corticosteroids during hospitalization, though we do not know if the indication for steroids was presumed adrenal insufficiency.

Interestingly, elevated interleukin-6, which was significantly related to hyponatremia in our study, is known to be a potent activator of the hypothalamic-pituitary-adrenal axis and is associated with elevated serum cortisol levels in the context of viral infection (3–5). Overall, although we cannot definitively say how many patients had hyponatremia due to adrenal insufficiency in our cohort, it is possibly a contributing factor and it is likely that the etiology of hyponatremia may be multifactorial among patients with severe COVID-19. Because adrenal insufficiency is readily treatable and may be fatal if untreated, it should be considered in the evaluation of hyponatremia.

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Is the Pa_{O_2}:F_{IO_2} Ratio the Best Marker to Monitor the Blood-Air Barrier Function in Acute Respiratory Distress Syndrome?

To the Editor:

We read with great interest the article of Lee et al (1), published in a recent issue of *Critical Care Medicine*, which supported the hypotheses that percentage improvement in Pa_{O_2}:F_{IO_2} ratio after the first prone position in moderate-to-severe acute respiratory distress syndrome (ARDS) patients could be a significant predictor of survival. We applaud to the valid contribution this work provided to such a controversial issue, but at the same time, we would like to underline some aspects which authors have not fully elucidated.

ARDS is characterized by acute noncardiogenic pulmonary edema and hypoxemia; an optimal ventilation management is fundamental to improve the outcome, and many authors tried to identify the best setting of mechanical ventilation (e.g., positive end-expiratory pressure, tidal volume) (2, 3).

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PaO_2:FIO_2 ratio is widely used in clinical practice as it is an easy tool to evaluate the alveolar-capillary membrane function in pulmonary diseases: in fact, it is intuitive that a lower PaO_2:FIO_2 ratio means that a greater oxygen concentration in the alveoli is needed to make the oxygen pass through the blood-air barrier to reach a given concentration of oxygen in the blood.

PaO_2:FIO_2 ratios have some limits to define the improvement in gas exchange. It strongly depends on pulmonary shunt; in fact, in healthy lung, as FIO_2 increases, PaO_2:FIO_2 ratio tends to rise, whereas if the amount of shunt is significant, the PaO_2:FIO_2 ratio is inversely correlated with FIO_2 (4). This factor should have been considered in the discussion particularly because ARDS is characterized by a dramatic shunt (5).

Furthermore, as shunt increases, PaO_2 tends to be more dependent on mixed venous oxygen content which is in turn correlated to the oxygen extraction rate, an extremely variable factor in critically ill patients: in fact, it can both increase, that is, in cardiogenic shock and decrease, that is, in sepsis (6, 7).

We strongly believe that a better index to evaluate the overall gas exchange efficiency and to monitor the function of the blood-air barrier of an injured lung is alveolar-arterial gradient (ΔA-a), which can be automatically obtained by the most blood gas analyzers. ΔA-a is the difference between PaO_2 and PaO_2. ΔA-a indicates the resistance of alveolar-capillary membrane to the passage of oxygen into the blood because the greater this difference is the greater is the strength needed to make the oxygen to cross the blood-air barrier and reach a given value of PaO_2. According to the alveolar gas equation, $PaO_2 = \left(P_{atm} - PH_2O\right) \cdot FiO_2 - PaCO_2 / RQ$

(RQ = respiratory quotient, P_{atm} = atmospheric pressure, PH_2O = partial pressure of water)

PAO_2 depends on $PaCO_2$, and patients with the same PaO_2 and FIO_2 (so with the same PaO_2:FIO_2 ratio) could have different PAO_2 and consequently different ΔA-a (8). The influence of $PaCO_2$ is not taken into account by PaO_2:FIO_2 ratio despite $PaCO_2$ could have a great variability in ARDS patients as also shown by study population of Lee et al (1).

We really appreciated the above-mentioned article (1) published in your remarkable journal, and our comments wanted to be only a suggestion for further research to implement the use of other simple indexes of pulmonary gas exchange function which are richer of information than PaO_2:FIO_2 ratio.

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The authors have disclosed that they do not have any potential conflicts of interest.

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