhat Meziani

Dear editor,

We thank Drs Natsuko Kaku et al. for their interest in our study "Longitudinal changes in compliance, oxygenation and ventilatory ratio in COVID-19 versus non-COVID-19 pulmonary acute respiratory distress syndrome" that was recently published in Critical Care [1]. We also thank them for their valuable comment, in which they point out that an increase in Ventilatory Ratio (VR), a surrogate marker of an increase in dead space fraction [6], may allow to predict a poor outcome in patients with COVID-19 associated acute respiratory distress syndrome (ARDS).

We found in our cohort of 135 patients with COVID-19 associated ARDS that VR at day 1, day 3 and day 7 after intubation was higher in non-survivors than in survivors at day 28 (2.1 [1.7–2.4] vs 1.7 [1.5–2.0], $p=0.006$; 2.4 [2.1–2.8] vs 1.9 [1.6–2.2], $p=0.003$ and 3.2 [2.3–3.9] vs 2.3 [1.8–2.7], $p=0.001$, respectively). Discrepancies between the two cohorts might be related to different time course evolutions which may be due to potential differences in non-invasive oxygenation strategies before intubation.

However, in line with the results reported by Drs. Natsuko Kaku et al., we found in patients with COVID-19 that the increase in VR from day 1 to day 7 tended to be higher in the non-survivors than in the survivors at day 28 (0.8 [0.3–1.8] vs 0.5 [0.1–0.9], $p=0.053$). This tendency was not observed in the control patients with non-COVID-19 pulmonary ARDS. High VR are known to be associated with poor outcomes in patients with non-COVID-19 ARDS [6, 7]. Even if it has to be confirmed in larger cohorts, the potential specific prognostic value of the changes in VR over time in COVID-19 associated ARDS may be consistent with the distinct evolution of clinical features observed in this population during the first week of mechanical ventilation. As highlighted in our paper, this particular evolution may be in part due to different ventilatory strategies (in particular of positive end-expiratory pressure (PEEP) titration). We agree with Drs. Natsuko Kaku et al. that whether VR changes may help the clinicians to assess the efficacy of some therapeutics as PEEP levels or prone positioning is an interesting question which remains to be addressed.

Abbreviations

COVID-19: Coronavirus disease of 2019; ARDS: Acute respiratory distress syndrome; VR: Ventilatory ratio; ROC: Receiver operating characteristic.

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Authors' contributions

NK, MS, and YK designed the concept of the study. NK, SS, KY, KS, YM, and RM conducted the study and performed the data acquisition. NK, YN, YN, and YK assessed the quality of the study and performed the analysis and interpretation. NK, YN, and YK wrote the manuscript, and the other authors made substantial revisions and edits. All authors read and approved the final manuscript.

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Availability of data and materials

The datasets analyzed in our study are available at https://www.medrxiv.org/content/10.1101/2021.07.20.21260754v1.supplementary-material.

Declarations

Ethics approval and consent to participate

This study was conducted under the approval of the Institutional Review Board of Osaka City University (#2020-003) and the Clinical Research Ethics Committee of the Osaka Municipal Hospital Organization (#2005020), Osaka,

Japan. All necessary patient consent has been obtained and the appropriate institutional form has been archived.

Consent for publication
Not applicable.

Competing interests
Not applicable.

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