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Combining L-Arginine with vitamin C improves long-COVID symptoms: The LINCOLN Survey

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A R T I C L E I N F O

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A B S T R A C T

Introduction: Recent evidence suggests that oxidative stress and endothelial dysfunction play critical roles in the pathophysiology of COVID-19 and Long-COVID. We hypothesized that a supplementation combining L-Arginine (to improve endothelial function) and Vitamin C (to reduce oxidation) could have favorable effects on Long-COVID symptoms.
Methods: We designed a survey (LINCOLN: L-Arginine and Vitamin C improves Long-COVID), assessing several symptoms that have been associated with Long-COVID to be administered nationwide to COVID-19 survivors; the survey also included effort perception, measured using the Borg scale. Patients receiving the survey were divided in two groups, with a 2:1 ratio: the first group included patients that received L-Arginine + Vitamin C, whereas the second group received a multivitamin combination (alternative treatment).
Results: 1390 patients successfully completed the survey. Following a 30-day treatment in both groups, the survey revealed that patients in the L-Arginine + Vitamin C treatment arm had significantly lower scores compared to patients who had received the multivitamin combination. There were no other significant differences between the two groups. When examining effort perception, we observed a significantly lower value ($p < 0.0001$) in patients receiving L-Arginine + Vitamin C compared to the alternative-treatment arm.
Conclusions: Our survey indicates that the supplementation with L-Arginine + Vitamin C has beneficial effects in Long-COVID, in terms of attenuating its typical symptoms and improving effort perception.

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1. Introduction

The *coronavirus disease 2019* (COVID-19) pandemic caused by the *severe acute respiratory syndrome coronavirus-2* (SARS-CoV-2) has led to a global healthcare crisis [1]. The global pandemic has resulted also in job losses and economic hardships [2]. Although efficacious vaccines have been recently developed [3–6], it is important to better understand SARS-CoV-2-mediated pathology, especially because many survivors are experiencing chronic symptoms of the disease, including metabolic disturbances, even months after the initial infection occurred ("Long-COVID") [7–18].

While initial studies on COVID-19 primarily focused on the pulmonary manifestations of the disease [19–24], other organs including heart, brain, kidney, and the pancreas, were shown to be affected by COVID-19 [25–27]. In the Spring of 2020, we were among the first groups to indicate a link between COVID-19 and endothelial dysfunction [28,29], and our view has been later confirmed by other investigators, associating the systemic manifestations of the disease to a direct or indirect involvement of the endothelium [30–39]. Indeed, endothelial cells express all co-factors necessary for the internalization of SARS-CoV-2 in host cells, including angiotensin converting enzyme 2 (ACE2), transmembrane protease serine 2 (TMPRSS2), cathepsins B and D, neuropilin-1, transferrin receptor, and others, thereby representing a natural target of SARS-CoV-2 [28,39–45]. Thus, COVID-19 affects not only the epithelial cells of the lung [46,47], but also endothelial cells across the whole body, leading to a generalized endothelial damage. Endothelial cells are known to play instrumental roles in the maintenance of vascular homeostasis and in the regulation of vascular tone [48–50]. Endothelial dysfunction, caused directly by SARS-CoV-2 infection and/or by the ensuing inflammation, can shift the vascular equilibrium towards an altered vascular tone, an increased permeabilization, with subsequent tissue edema, and a pro-coagulant state, which can lead to thromboembolism; most of these findings have been substantiated by autopsies of COVID-19 patients since the outbreak of the pandemic [51–53]. Further supporting our theory of a central role of the endothelium in COVID-19, patients with endothelial dysfunction (e.g. hypertension, smoking, pre-existing diabetes, obesity, and presence of cardiovascular disease) are particularly vulnerable and have adverse outcomes in COVID-19 [54]. Equally important, clinical trials testing whether interventions that ameliorate endothelial dysfunction can have beneficial effects in COVID-19 patients are ongoing [55–63] and we have obtained very encouraging interim results in a randomized study testing L-Arginine oral supplementation in COVID-19 hospitalized patients [55].

L-Arginine is an amino acid that acts as a substrate for endothelial nitric oxide (NO) synthase (eNOS), a key enzyme in endothelial cells [64–72]; it has been previously shown to significantly improve endothelial function, providing a strong rationale for its use in COVID-19 patients [58]. Additionally, beneficial effects of L-Arginine on the regulation of immune responses have been reported [73,74]. Similarly, recent clinical trials have demonstrated that Vitamin C improves the oxidative imbalance and vascular remodeling induced by different stressors and attenuates endothelial barrier permeability, an aspect that has major implications in infectious disorders (including COVID-19), which are also known to cause a systemic surge in oxidative stress [75]. So, the antioxidant roles of Vitamin C and its protective effects on endothelial permeability could come into effect especially in post-infection recovery [76–82].

Therefore, we inferred that associating Vitamin C with other nutraceuticals playing similar actions, like L-Arginine, could be useful. On these grounds, considering that both L-Arginine and Vitamin C are known to improve endothelial function and reduce vascular permeability during infectious disorders [75,83–86], and based on the emerging role of vascular permeability in Long-COVID [87,88], we designed a survey to assess the effects of a combination of L-Arginine and Vitamin C in Long-COVID.

2. Methods

2.1. Survey design and participants

This survey (LINCOLN: L-Arginine and Vitamin C improves Long-COVID) starts from the medical need to understand Long-COVID disease. For this reason, in January 2022, we designed a questionnaire based on a seminal *Nature Medicine* paper published in April 2021 [89] and on the national recommendations on the management of Long-COVID. Our research group includes 16 key opinion leaders belonging to different Italian Regions; a group of physicians (please see appendix) participated in actually administering the LINCOLN survey to patients. The questionnaire was revised by the key opinion leaders and shared with the general practitioners of the nation with the aim to enroll the highest number of patients.

The LINCOLN survey included the following evaluations: patient age, sex, days from RT-qPCR negativization, and hospitalization for moderate/severe COVID-19. Furthermore, the physicians needed to assess on a scale from 1 to 3 (where 1 is absence of the symptom, 2 is the presence of a mild symptom, and 3 is the presence of a severe symptom) - the following symptoms: fatigue, shortness of breath, chest tightness, dizziness, gastrointestinal disorders, headache, anosmia, difficulties in concentrating, sleep disturbances.

Finally, effort perception was evaluated in the survey using the *Borg modified 0–10 Rating of perceived exertion* scale, with a score from 0 to 10 (where 10 indicate no tolerance), as we previously described [90]. The survey was administered to two groups of COVID-19 survivors who had been COVID-19 negative (confirmation to be SARS-CoV-2 negative via RT-qPCR test [91]) for at least 4 weeks. The first group included patients who had received 2 vials/day of L-Arginine 1.66 g in association with 500 mg of liposomal Vitamin C. The second group (alternative treatment) had been treated with a multivitamin combination (Vitamin B1: 388 mg; Vitamin B2: 443 mg; Nicotinamide:18 mg; Folic Acid: 200 μg; Pantothenic acid: 2493 g; Vitamin B6: 831 mg; Vitamin B12: 416 μg). Physicians were asked to maintain a ~2:1 ratio (L-Arginine + Vitamin C *vs* alternative treatment) in administering the survey; therefore, they were not blinded; actually, when the questionnaire was administered, patients of both groups had already completed 30 days of treatment.

2.2. Inclusion and exclusion criteria

Eligible patients were men and non-pregnant women who were at least 18-year-old, screened by applying the following eligibility criteria:

Inclusion criteria

Presence of the following conditions:
Previous diagnosis of COVID-19 confirmed by RT-qPCR;
COVID-19 negativization confirmed by RT-qPCR from at least 4 weeks;
Presence of COVID-19 sequelae that extend beyond four weeks after initial infection.

Exclusion criteria

- Refusal to participate;
- History of intolerance to L-Arginine, Vitamin C, or components of the multivitamin combination;
- Pregnancy or breastfeeding;
- Cancer;
- Diagnosis of chronic pulmonary disease - currently under treatment;
- Use of immunosuppressive drugs, or cytotoxic chemotherapy within the previous three weeks;
- Enrollment into an investigational treatment study for COVID-19 in the 30 days before screening.

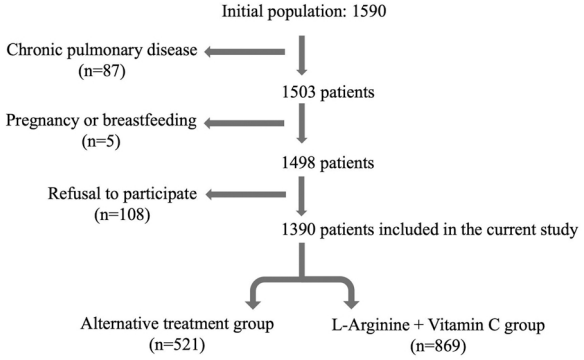

Fig. 1. Flow chart.

2.3. Ethical aspects

The survey was distributed to patients who had already received the treatments. A clear and informative description of the survey and an explanation of how collected data would have been used were given to respondents; participation was voluntary. According to the Italian regulatory framework, all of the data were anonymized and aggregated, and no personally identifiable information was collected.

2.4. Statistical analysis

The main characteristics of the participants are reported as mean ± SD or percentage. Statistical significance was determined by a p value <0.05. In the statistical analysis, differences for continuous variables were evaluated using two-sample t-test for approximately normally distributed variables and Mann-Whitney U test for severely skewed variables. Chi-square or Fisher tests were used to measure associations between dichotomous and categorical variables. All analyses were performed using SPSS 26.0.

3. Results

1590 patients were initially enrolled, of which 1390 fulfilled the eligibility criteria and successfully completed the survey, as shown in the flow chart in Fig. 1.

There were no significant differences in terms of age, male sex, or hospitalization due to COVID-19 between the group treated with L-Arginine + Vitamin C and the arm treated with the alternative treatment (Table 1). Notably, no difference in the time from SARS-Cov-2 negativization was noted between the two groups of patients (33.8 ± 24.9 vs 31.5 ± 24.0 days; ns).

Following a 30-day treatment with L-Arginine + Vitamin C, the survey revealed that patients in this treatment group had significantly lower scores (which means less severe long-COVID symptoms) compared to the other group (L-Arginine + Vitamin C: 8.15 ± 1.3 vs Alternative treatment: 13.9 ± 2.3, $p < 0.001$); remarkably, the treatment with L-Arginine + Vitamin C had favorable effects on all the symptoms explored by the survey (Table 2).

When examining the effort perception (modified Borg scale), we observed a significantly lower value ($p < 0.0001$; Fig. 2) in patients receiving L-Arginine + Vitamin C, compared to the alternative-treatment arm, indicating that L-Arginine + Vitamin C led to a better effort perception.

Table 1
Main characteristics of the two populations.

	Alternative Treatment	L-Arginine + Vitamin C	p
N	521	869	-
Age (y)	55.5±15.6	55.4±15.8	0.854
Male sex (%)	51.8	49.8	0.471
Hospitalization for COVID-19 (%)	9.2	7.9	0.408

4. Discussion

This survey is the first to show the beneficial effects of the combination of L-Arginine and Vitamin C in Long-COVID. Our investigation was based on a robust rationale, *i.e.* targeting endothelial dysfunction in Long-COVID. Indeed, endothelial cell infection with consecutive inflammatory cell recruitment and endothelial dysfunction could explain the impaired microcirculation observed across vascular beds in COVID-19, triggering vasoconstriction, ischemia, and a pro-coagulant state [92–95]. Consistent with our view, several investigators had proposed that endotheliitis could be a critical mechanism underlying systemic impaired microcirculatory function observed in different vascular beds in patients experiencing Long-COVID symptoms [92,96].

Of note, a recent clinical study has demonstrated that COVID-19 patients develop endothelial dysfunction, which remains significantly impaired compared to healthy controls subjects at a 6-month follow-up [97], implicating that endothelial dysfunction is a main player in both acute COVID-19 and Long-COVID. Interestingly, increased numbers of circulating endothelial cells, a biomarker of vascular injury [98], most likely detached from the vessel wall due to pathological insults, were found to significantly correlate with the severity of COVID-19 outcome [99]. Strikingly, elevated levels of circulating endothelial cells persisted in recovered COVID-19 convalescent patients [100], denoting long-term detrimental effects of SARS-CoV-2 infection on endothelial function. Actual signs of endothelial dysfunction (denoted by glycocalyx damage) have been reported in convalescent COVID-19 patients after mild disease progression without hospitalization [101]. Other studies evidenced that sustained endotheliopathy is common in convalescent COVID-19 subjects [102], and that Long-COVID symptoms, specifically non-respiratory symptoms, are mainly due to persistent endothelial dysfunction [103].

Our data are fully in agreement with previous reports implying that after the acute phase of COVID-19, the disease is dominated by immunopathological pro-inflammatory elements [104–110]. In fact, previous investigations have actually demonstrated that reduced levels of L-Arginine increase the generation of reactive oxygen species (ROS), aggravating inflammation [111]. Besides, in vitro assays revealed that the T cell proliferative capacity is significantly reduced among COVID-19 patients and can be restored through L-Arginine supplementation [112]. COVID-19 patients with severe symptoms present an increased level of myeloid-derived suppressor cells, directly correlated to an enhanced activity of arginase – the enzyme responsible for metabolizing L-Arginine to ornithine and urea [112,113]. Another recent investigation has demonstrated an inverse correlation between L-Arginine level and platelet activation [114], a major contributor to thromboembolic complications of COVID-19. While eNOS produces

Table 2
Survey results in the two groups of patients.

		Alternative Treatment (N=521)	L-Arginine + Vitamin C (N=869)	p
Asthenia	Absent (%)	0.4	94.9	<0.0001
	Mild (%)	5.2	4.0	
	Severe (%)	94.4	1.1	
Dyspnea	Absent (%)	5.4	74.2	<0.0001
	Mild (%)	55.1	25.4	
	Severe (%)	39.5	0.4	
Chest tightness	Absent (%)	26.3	86.1	<0.0001
	Mild (%)	50.9	13.4	
	Severe (%)	22.8	0.5	
Dizziness	Absent (%)	66.6	87.3	<0.0001
	Mild (%)	25.9	11.6	
	Severe (%)	7.5	1.1	
Gastrointestinal disorders	Absent (%)	63.3	87.7	<0.0001
	Mild (%)	26.7	11.7	
	Severe (%)	10.0	0.6	
Headache	Absent (%)	39.2	81.8	<0.0001
	Mild (%)	44.1	16.8	
	Severe (%)	16.7	1.4	
Anosmia	Absent (%)	52.0	87.2	<0.0001
	Mild (%)	34.0	11.0	
	Severe (%)	14.0	1.8	
Concentration difficulty	Absent (%)	32.8	79.1	<0.0001
	Mild (%)	46.8	19.4	
	Severe (%)	20.4	1.5	
Sleeplessness	Absent (%)	39.5	80.7	<0.0001
	Mild (%)	42.6	17.5	
	Severe (%)	17.9	1.8	

physiological levels of NO, the inducible NO synthase (iNOS) is mainly expressed under inflammatory stimuli in parenchymal cells and leucocytes, producing much larger amounts of NO, and its exact role in COVID-19 remains to be fully clarified [115,116].

As a critical driver of inflammation and oxidative stress [117], endothelial dysfunction has also been involved in the pathophysiology of the neurological symptoms of COVID-19 and Long-COVID [118–120]. Fatigue is a prevailing symptom in Long-COVID patients [121], and previous trials have evidenced a significant decrease in fatigue in subjects treated with Vitamin C [122,123], fully consistent with our present results. Supporting our strategy to combine L-Arginine to Vitamin C, previous investigations have shown that ascorbic acid can synergistically improve the effects of other agents: for example, if added to glucagon-like peptide 1 (GLP-1) agonists, it reduces ROS generation in diabetic patients [124], in combination with metformin, it reduces macro- and microvascular diabetic complications [125].

Strengths of this survey include the large population enrolled and the fact that the questionnaire was administered in multiple centers throughouth Italy. Nevertheless, we do reckon that our research is not exempt from limitations. For instance, we did not assess blood levels of nitrates and nitrite, Vitamin C, or citrulline in our patients; moreover, we did not administer the survey at baseline but only after 30 days. Hence, one may argue that the patients who received L-Arginine + Vitamin C could have been somehow healthier than the other group before starting the treatment. However, albeit we do not have full clinical data for all patients, this hypothesis seems unlikely since patients were enrolled by their family physicians who had prescribed different treatments to patients with similar clinical characteristics only on account of little guidance on managing Long-COVID. Further dedicated interventional studies are warranted to endorse our findings.

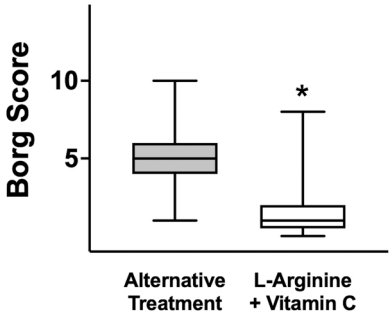

Fig. 2. Borg score assessed after 1 month in the groups of patients receiving L-Arginine + Vitamin C or alternative treatment. Box plots indicate upper/lower quartiles, the line in the middle of each box is the mean, and the whiskers represent the min–max of values; *:P < 0.0001.

CRediT authorship contribution statement

Raffaele Izzo: Writing - original draft, Writing - review & editing. **Valentina Trimarco:** Conceptualization, Data curation, Formal analysis, Software. **Pasquale Mone:** Visualization, Writing – review & editing. **Teresita Aloè:** Investigation, Visualization. **Massimo Capra Marzani:** Investigation, Visualization. **Antonio Diana:** Investigation, Visualization. **Giovanni Fazio:** Investigation, Visualization. **Mario Mallardo:** Investigation, Visualization. **Mauro Maniscalco:** Investigation, Visualization. **Giuseppe Marazzi:** Investigation, Visualization. **Nunzia Messina:** Investigation, Visualization. **Simone Mininni:** Investigation, Visualization. **Chiara Mussi:** Investigation, Visualization. **Girolamo Pelaia:** Investigation, Visualization. **Alfio Pennisi:** Investigation, Visualization. **Pierachille Santus:** Investigation, Visualization. **Francesco Scarpelli:** Investigation, Visualization. **Francesco Tursi:** Investigation, Visualization. **Alessandro Zanforlin:** Investigation, Visualization. **Gaetano Santulli:** Writing - original draft, Writing - review & editing. **Bruno Trimarco:** Writing - original draft.

Declaration of Competing Interest

None.

Data availability

Data will be made available on request.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.phrs.2022.106360.

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