
Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Pharmacological Research 184 (2022) 106451

Contents lists available at ScienceDirect

Pharmacological Research

journal homepage: www.elsevier.com/locate/yphrs

# Targeting endothelial dysfunction and oxidative stress in Long-COVID

We thank Dr. Hsu and Dr. Lai for their interest in our work on COVID-19 and Long-COVID.

We fully agree with them on the fact that several factors need to be pondered in order to evaluate the risk of developing Long-COVID [1,2]. However, we respectfully believe that these considerations are not pertinent to our study [3]. Indeed, we designed the LINCOLN (L-Arginine and Vitamin C improves Long-COVID) survey to determine whether a supplementation combining L-Arginine (to improve endothelial function) and Vitamin C (to reduce oxidation) could have favorable effects in patients with Long-COVID [3]. Thus, in our study we did not assess the risk of developing Long-COVID; in fact, as clearly specified in our article, all the enrolled patients had Long-COVID when the survey was administered. Nevertheless, potential differences in health conditions between the group that had received L-Arginine + Vitamin C and the group that had received the alternative treatment were ruled out by their family physicians. When comparing the two groups, we did not observe any significant difference in terms of age, sex, hospitalization due to COVID-19, and time from SARS-Cov-2 negativization. Moreover, bearing in mind the limitations that all surveys have, we had concluded our article stating that further dedicated interventional studies were warranted to endorse our findings.

Of note, we have previously conducted a randomized, double-blind, placebo-controlled, parallel-group, clinical trial testing the effects of L-Arginine oral supplementation in patients hospitalized for COVID-19, demonstrating that this treatment significantly decreases the length of hospitalization and reduces the respiratory support [4]. Additionally, we have identified endothelial exosomes enriched in miR-24 as a reliable biomarker to predict cerebrovascular complications of COVID-19 [5], corroborating the fundamental role of endothelial dysfunction in the pathobiology of COVID-19 and its clinical sequelae [6].

## Funding

None.

## Declarations of interest

None.

## Data Availability

Data will be made available on request.

## References

[1] Z. Al-Aly, Y. Xie, B. Bowe, High-dimensional characterization of post-acute sequelae of COVID-19, Nature 594 (2021) 259–264.
[2] A. Subramanian, et al., Symptoms and risk factors for long COVID in non-hospitalized adults, Nat. Med. 28 (2022) 1706–1714.
[3] R. Izzo, et al., Combining L-Arginine with vitamin C improves long-COVID symptoms: the LINCOLN Survey, Pharm. Res. 183 (2022), 106360.
[4] G. Fiorentino, et al., Effects of adding L-arginine orally to standard therapy in patients with COVID-19: a randomized, double-blind, placebo-controlled, parallel-group trial. Results of the first interim analysis, eClinicalMedicine 40 (2021), 101125.
[5] J. Gambardella, et al., Role of endothelial miR-24 in COVID-19 cerebrovascular events, Crit. Care 25 (2021) 306.
[6] C. Sardu, et al., Hypertension, thrombosis, kidney failure, and diabetes: is COVID-19 an endothelial disease? A comprehensive evaluation of clinical and basic evidence, J. Clin. Med. 9 (2020).

Valentina Trimarco[a], Raffaele Izzo[b], Pasquale Mone[c], Bruno Trimarco[b], Gaetano Santulli[b,c,*]

[a] *Department of Neuroscience, Reproductive Sciences and Dentistry, Federico II University, Naples, Italy*

[b] *Department of Advanced Biomedical Sciences, Federico II University, Naples, Italy*

[c] *Department of Medicine, Albert Einstein College of Medicine, New York, NY, USA*

[*] Corresponding author at: Department of Medicine, Albert Einstein College of Medicine, New York, NY, USA.
*E-mail address:* gsantulli001@gmail.com (G. Santulli).

https://doi.org/10.1016/j.phrs.2022.106451
Received 11 September 2022; Accepted 11 September 2022
Available online 13 September 2022