Vitamin C levels in patients with SARS-CoV-2-associated acute respiratory distress syndrome

Luis Chiscano-Camón, Juan Carlos Ruiz-Rodriguez, Adolf Ruiz-Sanmartin, Oriol Roca and Ricard Ferrer

Vitamin C is an antioxidant with anti-inflammatory and immune-supportive properties. Its levels are decreased in patients with sepsis-related acute respiratory distress syndrome (ARDS). Moreover, a significant number of patients with severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) disease developed ARDS. Therefore, we hypothesized that ARDS coronavirus disease 2019 (COVID-19) patients may present vitamin C deficiency.

Plasma vitamin C levels in a population of adult ICU patients COVID-19 who met ARDS criteria according to the Berlin definition were prospectively measured. The study was approved by the local Clinical Research Ethics Committee (PR (AG)270/2020). Main characteristics of the population included are presented in Table 1. None of the patients included presented shock or sepsis on admission. Equally, no bacterial co-infection during their ICU course was documented. All patients survived. Vitamin C was determined by high-performance liquid chromatography with photodiode detector (detection limit 1.5 mg/L). Vitamin C reference values in general population used to be above 5 mg/L. Seventeen patients (94.4%) had undetectable vitamin C levels and 1 patient had low levels (2.4 mg/L).

To our knowledge, this is the first study to analyze the levels of vitamin C in patients with SARS-CoV-2-associated ARDS. Our study revealed that vitamin C levels are undetectable in more than 90% of the patients included. The mechanisms of this significant reduction in vitamin C are uncertain. We hypothesized that several mechanisms, such as increased metabolic consumption due to the enhanced inflammatory response, glomerular hyperfiltration, dialysis, decreased gastrointestinal absorption, or decreased recycling of dehydroascorbate to ascorbic acid, may be involved.

Moreover, vitamin C may have implications for treatment of COVID-19-associated ARDS. Indeed, one preclinical study showed that vitamin C increased resistance to infection caused by coronavirus. Moreover, other clinical studies that included surgical patients and patients with pneumonia showed encouraging results in terms of decreased incidence and severity of lung injury and mortality.
Our study has several limitations mainly related with the fact that it is a unicentric study with small sample size and blood sample was obtained in different days of their course in the ICU.

In conclusion, in our cohort of patients with COVID-19-associated ARDS, the levels of vitamin C are extremely low. Despite the limited generalization of these results, we think these findings might stimulate clinicians to measure vitamin C levels in COVID-19 patients to describe the real impact of this alteration.

Acknowledgements
No contributions from individuals or organizations.

Disclosure statement
The authors have no conflicts of interest to declare.

Authors' contributions
We were all involved in providing care for the patient. We were all involved in writing and reviewing the manuscript. The authors read and approved the final manuscript.

Funding
No funding.

Availability of data and materials
The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate
We complied with the guidelines for human studies and our research was conducted ethically in accordance with the World Medical Association Declaration of Helsinki. Information revealing the subject’s identity is to be avoided. The study was approved by the local Clinical Research Ethics Committee (PR (AG)270/2020) with exemption from informed consent.

Competing interests
The authors declare that they have no competing interests.

Table 1 Clinical characteristics of the COVID-19 patients included. We have included the worst PF and highest PEEP. Results of continuous variables are expressed as mean and standard deviation or median and interquartile range as appropriate. Categorical variables are expressed as frequency (percentage). SOFA sequential organ failure assessment, APACHE II Acute Physiology and Chronic Health disease Classification System II, ICU intensive care unit, PF PaO2/FiO2 ratio, PEEP positive end-expiratory pressure, AKI acute kidney injury, CRRT continuous renal replacement therapy, LMWH low-molecular-weight heparin

| Clinical characteristics | COVID-19 ARDS (n = 18) |
|--------------------------|------------------------|
| Age (mean, standard deviation, years) | 59 ± 9 |
| Male (n, %) | 7 (38) |
| SOFA score (median, interquartile range, points) | 4 (1) |
| APACHE II score (mean, standard deviation, points) | 16.2 ± 1.6 |
| Interval between ICU admission and blood samples extraction for vitamin C measurement (mean, standard deviation, days) | 17.5 ± 1.7 |
| Interval between intubation and blood samples extraction for vitamin C measurement (mean, standard deviation, days) | 17.5 ± 1.7 |

ARDS-related variables

| Variable | Value |
|----------|-------|
| PaO2/FiO2 at the time of vitamin C measurement (mean, standard deviation, mmHg) | 94.4 ± 5.9 |
| PEEP (cmH2O) at the time of vitamin C measurement (median, interquartile range, points) | 13.6 (3) |
| Neuromuscular blockade during ICU admission (n, %) | 18 (100) |
| Prone position during ICU admission (n, %) | 17 (94) |

Renal failure

| Variable | Value |
|----------|-------|
| AKI (n, %) | 3/18 (16) |
| AKI I (n, %) | 2/3 (66) |
| AKI III (n, %) | 1/3 (33) |
| CRRT (n, %) | 1/18 (6) |

COVID-19-related therapies

| Therapy | Value |
|---------|-------|
| Antivirals (n, %) | 14 (77) |
| Hydroxychloroquine (n, %) | 17 (94) |
| Tocilizumab (n, %) | 13 (72) |
| Methylprednisolone (n, %) | 10 (55) |
| LMWH anticoagulant (n, %) | 8 (44) |

Outcomes

| Outcome | Value |
|---------|-------|
| Length of ICU stay (mean, standard deviation, days) | 28.4 ± 3.4 |
| Number of hospital survivors (n, %) | 18 (100) |
Author details
1Intensive Care Department, Vall d’Hebron Hospital Universitari, Vall d’Hebron Barcelona Hospital Campus, Passeig Vall d’Hebron 119-129, Barcelona 08035, Spain. 2Shock, Organ Dysfunction and Resuscitation Research Group, Vall d’Hebron Hospital Universitari, Vall d’Hebron Barcelona Hospital Campus, Passeig Vall d’Hebron 119-129, Barcelona 08035, Spain. 3Departament de Medicina, Universitat Autònoma de Barcelona, Bellaterra 08193, Spain. 4Ciber Enfermedades Respiratorias (Ciberes), Instituto de Salud Carlos III, Madrid, Spain.

Received: 16 July 2020 Accepted: 12 August 2020
Published online: 26 August 2020

References
1. Murthy S, Gomersall C, Fowler R. Care for critically ill patients with COVID-19. JAMA. 2020. https://doi.org/10.1001/jama.2020.3633.
2. ARDS Definition Task Force, Ranieri VM, Rubenfeld GD, Thompson BT, Ferguson ND, Caldwell E, Camporota L, Slutsky AS. Acute respiratory distress syndrome: the Berlin definition. JAMA. 2012;307(23):2526–33.
3. Carr A. A new clinical trial to test high-dose vitamin C in patients with COVID-19. Crit Care. 2020;24:133.
4. Atherton JG, Kratzing CC, Fisher A. The effect of ascorbic acid on infection of chick-embryo ciliated tracheal organ cultures by coronavirus. Arch Viro. 1978;56:195–9.
5. Nathens AB, Neff MJ, Jurkovich GJ, Klotz P, Farver K, Ruzinski JT, et al. Randomized, prospective trial of antioxidant supplementation in critically ill surgical patients. Ann Surg. 2002;236:814–22.

Publisher’s Note
Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.