Alveolar SARS-CoV-2 viral load is tightly correlated with severity in COVID-19 ARDS

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Dear Editor

Magleby *et al*. recently reported the prognostic value of the baseline SARS-CoV-2 viral load as assessed by nasopharyngeal swab sampling obtained upon hospital admission (1). In a large group of patients from two American hospitals, the authors showed that the greater the viral load, the higher the risk of requiring ventilator support. As a prognostic tool, PCR appears to be clinically relevant given the 5 to 12-day timeframe generally preceding ICU admission in patients with respiratory symptoms. These results raise several issues.

First, the host's ability to clear SARS-CoV-2 from the upper airways seems to be correlated with the risk of further respiratory distress. Accordingly, the so-called "cytokine storm" paradigm remains questionable (2,3). However, Magleby *et al*. do not depict the viral status of patients who have reached the stage at which intubation is required. It is thus speculative to explain poor clinical outcome by a lack of viral clearance since a stronger inflammatory response may be triggered by a higher viral load, leading in turn to more severe lung injury.

Accordingly, our group performed a prospective study as part of the PNEUMOCHONDRIE project (ClinicalTrials.gov NCT03955887). Between March and April 2020, we included 14 patients with SARS-CoV-2-related (positive PCR on a nasopharyngeal sample) acute respiratory distress syndrome (ARDS) who required mechanical ventilation. A bronchoalveolar lavage (BAL) was performed shortly after intubation. The number of RNA copies of SARS-CoV-2 was quantified by RT-PCR targeting RNA-dependent RNA polymerase IP4 region. To correct for dilution, the epithelial lining fluid (ELF) concentration of SARS-CoV-2 RNA was calculated by multiplying BALF concentration with the [urea]BALF/[urea]plasma (4). The median [interquartile range (IQR)] age in the study population was 67 [63-70] years. Median [IQR] Sepsis-related Organ Failure Assessment (SOFA) score was 4 [4-5] and 5.5 [3-6.8] at day 0 and 2, respectively. Median PaO_2:FiO_2 [IQR] was 88 [19-117] and 150 [131-185] at day 0 and 2, respectively. The SARS-CoV-2

genome was detected in BAL fluid in all but one patient, with a median of 20,449 (IQR=893-2,092,104) copies per microliter of ELF. Although no correlation was found with baseline SOFA scores or baseline PaO_2:FiO_2, on day 2 there was a significant positive correlation with SOFA score values (r=0.658; p=0.013) (Figure 1) and a negative correlation with the PaO_2:FiO_2 ratio (r=-0.556; p=0.042).

In line with the findings of Magleby *et al*, we showed that the alveolar viral load at the onset of ARDS is tightly correlated with subsequent clinical worsening, especially in terms of hypoxemia. These findings suggest that COVID-19 ARDS severity is not solely explained by a self-sustaining dysregulated immune response, but also by the host's inability to keep the virus in check within the lung compartment.

While anti-inflammatory approaches (i.e. dexamethasone) have shown promising results in the most severe cases (5), efforts still need to be made to find effective anti-viral therapies in order to combine antiviral and immune-modulator effects as parts of COVID-19 ARDS management.

NOTES

Author Contributions:

MB, CM and PEC had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Concept and design: MB, LP, PEC

Acquisition, analysis, or interpretation of data: MB, MJ, CM, LP, PEC

Drafting of the manuscript: MB, PEC

Critical revision of the manuscript for important intellectual content: CM, LP

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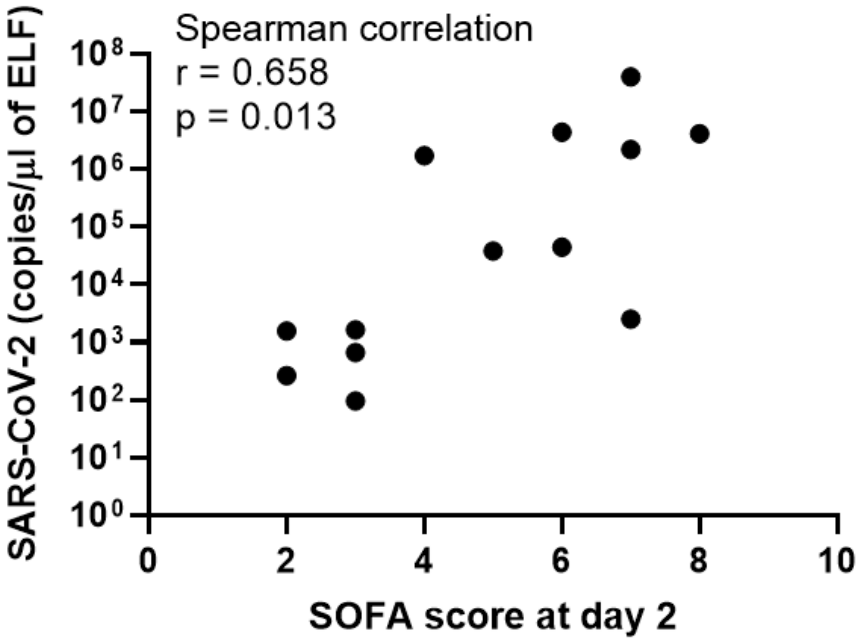
Figure 1. Spearman correlation between the alveolar concentration of SARS-CoV-2 and SOFA score at day 2.

The epithelial lining fluid (ELF) concentration of SARS-CoV-2 was tightly correlated with the SOFA score at day 2 in COVID-19 patients with acute respiratory distress syndrome (r=0.658, p=0.013; Spearman correlation).

Abbreviations: COVID-19: coronavirus disease 2019; ELF: epithelial lining fluid; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2; SOFA: Sepsis-related Organ Failure Assessment

Figure 1.


Spearman correlation
r = 0.658
p = 0.013
SARS-CoV-2 (copies/µl of ELF)
10^8
10^7
10^6
10^5
10^4
10^3
10^2
10^1
10^0
0
2
4
6
8
10
SOFA score at day 2