MATTEO TOSATO

BIO-ARGININA E PERFORMANCE MUSCOLARE

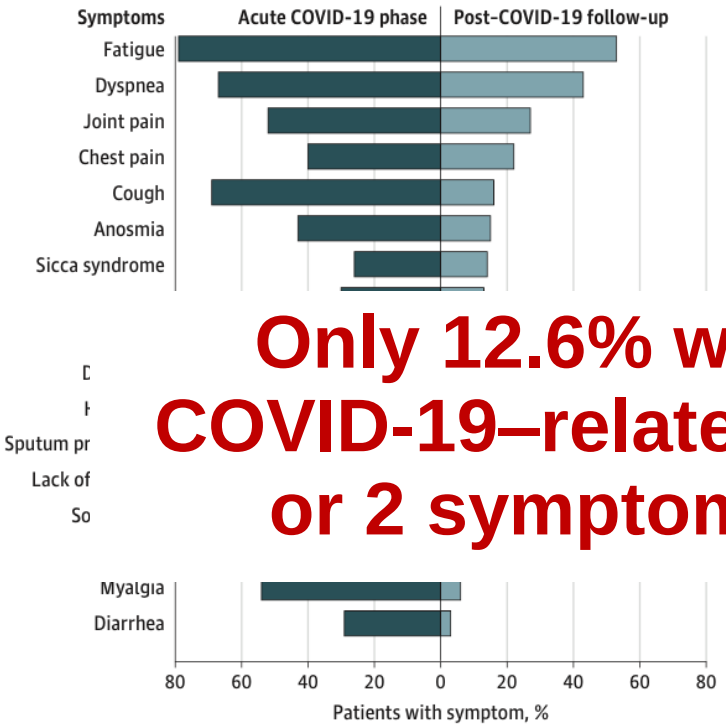
SOCIETÀ ITALIANA
DI GERONTOLOGIA
E GERIATRIA

Roma, 30 novembre - 3 dicembre 2022
UNIVERSITÀ CATTOLICA DEL SACRO CUORE

Persistenza dei sintomi

JAMA

Figure. COVID-19–Related Symptoms



The figure shows percentages of patients presenting with specific coronavirus disease 2019 (COVID-19)–related symptoms during the acute phase of the disease (left) and at the time of the follow-up visit (right).

(n = 143)	
Age, mean (SD), y	56.5 (14.6)
Female sex, No. (%)	53 (37.1)
Pneumonia	104 (72.7)
Oxygen therapy	77 (53.8)
Noninvasive Ventilation	21 (14.7)
Mechanical Ventilation	7 (4.9)

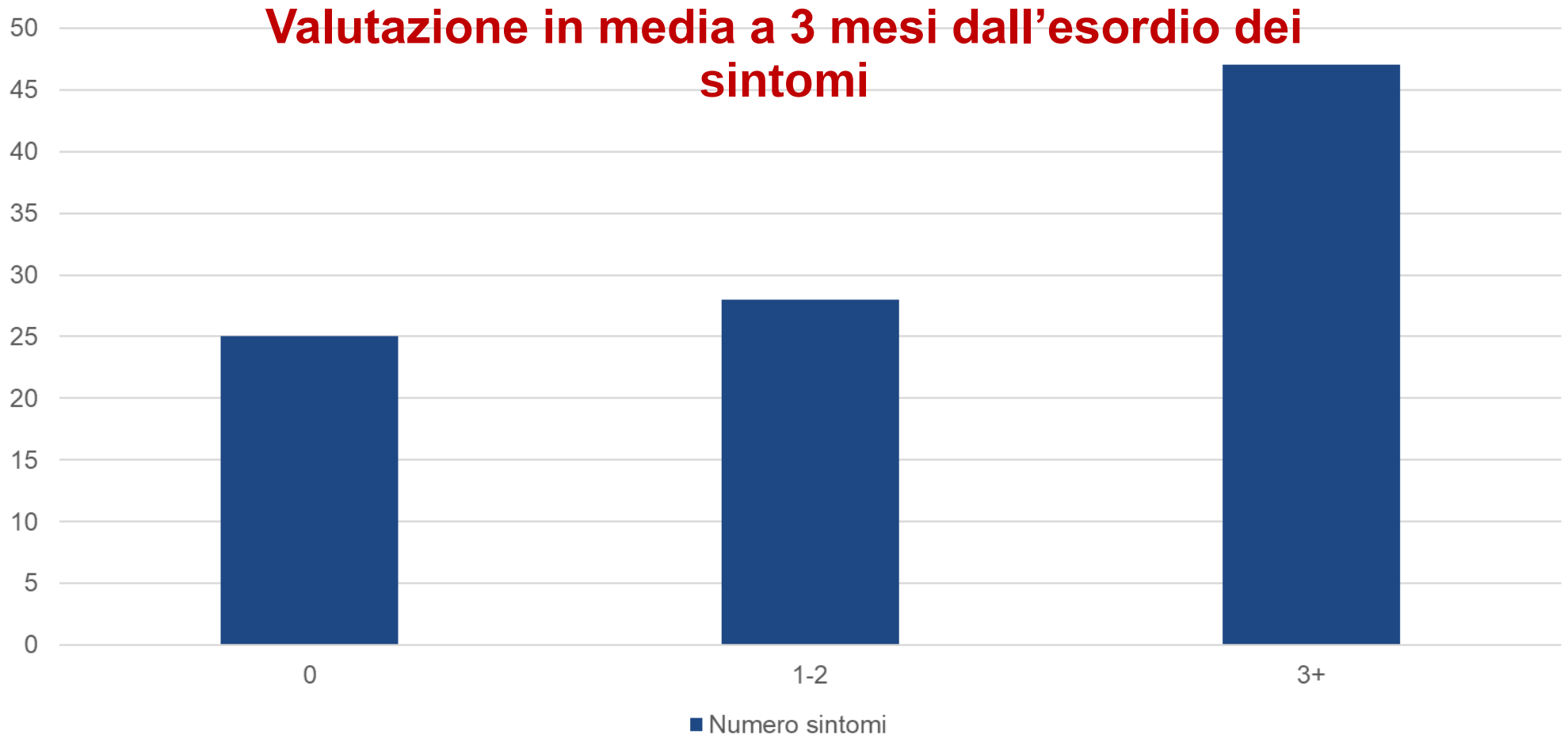
Only 12.6% were completely free of any COVID-19–related symptom, while 32% had 1 or 2 symptoms and 55% had 3 or more

Carfì A, et al JAMA 2020

Pazienti afferenti ambulatorio

Patients	3213
Age, mean (SD), y	50 (±17)
Female sex, No. (%)	1590 (49,5%)
BMI (DS)	25.8 (±4.4)
Flu vaccination	739 (23%)
Cardiovascular disease	257 (8%)
Hypertension	299 (28%)
Diabetes	255 (8%)
COPD	256 (8%)
Number of drugs	2 (±2)
Hospitalized	1767 (55%)
ICU	385 (12%)

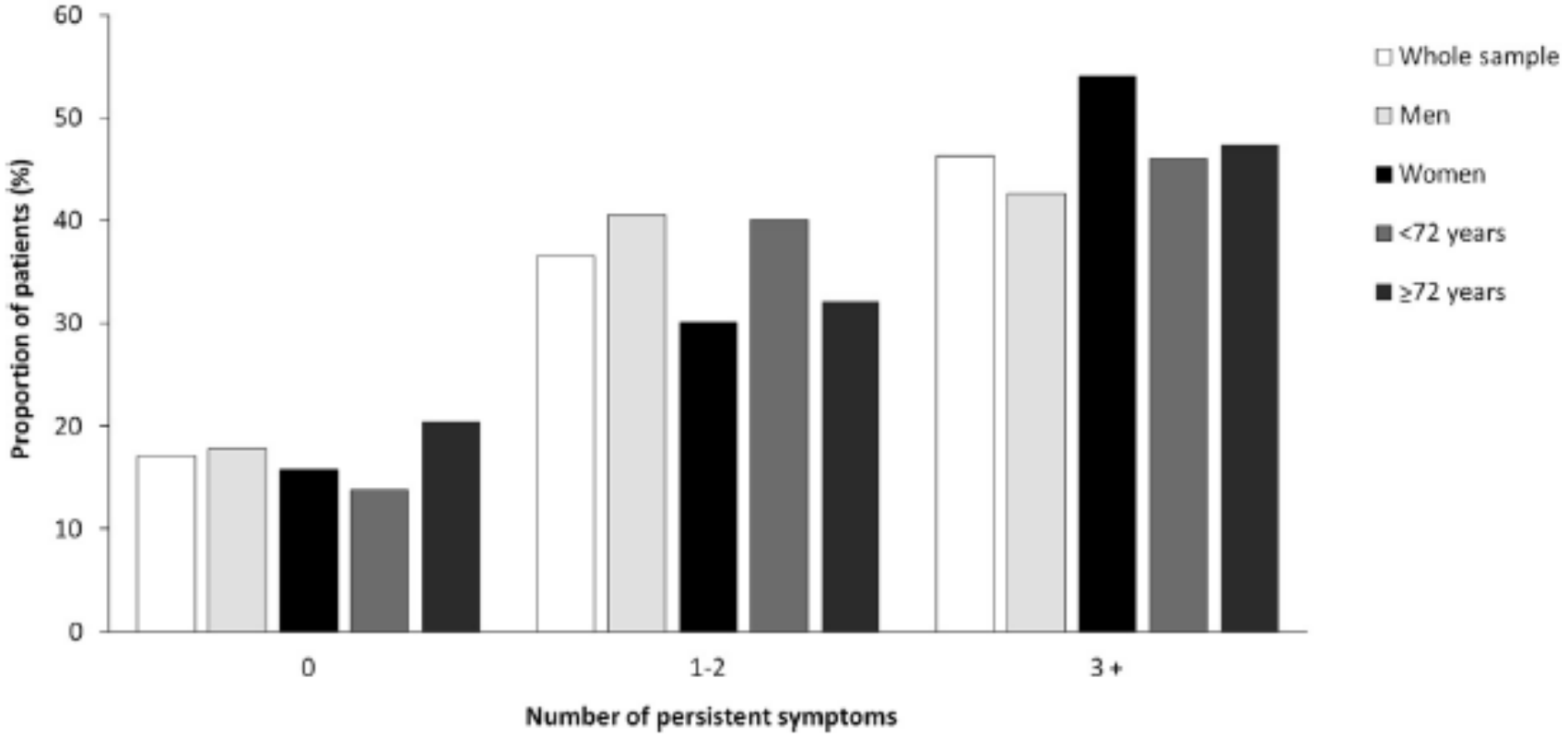
Persistenza dei sintomi



Persistenza dei sintomi

Original Study

Prevalence and Predictors of Persistence of COVID-19 Symptoms in Older Adults: A Single-Center Study



Tosato et al., J Am Med Dir Assoc. 2021

Persistenza dei sintomi

Original Study

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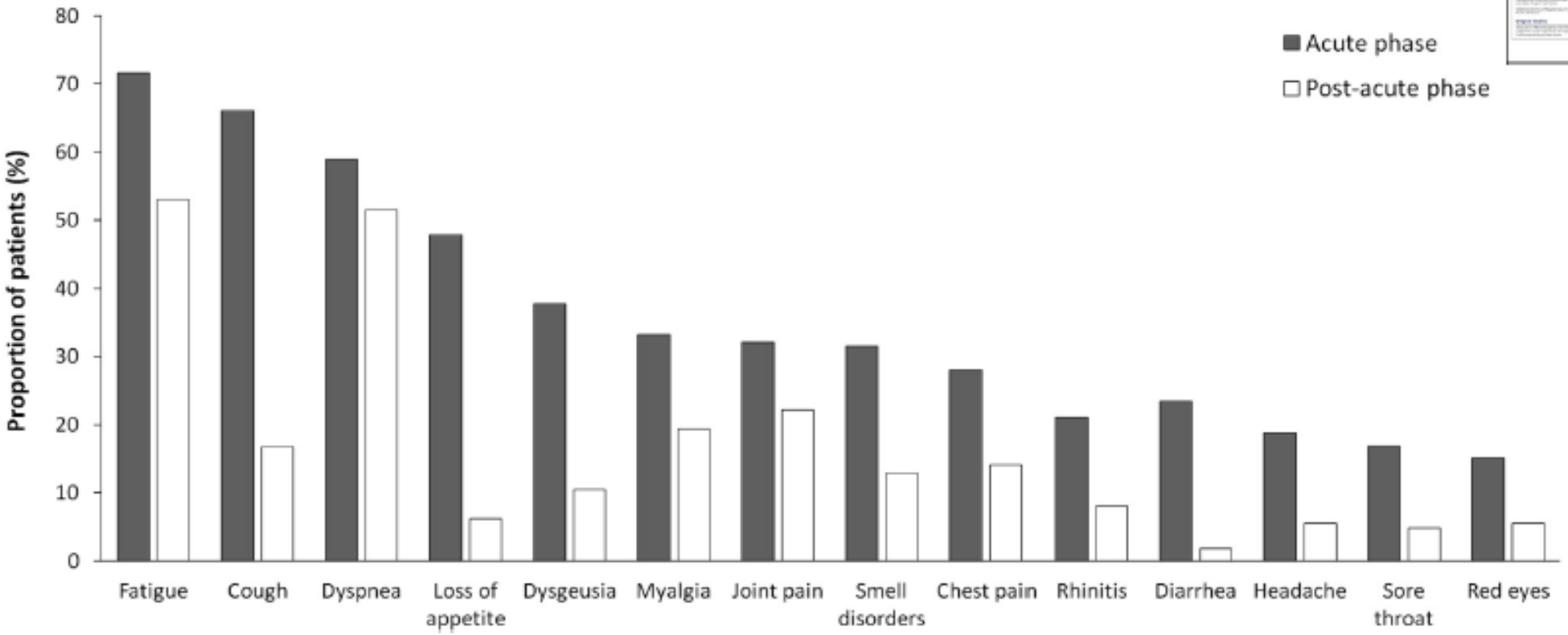
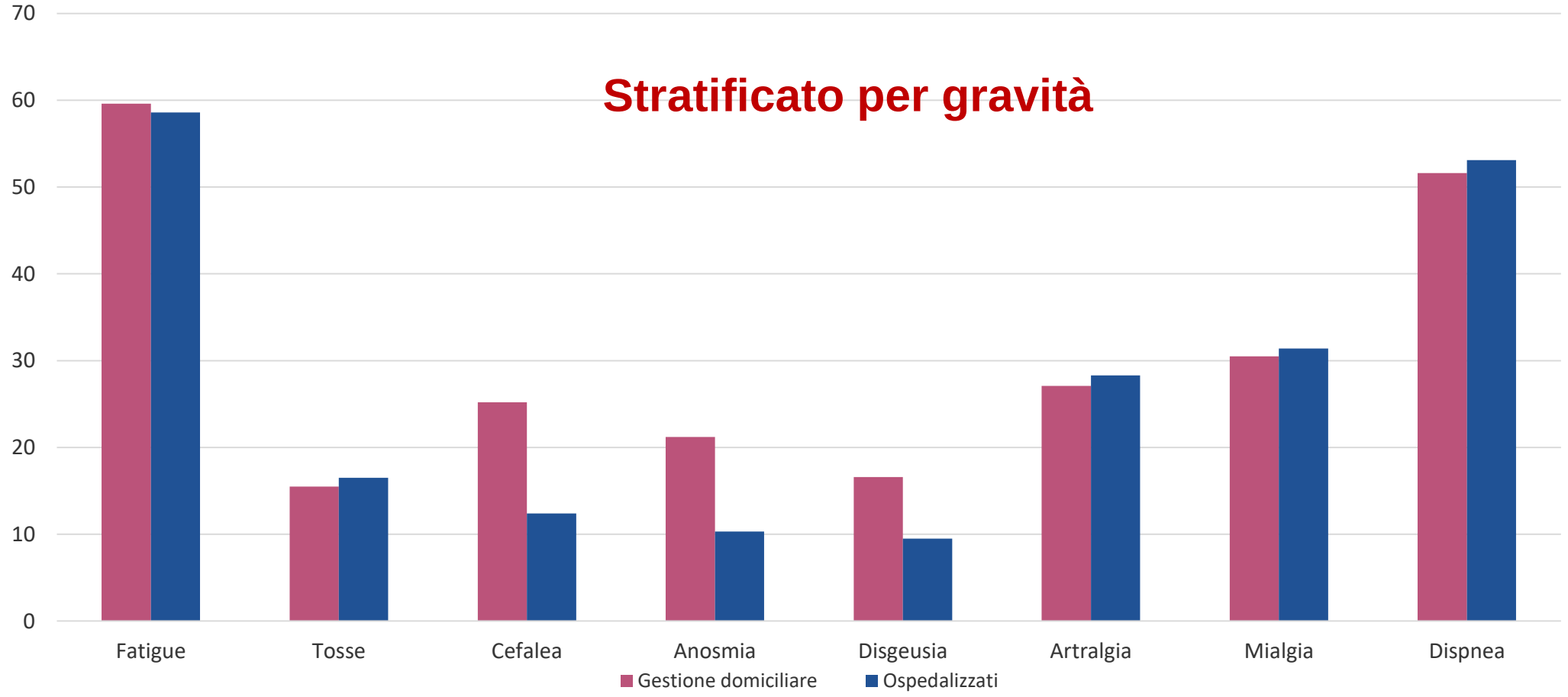


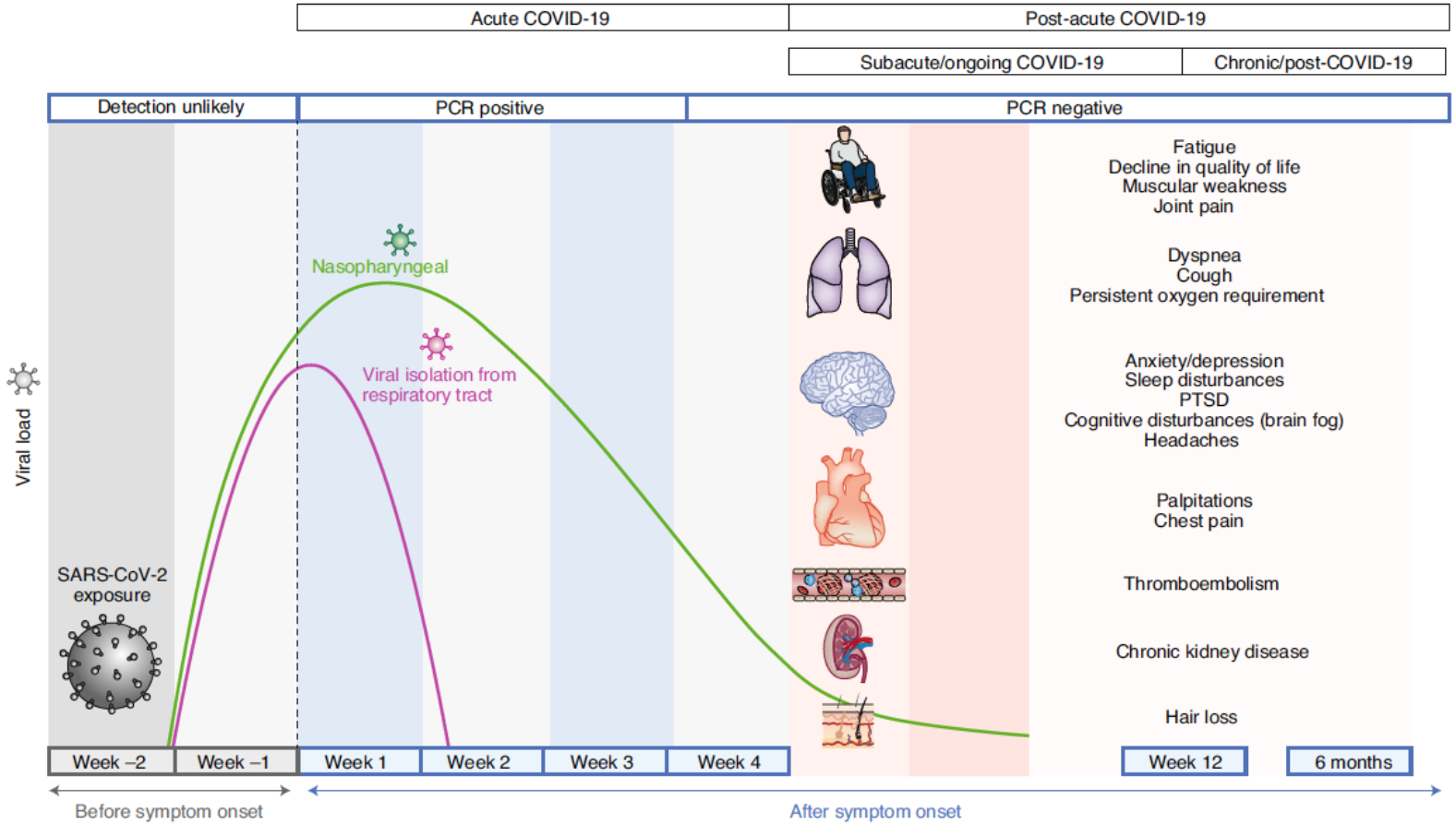
Tosato et al., J Am Med Dir Assoc. 2021

Persistenza dei sintomi



Post-acute COVID-19 syndrome

nature medicine

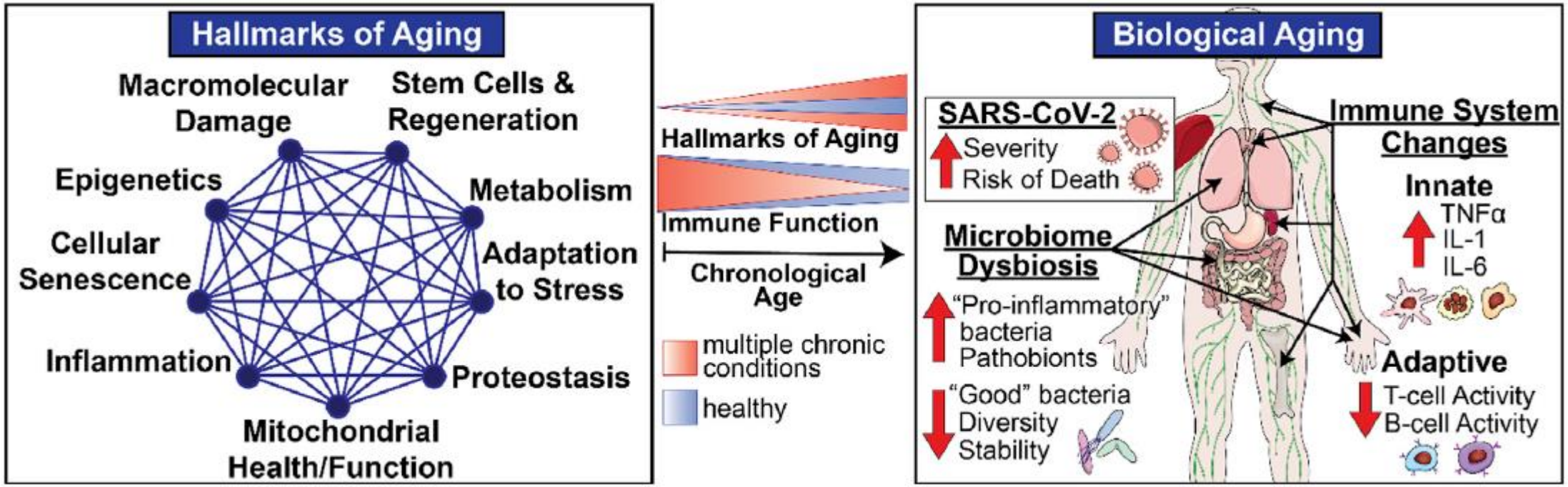


- Danno d'organo diretto o mediato
- Stato infiammatorio
- Alterazioni immunologiche
- Alterazioni del microcircolo
- Disfunzione endoteliale
- Trombosi

Covid-19 ed invecchiamento

Network Topology of Biological Aging and Geroscience-Guided Approaches to COVID-19

frontiers in Aging
SYSTEMATIC REVIEW
published: 23 July 2021
doi: 10.3389/fragi.2021.695218



Covid-19 ed invecchiamento

nature COMMUNICATIONS

https://doi.org/10.1038/s41467-022-29801-8 OPEN

Accelerated biological aging in COVID-19 patients

Xue Cao[1,2,3], Wenjuan Li[4], Ting Wang[5], Dongzhi Ran[6,7], Veronica Davalos[8], Laura Planas-Serra[9,10], Aurora Pujol[9,10,11], Manel Esteller[8,11,12,13], Xiaolin Wang[2] & Huichuan Yu[2,3]✉

Sarcopenia probabile/dinapenia

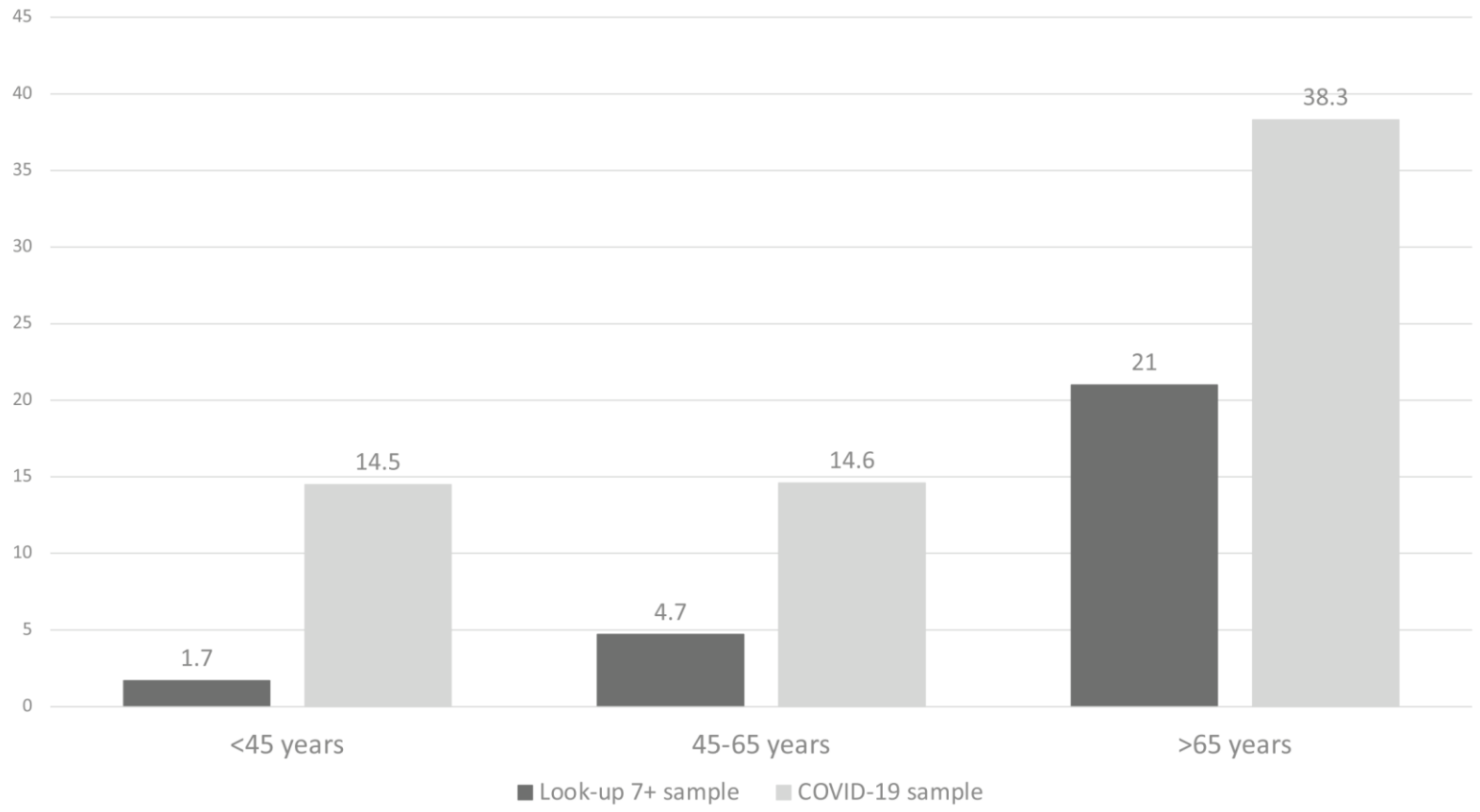


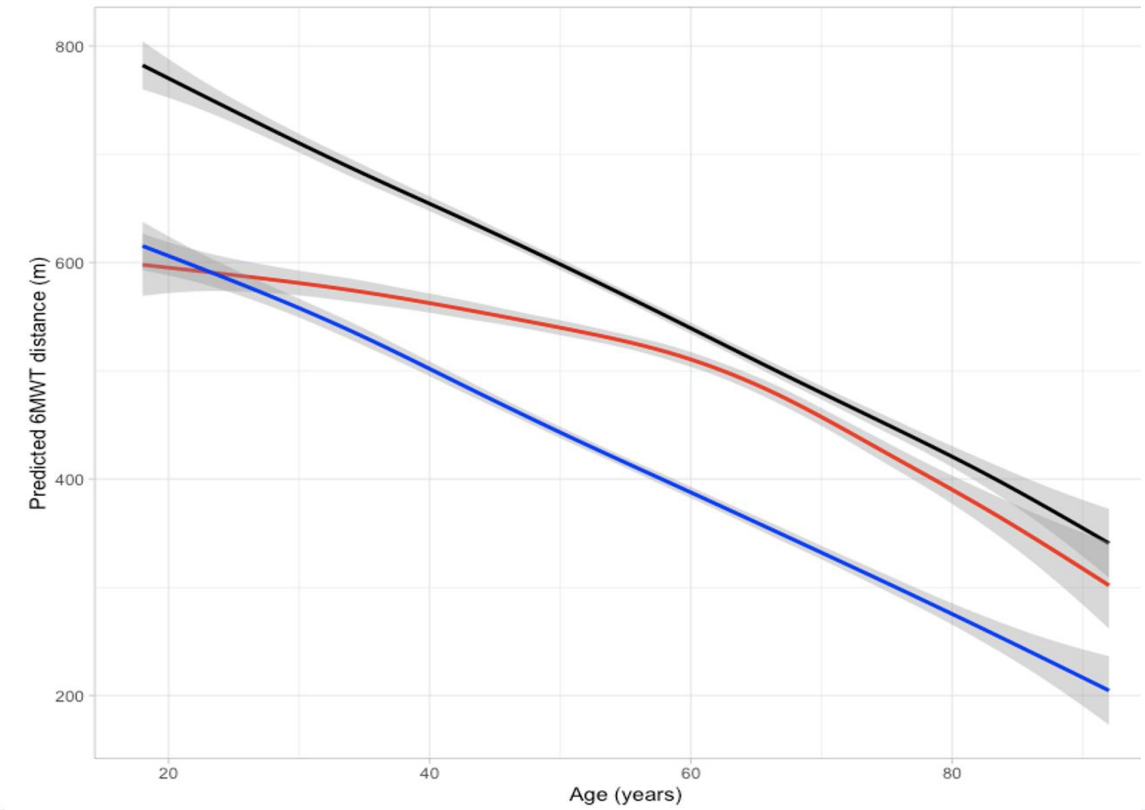
Figure 1 Prevalence of sarcopenia according to age group and study sample (COVID-19 sample vs. Lookup 7+ community sample).

Martone et al., J Cachexia Sarcopenia Muscle. 2022

Riduzione della performance

Distanza percorsa al 6MWT

Enright-Sherrill, 1998



Nero = predicted
Rosso = distanza percorsa
Blu = lower limit of normal range

Covid-19 e disfunzione endoteliale

Preprint | File available

Is COVID-19 an Endothelial Disease? Clinical and Basic Evidence

March 2020
DOI: 10.20944/preprints202004.0204.v1

Celestino Sardu · Jessica Gambardella · Marco Bruno Morelli · Show all 6 authors · Gaetano Santulli

JAMA

COVID-19 and Endothelial Dysfunction

Jessica Gambardella, PhD; Celestino Sardu, MD, PhD; Gaetano Santulli, MD, PhD

nature

Targeting Endothelial Dysfunction in COVID-19

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thebmj covid-19 Research Education News & Views Campaigns

Is Endothelial Dysfunction the Concealed Cornerstone of COVID-19?

Gaetano Santulli
Cardiologist
Marco Bruno Morelli, Jessica Gambardella

Covid-19 e disfunzione endoteliale

Article

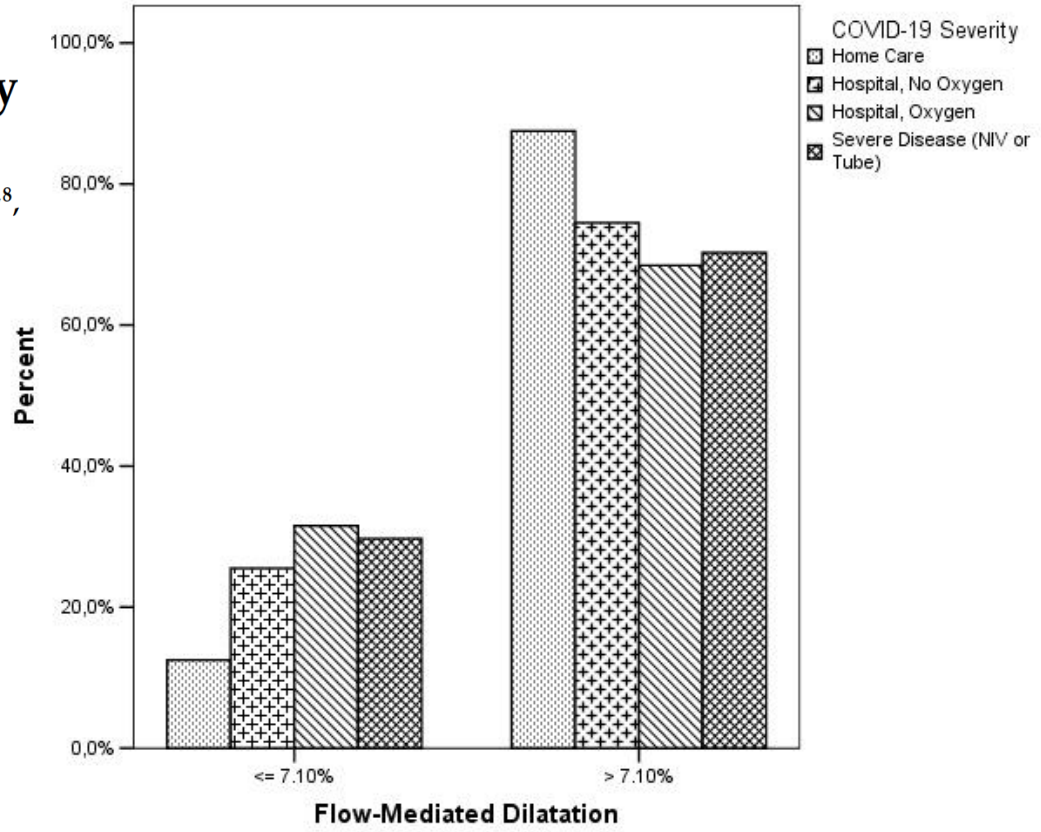
Impaired Endothelial Function in Convalescent Phase of COVID-19: A 3 Month Follow Up Observational Prospective Study

Luca Santoro [1,†], Lorenzo Falsetti [2,†], Vincenzo Zaccone [2,*], Antonio Nesci [1], Matteo Tosato [3], Bianca Giupponi [4], Maria Cristina Savastano [5], Gianluca Moroncini [6], Antonio Gasbarrini [7,8], Francesco Landi [3,8], Angelo Santoliquido [1,8] and on behalf of Gemelli against COVID-19 Post-Acute Care Study Group [‡]

Table 5. Multinomial regression analysis (reference category: not hospitalized).

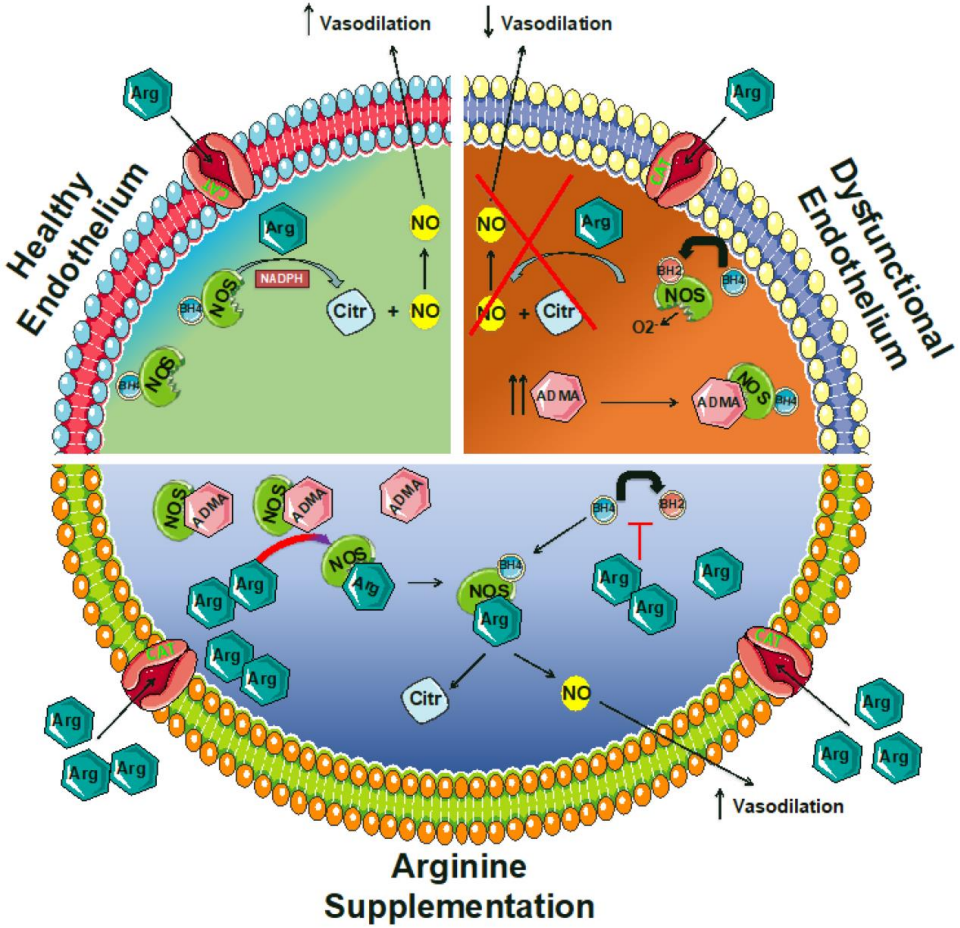
Severity		*p*	OR	95% CI	
				Lower	Upper
Hospital, no oxygen	FMD ≤ 7.10%	0.005	2.39	1.29	4.42
Hospital, oxygen	FMD ≤ 7.10%	0.0001	3.22	1.88	5.51
Hospital, NIV, or ICU	FMD ≤ 7.10%	0.0009	2.96	1.55	5.65

Legend: CI = confidence interval; FMD = flow-mediated dilation; NIV = non-invasive ventilation; OR= odds ratio.



Journal of Clinical Medicine

Arginina e Ossido nitrico

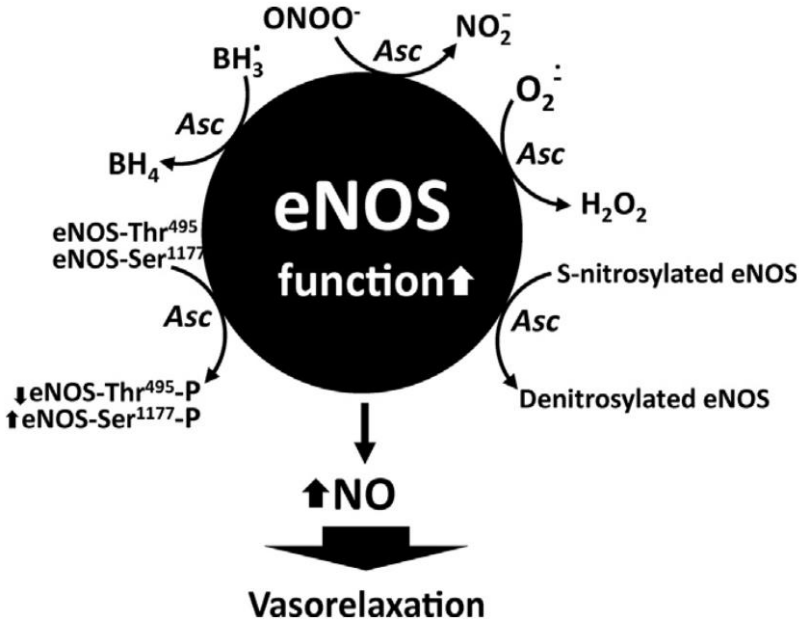


Vit C e Ossido nitrico

Review

Does vitamin C enhance nitric oxide bioavailability in a tetrahydrobiopterin-dependent manner? *In vitro*, *in vivo* and clinical studies

Alan Mortensen, Jens Lykkesfeldt *

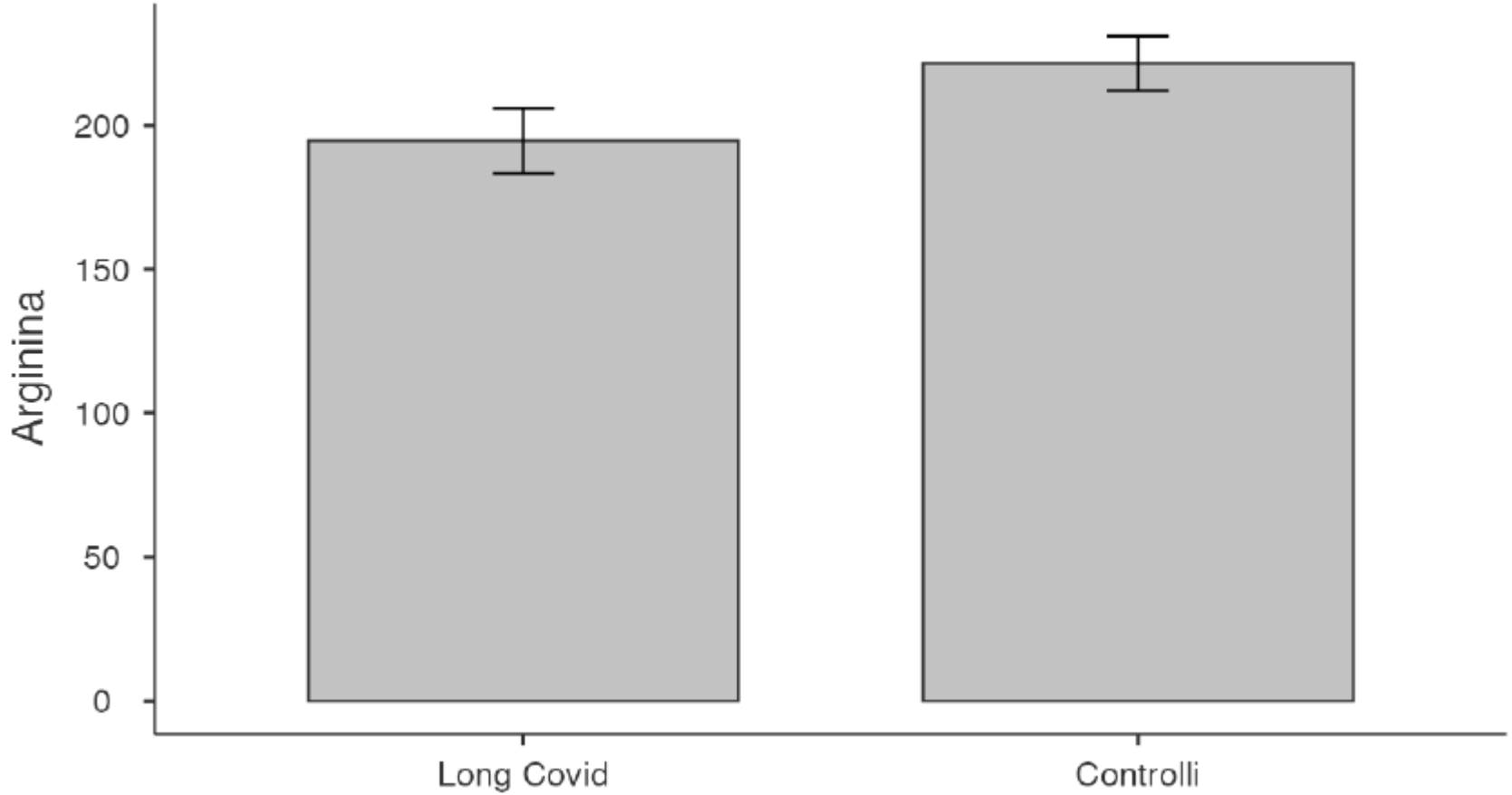


A B S T R A C T

Ascorbate (Asc) has been shown to increase nitric oxide (NO) bioavailability and thereby improve endothelial function in patients showing signs of endothelial dysfunction. Tetrahydrobiopterin (BH_4) is a cofactor of endothelial nitric oxide synthase (eNOS) which may easily become oxidized to the inactive form dihydrobiopterin (BH_2). Asc may increase NO bioavailability by a number of mechanisms involving BH_4 and eNOS. Asc increases BH_4 bioavailability by either reducing oxidized BH_4 or preventing BH_4 from becoming oxidized in the first place. Asc could also increase NO bioavailability in a BH_4-independent manner by increasing eNOS activity by changing its phosphorylation and S-nitrosylation status or by upregulating eNOS expression. In this review, we discuss the putative mechanisms by which Asc may increase NO bioavailability through its interactions with BH_4 and eNOS.

Nitric Oxide 36 (2014) 51–57

Livelli circolanti di Arginina nel Long COVID



Protocollo di studio

Treatment Group:

1 bottle twice per day orally containing:
L-arginine 1,66 g
Vitamin C 500 mg

Placebo Group:

1 bottle twice per day orally containing:
placebo (solution with same colour and flavour)

Outcomes:

Fatigue persistence, changes in handgrip strength

distance covered at 6MWT and FMD

Visit 1 (T_0)	Visit 2 (T_1) – 28 days
Blood collection for metabolic markers and immune cells characterization (phenotype and activity)	Blood collection for metabolic markers and immune cells characterization (phenotype and activity)
Assessment of physical performance and fatigue 1. 6MWT 2. Borg rating perceived exertion scale	Assessment of physical performance and fatigue 1. 6MWT 2. Borg rating perceived exertion scale
Handgrip Exhaustion time	Handgrip Exhaustion time
Flow-mediated dilation test	Flow-mediated dilation test

nutrients

MDPI

Article

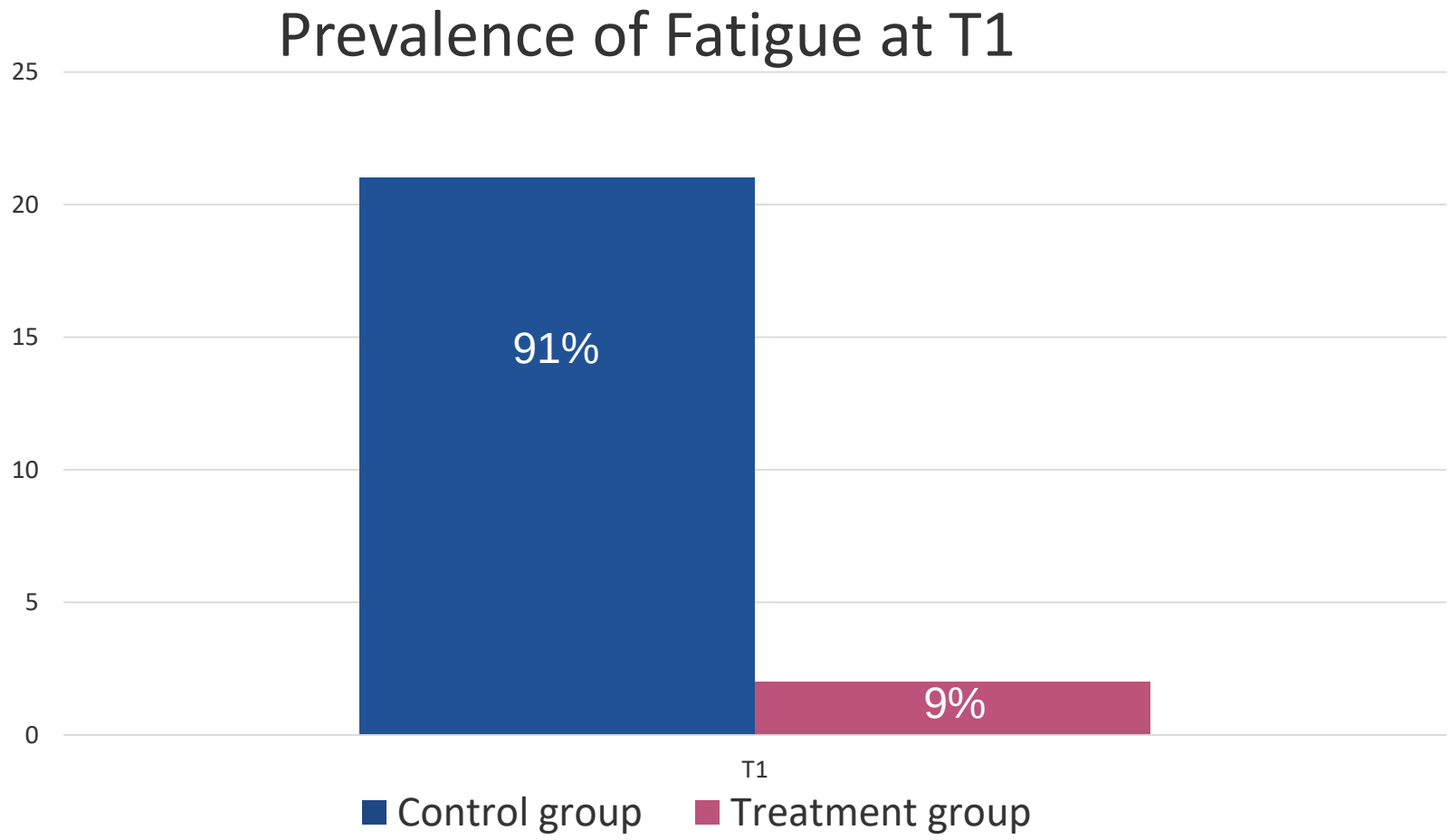
Effects of L-Arginine Plus Vitamin C Supplementation on Physical Performance, Endothelial Function, and Persistent Fatigue in Adults with Long COVID: A Single-Blind Randomized Controlled Trial

Matteo Tosato [1], Riccardo Calvani [1,*], Anna Picca [1,2], Francesca Ciciarello [1], Vincenzo Galluzzo [1], Hélio José Coelho-Júnior [1,3], Angela Di Giorgio [1], Clara Di Mario [4], Jacopo Gervasoni [1], Elisa Gremese [1,3,4], Paolo Maria Leone [1], Antonio Nesci [1], Anna Maria Paglionico [1], Angelo Santoliquido [1,5], Luca Santoro [1], Lavinia Santucci [6], Barbara Tolusso [4], Andrea Urbani [1,7], Federico Marini [8], Emanuele Marzetti [1,3] and Francesco Landi [1,3] on behalf of the Gemelli against COVID-19 Post-Acute Care Team

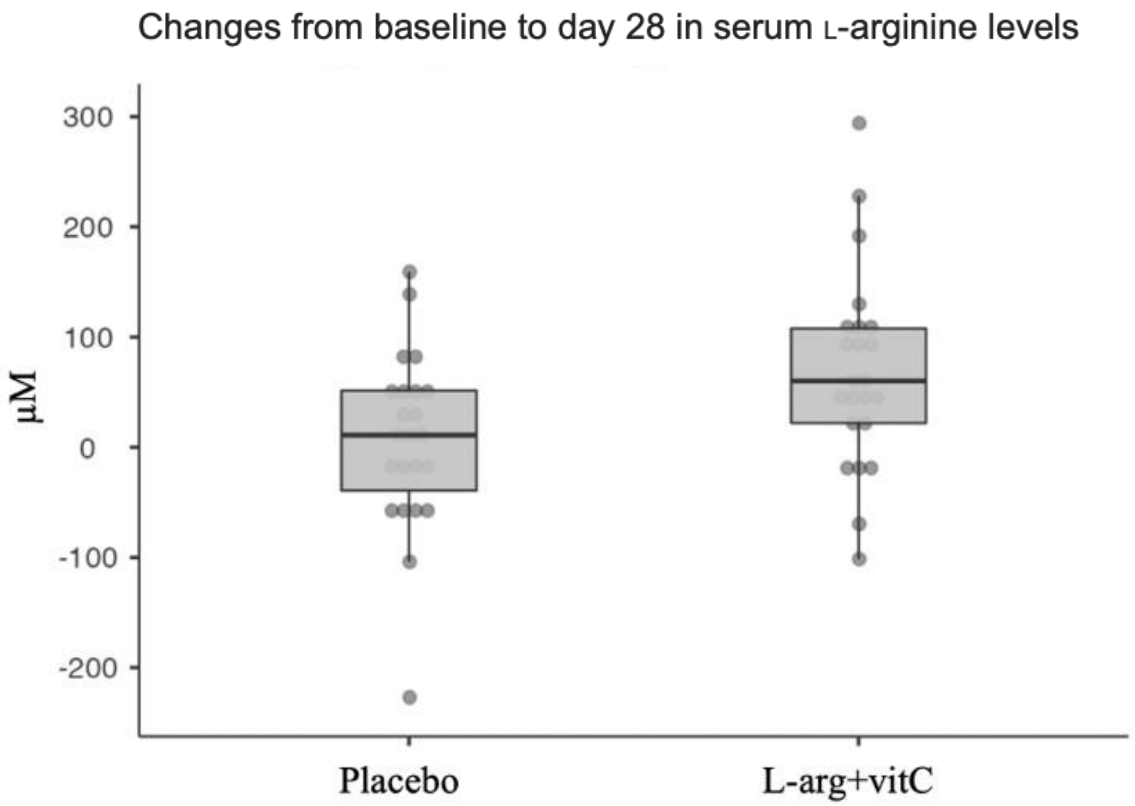
Caratteristiche del campione

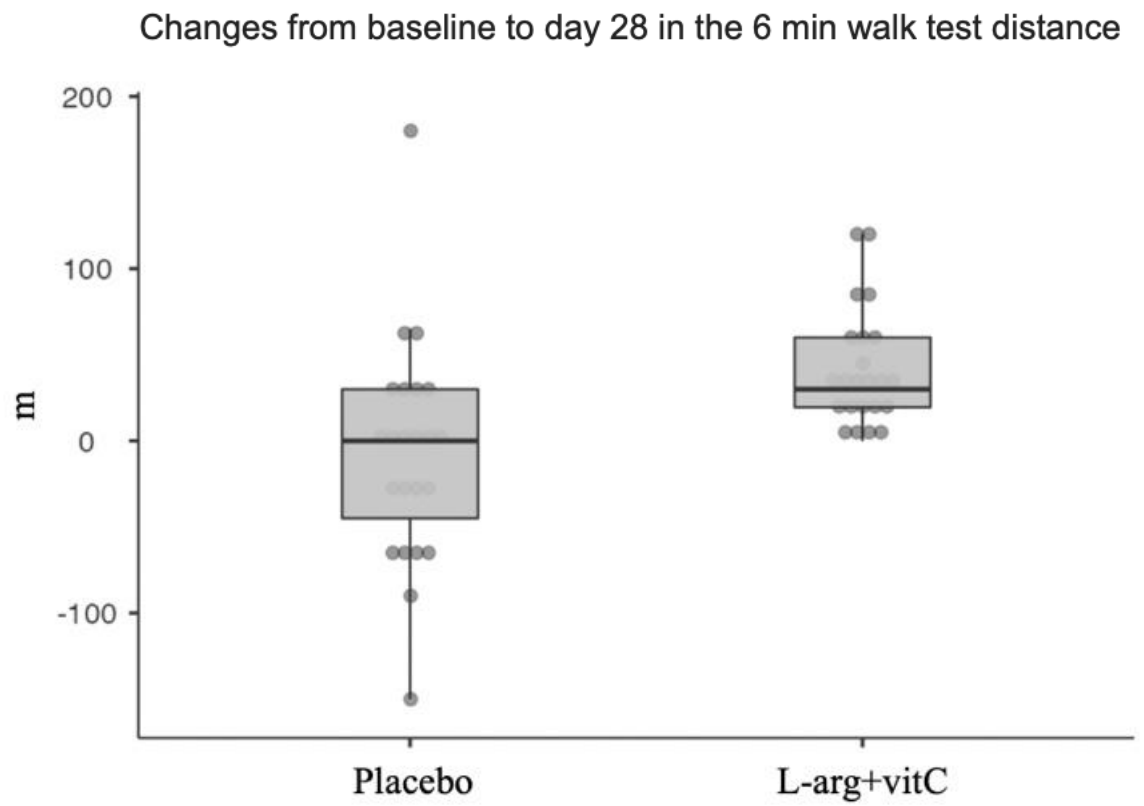
Characteristic	L-arginine+Vitamin C (n=23)	Placebo (n=23)	Total (n=46)
Age, y	50 (16.5)	51 (11)	51 (14)
Women, No. (%)	15 (65.2)	15 (65.2)	30 (65.2)
BMI	24.8 (5.9)	25.5 (6.5)	25.0 (6.5)
Severity of acute COVID-19,			
No hospitalization	8 (34.8)	12 (52.2)	20 (43.5)
Hospitalization	13 (50.0)	9 (39.2)	22 (47.8)
ICU admission	2 (8.7)	2 (8.7)	4 (8.7)
Time from symptoms onset, days	240 (119)	269 (127)	254 (137)
Arginine, µM	167.2 (76.8)	175.0 (93.1)	170.6 (88.0)
Six-minute walking test distance, m	520 (50)	540 (120)	520 (90)
Handgrip, kg	22.5 (16.0)	22.6 (12.3)	22.6 (14.4)
Flow-mediated dilation, %	10.5 (5.2)	8.9 (5.8)	9.8 (6.0)

Risultati

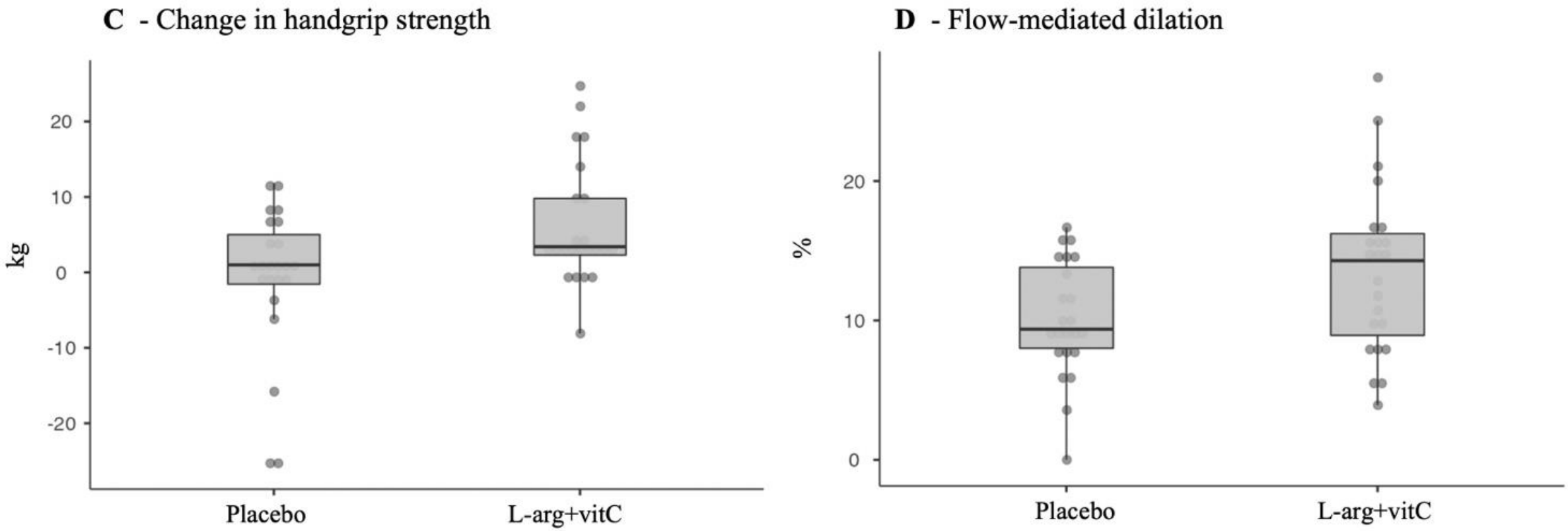

Prevalence of Fatigue at T1
25
20
15
10
5
0
91%
9%
T1
Control group
Treatment group

Risultati


Changes from baseline to day 28 in serum L-arginine levels
300
200
100
0
-100
-200
µM
Placebo
L-arg+vitC

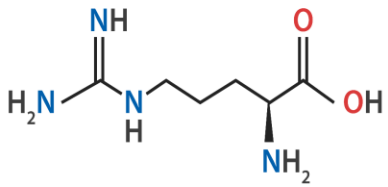

Changes from baseline to day 28 in the 6 min walk test distance
200
100
0
-100
m
Placebo
L-arg+vitC

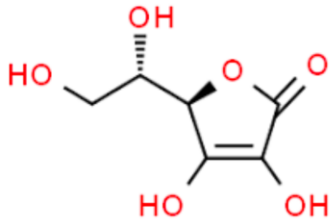
Risultati

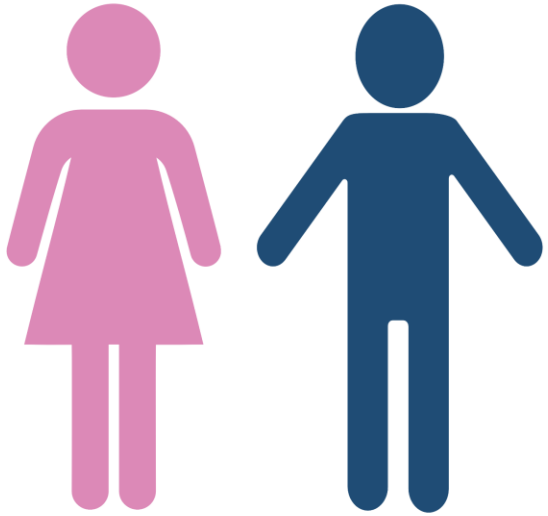

C - Change in handgrip strength
kg
20
10
0
-10
-20
Placebo
L-arg+vitC
D - Flow-mediated dilation
%
20
10
0
Placebo
L-arg+vitC

L-arginine (1.66 g) + vitamin C (500 mg) b.i.d.

28 day-intervention/Placebo-controlled





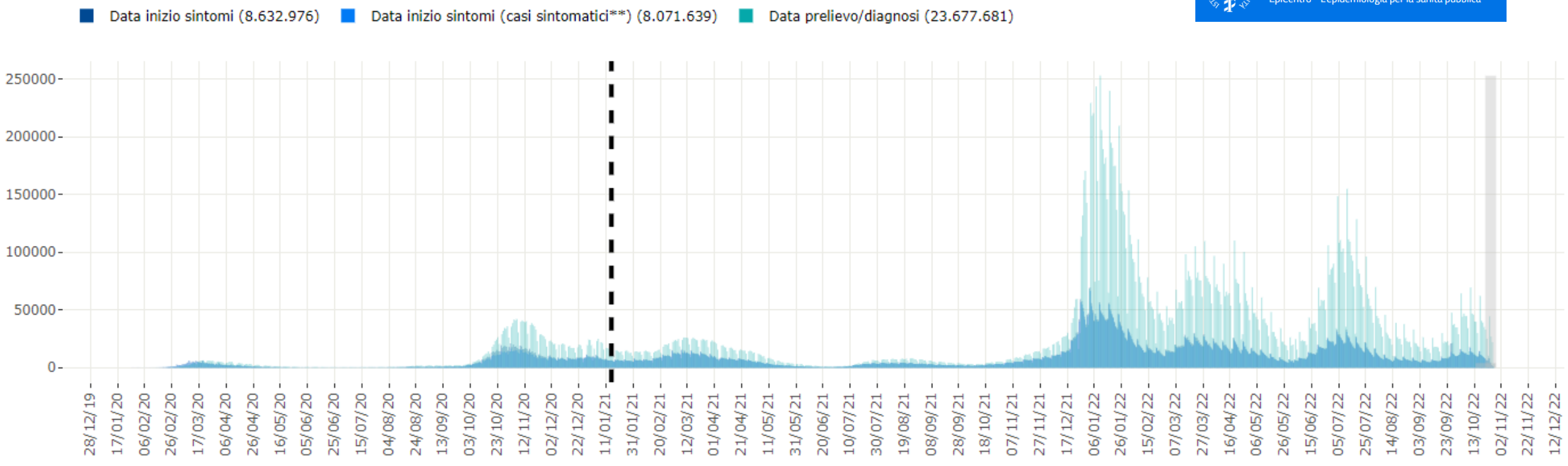


20-60 year-old
Long COVID (persistent fatigue)

- \+ Serum L-arginine
- \+ 6-minute walk distance
- \+ Handgrip strength
- \+ Flow-mediated dilation
- — Fatigue

23.677.681	434.417	43 anni	46,7% | 53,3%	175.960 (0,7%)	21.823.948
Casi***	Casi tra gli operatori sanitari*	Età mediana dei casi	Maschi (%) | Femmine (%)	Deceduti (CFR)	Guariti

Istituto Superiore di Sanità
EpiCentro - L'epidemiologia per la sanità pubblica



The data is clear: long Covid is devastating people's lives and livelihoods

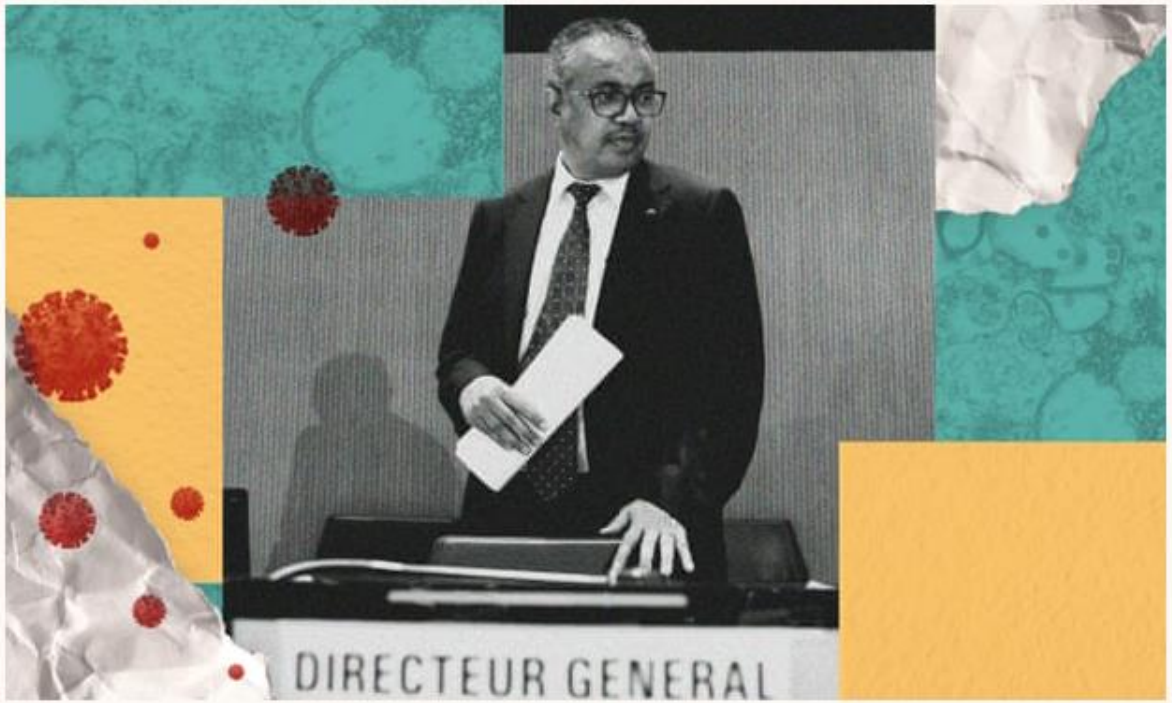
Tedros Adhanom Ghebreyesus

The impact of long Covid needs urgent action – and there are five key elements to drive the effort forward, writes the WHO director general

WHO chief urges immediate action to tackle 'devastating' long Covid

Wed 12 Oct 2022 09.00 BST

The Guardian

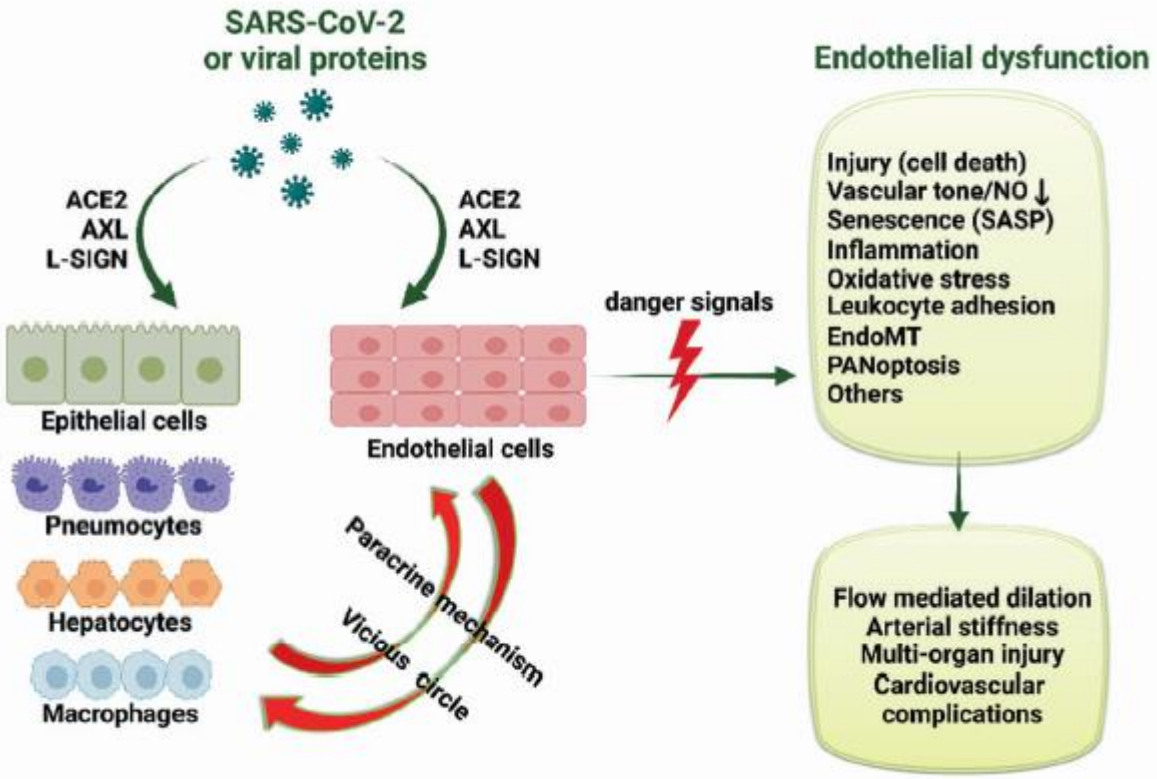


'Delayed clinical care in patients with long Covid not only impacts their quality of life but the length of time they have symptoms.' Composite: Guardian Design/Reuters

REVIEW ARTICLE

Endothelial dysfunction in COVID-19: an overview of evidence, biomarkers, mechanisms and potential therapies

Suo-wen Xu[1], Iqra Ilyas[1] and Jian-pi



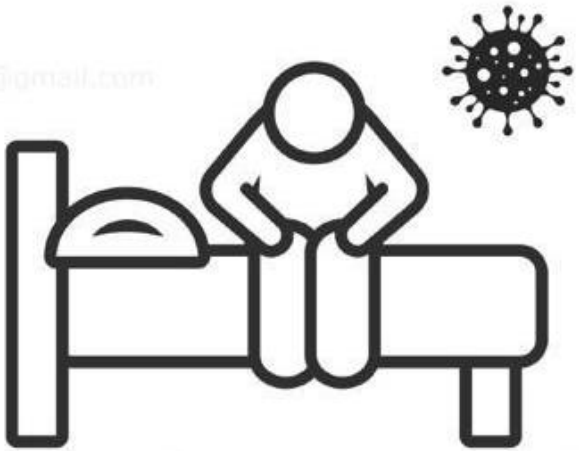
Acta Pharmacologica Sinica (2022) 0:1–15; https://doi.org/10.1038/s41401-022-00998-0

Take Home Messages

- Il Long COVID condivide alcuni meccanismi eziopatogenetici con l'invecchiamento e sembra rappresentare un prototipo di invecchiamento accelerato
- La supplementazione con L-arginina + Vit C migliora la performance fisica, la forza muscolare e riduce la persistenza di fatigue nei pazienti Long COVID
- Necessari nuovi studi su condizioni/sindromi geriatriche

THURSDAY, MARCH 18, 2021 · THE WASHINGTON POST A7

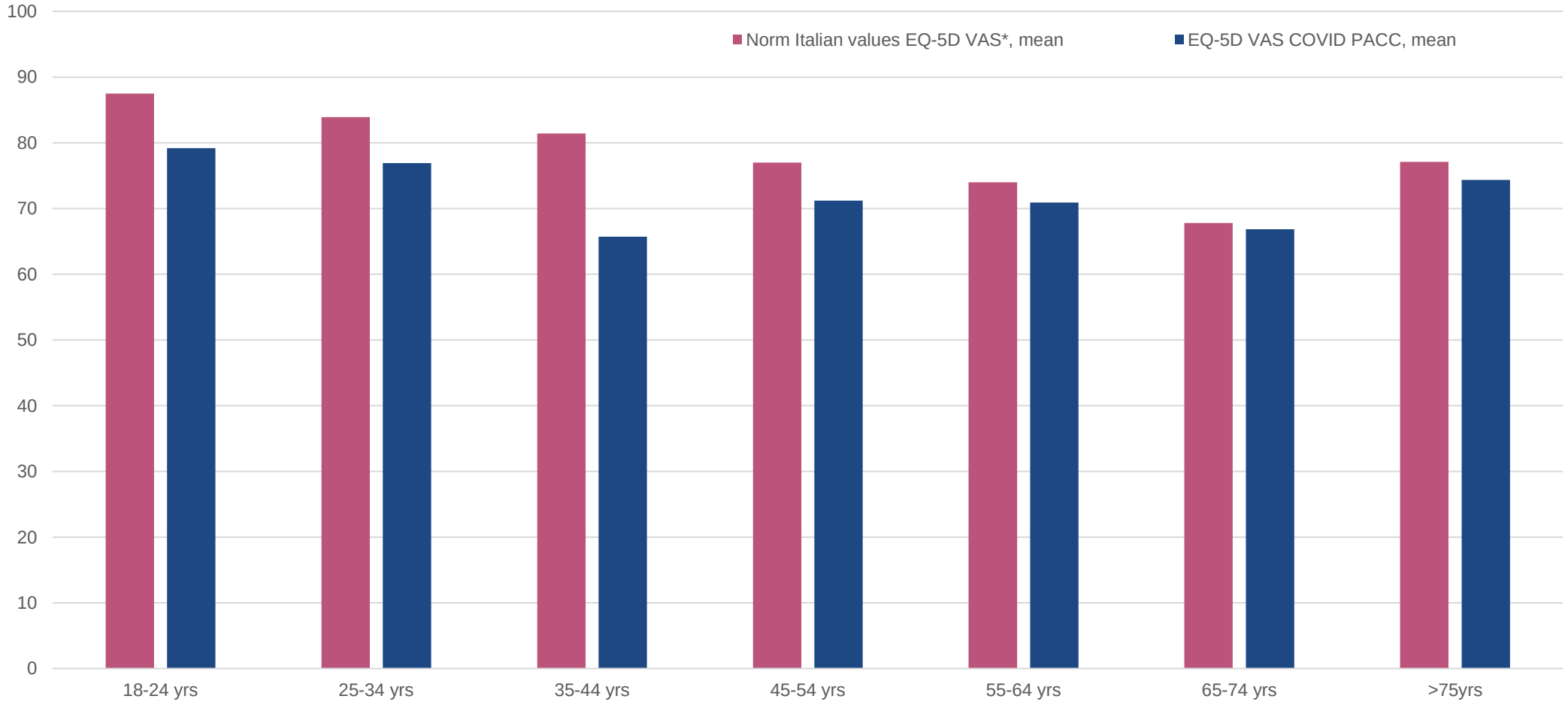
President Biden and Congress:
America needs a comprehensive national plan
to meet and defeat the Long COVID crisis.



Millions of Americans have survived COVID-19. Months later, many still struggle to get out of bed.

matteo.tosato@policlinicogemelli.it

Qualità della vita EQ5D VAS

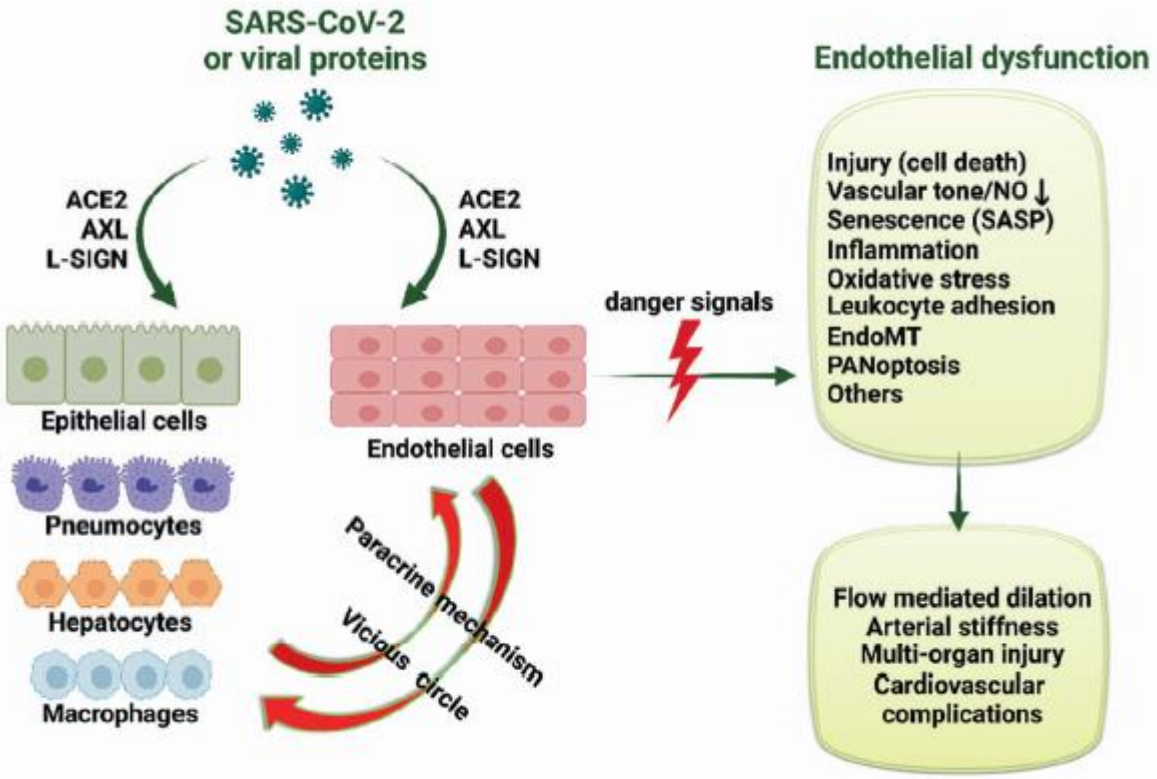


Murri R. et al in press

REVIEW ARTICLE

Endothelial dysfunction in COVID-19: an overview of evidence, biomarkers, mechanisms and potential therapies

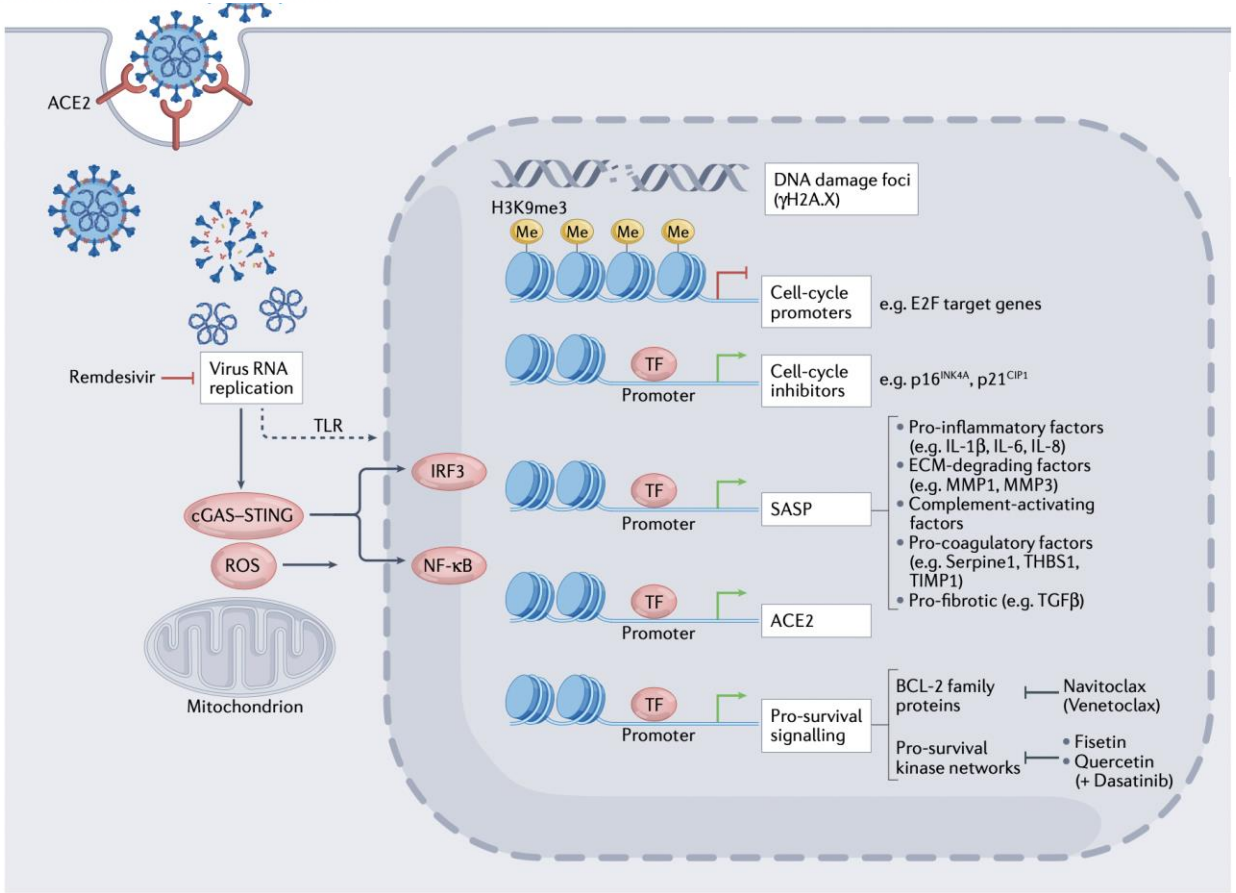
Suo-wen Xu[1], Iqra Ilyas[1] and Jian-pi



Acta Pharmacologica Sinica (2022) 0:1–15; https://doi.org/10.1038/s41401-022-00998-0

Covid-19 ed invecchiamento

COVID-19 and cellular senescence



https://doi.org/10.1038/s41577-022-00785-2
Published online: 05 October 2022
NATURE REVIEWS | IMMUNOLOGY

Background

POINT OF VIEW

Post-COVID-19 global health strategies: the need for an interdisciplinary approach

Gemelli Against COVID-19 Post-Acute Care Study Group[1]

Aging Clinical and Experimental Research

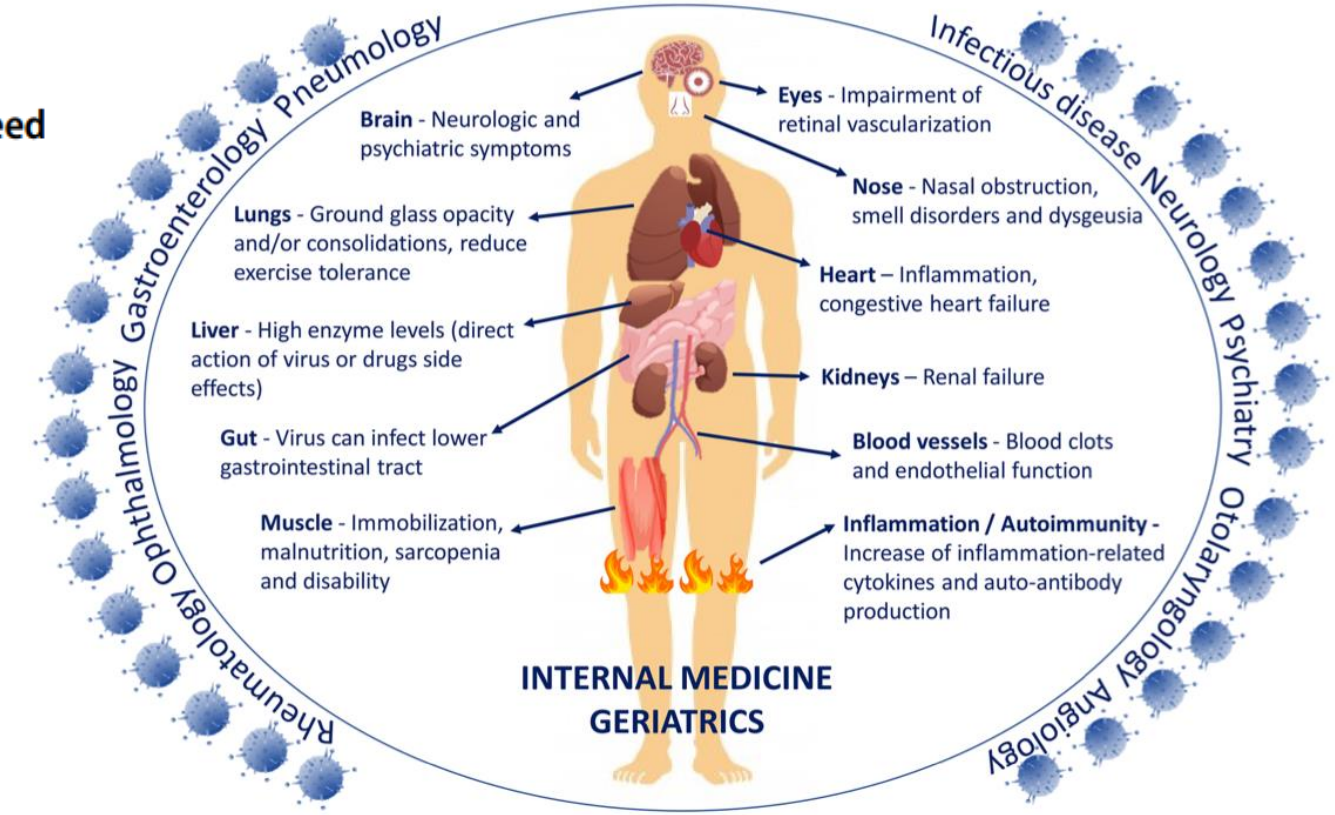


Fig. 1 Multi-organ impairment caused by SARS-CoV-2 infection: holistic approach coordinated by internal medicine–geriatrics