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Letter to the Editor

Standardized PaO2/FiO2 ratio in COVID-19: added Added value or risky assumption. Author's reply[1][1]

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Dear Editor,

We have read with great interest the comment of Luciano Gattinoni and coworkers who carefully reviewed our paper *"Standardized PaO_2/FiO_2 ratio in COVID-19: Added value or risky assumptions"* recently published in the European Journal of Internal Medicine [1, 2]. We agree with most of their comments on the potential limitations of the standardized PaO_2/FiO_2 approach. There are, however, a few points that we would like to further discuss and clarify.

First, we do not entirely agree on the need to systematically correct the alveolar partial pressure of oxygen (PAO_2) using the respiratory quotient (RQ). This is usually measured at the mouth (respiratory exchange ratio, R, $V'CO_2/V'O_2$) and therefore it is extremely difficult, if not impossible, to measure during helmet CPAP or high oxygen flow supplementation (HOF) and, because of the contribution/changes in lung gas stores, R does not reflect changes in RQ. Thus, the correction for R is impractical not reflecting the metabolic state (RQ), and as pointed out in a previous work by Gattinoni and his group "the impact of the $PaCO_2/R$ ratio on alveolar PO_2 (PAO_2) is less dramatic unless extracorporeal CO_2 removal is in use" [3].

Second, as pointed out by Gattinoni and coworkers, the advantage of standardized PaO_2/FiO_2 over PaO_2/FiO_2 is that standardized PaO_2/FiO_2, (i.e. PaO_2 corrected for the $PaCO_2$), takes in account the contribution of the respiratory effort sustained by the patient which has been demonstrated to be a predictor of poor outcome in acute respiratory failure. We would like to add that it also reflects the need to increase PAO_2 to maintain an adequate arterial oxygenation (i.e. PaO_2) at the cost of a left shift in arterial Hb-O_2 dissociation curve due to respiratory alkalosis. This is a well-known compensation mechanism that occurs for example at high altitude where the need to preserve arterial oxygenation (i.e., increased Hb-O_2 affinity at the lung due to increased pH) prevails on the diffusion of oxygen, from peripheral arterial capillaries at tissue levels. Obviously, other factors, such as body temperature, Hb levels and cardiac output should be taken in account to a have a clear picture of the O_2 transport efficiency.

Third, we do agree that standardized PaO_2/FiO_2 ratio should be used with caution when tracking patients over time, because of the influence of dead space of shunt fractions that may change along the illness. This, in fact, was not the aim of our study in which we tested the superiority of the standardized PaO_2/FiO_2 ratio versus the PaO_2/FiO_2 ratio in predicting the outcome failure and mortality measured at the time of admission to the Pulmonology unit. It should be pointed out, however, that also the use of the "classical" PaO_2/FiO_2 ratio has limitations not only as a single observation but also when it is used for tracking patients over time. In particular, the PaO_2/FiO_2 ratio is significantly influenced by the fraction of inspired oxygen (FiO_2). Of notice when the patient is breathing $FiO_2 \leq 0.6$ the possible contribution of V'/Q' mismatch and diffusion limitation from shunt cannot be ruled out. By contrast when breathing $FiO_2 > 0.6$ the contribution of shunt mechanisms becomes clearer [4].

In conclusion, although we do agree with Gattinoni and coworkers in their analysis on the need to consider all the variables that may influence gas exchange impairment in severe ARF, we believe that the standard PaO_2/FiO_2 ratio should be utilized in the prognostic evaluation of patients with COVID-19 acute respiratory failure.

Declaration of Competing Interest

The authors declare they have no conflict of interest.

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[1] on behalf of the authors of "Standardizing PaO2 for PaCO2 in P/F ratio predicts in-hospital mortality in acute respiratory failure due to Covid-19: a pilot prospective study"Author's contribution: IP draft preparation. IP, SN and PP co-write the manuscript. SN and PP supervised the final revision.

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