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.

Archives of Cardiovascular Disease xxx (xxxx) xxx–xxx

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Research letter

Endothelial dysfunction in convalescent COVID-19 patients: Systematic review and meta-analysis

The coronavirus disease 2019 (COVID-19) pandemic constitutes a public health threat, placing a considerable burden on healthcare systems. Although the acute phase of the disease has been well-characterized, persistent long-COVID symptoms have been reported in a significant proportion of patients, affecting their return to work and quality of life. Several studies propose that the side-effects of long COVID may be due to persistent endothelial dysfunction. Even though endothelial function appears to improve over time, it can remain significantly impaired, relative to non-COVID 19 controls, beyond 6 months after discharge from hospital [1]. Therefore, the aim of this systematic review and meta-analysis was to evaluate the degree of endothelial impairment, assessed by flow-mediated dilation (FMD) of the brachial artery, in individuals recovering from COVID-19 compared with non-COVID-19 controls.

This study was designed according to the Preferred Reporting Items for Systematic reviews and Meta-Analysis (PRISMA) statement and was registered in the PROSPERO registry (registration number: CRD42022342040). A systematic literature search was conducted up to 1 May 2022 on the PubMed, SCOPUS and Cochrane Library databases using the following search term: ("flow-mediated dilation" OR "flow-mediated vasodilation" OR "FMD" OR "FMV" OR "endothelium-dependent dilation" OR "endothelial-dependent dilation" OR "endothelium-dependent vasodilation" OR "endothelial-dependent vasodilation") AND ("severe acute respiratory syndrome coronavirus 2" OR "SARS-CoV-2" OR "COVID-19" OR "coronavirus" OR "coronavirus disease 19"). All relevant observational studies (cohort, cross-sectional and case-control) were included, based on the following exclusion criteria:

- COVID-19 not confirmed by real-time polymerase chain reaction or rapid antigen test;
- absence of a control group;
- measurement of FMD during the acute phase of the disease only;
- not reporting FMD in percentage change;
- studies involving adolescents/children.

Two reviewers (P.T. and S.L.) evaluated each article separately and performed the data extraction, consisting of the FMD value (in per cent) in the convalescent COVID-19 group and in the control group, duration of follow-up, and characteristics of the control group (risk-factor–matching or not). Any discrepancies were resolved through repeated reviewing and consensus among the two review authors and a third independent author (E.O.). We repeated the literature search before drafting the manuscript and added any recently published studies that met the inclusion criteria. Extrapolation of data from graphs using Adobe Photoshop CS6 was performed in one study. All numerical continuous data were transformed to mean ± standard deviation for the final analysis, as previously described [2]. The quality assessment and risk of bias assessment for the studies were conducted according to the Newcastle–Ottawa Quality Assessment Scale (NOS) criteria.

Effect sizes were pooled via a random-effects model and the results are expressed as uncorrected standardized mean difference, using Cohen's d as the effect size metric, with 95% confidence intervals (CI). Between-study heterogeneity was assessed through the calculation of I^2 and was considered significant if I^2 values exceeded 50%. Prespecified subgroup analysis according to follow-up duration and presence of cardiovascular risk-factor–matched controls was carried out. Publication bias was assessed through funnel plot inspection and Egger's regression test. Sensitivity analysis through the leave-one-out method was also performed. Two-tailed P values of < 0.05 were considered statistically significant. Statistical analysis was performed using the meta and dmetar packages in R studio v.2021.09.2.

Concerning the study selection process, we identified 144 studies from the initial database search. After removal of duplicates, we excluded 60 studies during the title and abstract screening (Fig. S1). Consequently, the full text of 22 studies was assessed for eligibility and 12 studies were further excluded due to the lack of a control group ($n = 8$) or the measurement of FMD during only the acute phase of COVID-19 ($n = 4$). Ultimately, 10 studies were included in the meta-analysis, with a total of 515 convalescent COVID-19 subjects and 437 controls. COVID-19 diagnosis was based on upper respiratory tract polymerase chain reaction in seven studies. Moreover, in six studies, COVID-19 patients requiring hospitalization in the acute phase of the disease were included. However, four studies enrolled young, healthy subjects who were not admitted to hospital [3–6]. Regarding the control group, age- and sex-matched [7,8], risk-factor–matched [9], age-, sex-, and risk-factor–matched controls [1,10] were recruited in five studies. One study enrolled control subjects with atherosclerotic cardiovascular disease [11], whereas no specific information about the control groups was given in four studies [3–5,8]. Concerning follow-up duration, six studies evaluated convalescent COVID-19 subjects within 3 months of the acute phase, whereas four studies had a longer follow-up (4–11 months).

According to the results of the meta-analysis, convalescent COVID-19 subjects had significantly impaired FMD versus controls (standardized mean difference −0.76, 95% CI −1.31 to −0.21; $P < 0.01$) (Fig. 1, Panel A). There was considerable between-study heterogeneity (I^2 88%; $P < 0.001$). We conducted a leave-one-out sensitivity analysis in which the exclusion of any single study had no major impact on the overall effect size (Fig. S2). Moreover, we performed subgroup analyses according to the duration of follow-up and the presence of risk-factor–matched controls

Abbreviations: COVID-19, Coronavirus disease 2019; FMD, flow-mediated dilation.

https://doi.org/10.1016/j.acvd.2022.09.001

Please cite this article as: P. Theofilis, S. Lampsas, E. Oikonomou et al., Endothelial dysfunction in convalescent COVID-19 patients: Systematic review and meta-analysis, Arch Cardiovasc Dis, https://doi.org/10.1016/j.acvd.2022.09.001

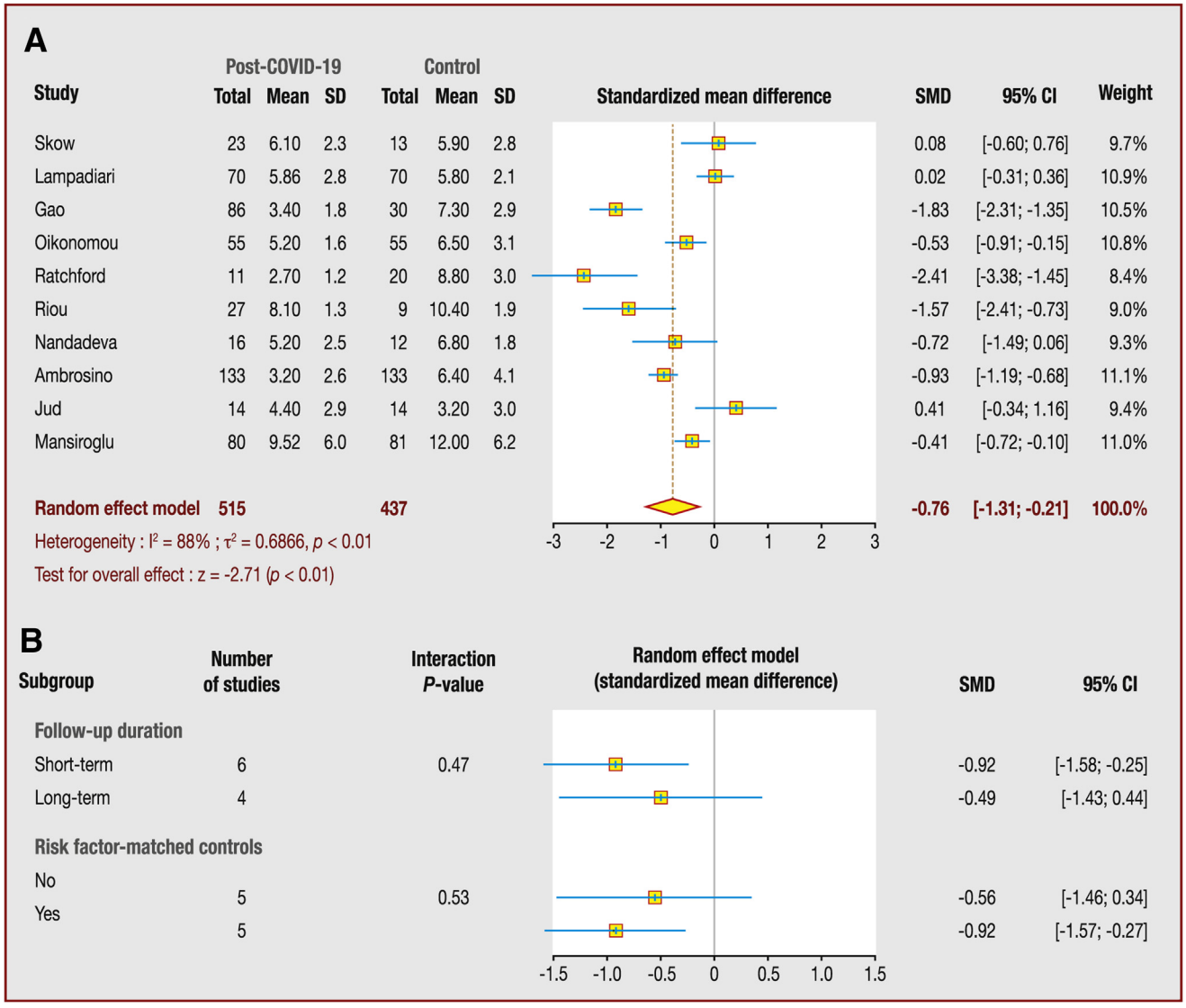

Fig. 1. A. Forest plot demonstrating significantly impaired FMD in convalescent COVID-19 patients compared with controls. B. The degree of FMD impairment was not influenced by the duration of follow-up or comparison with risk-factor–matched controls. COVID-19: coronavirus disease 2019; FMD: flow-mediated dilation.

(Fig. 1, Panel B). Although no significant differences were detected, there was a numerically lower effect size in studies with long-term follow-up. Finally, the inspection of a symmetrical funnel plot (Fig. S3) and insignificant Egger's regression test (intercept −1.139, 95% CI −5.68 to −3.40; P = 0.64) indicated the absence of publication bias.

This systematic review and meta-analysis assessed the degree of endothelial impairment in patients recovering from COVID-19. Our study revealed that subjects recovering from COVID-19 had impaired FMD compared with controls. The results remained largely unaffected irrespective of the follow-up duration and the presence of risk factor-matched controls, according to the subgroup analysis. Importantly, although endothelial function may gradually improve over time, it remains impaired compared with that in non-COVID-19 subjects. The cardiovascular implications of long COVID-19 endothelial impairment have not been explored to date. Therefore, as FMD has been widely associated with an increased risk for atherosclerotic complications, future studies should assess the prognostic significance of this observation and its association with the incidence of major adverse cardiovascular events in this population.

Our findings are limited by the high between-study heterogeneity, which may be attributed to several factors, such as differences in the risk-factor profiles of the study and control groups (younger age, presence of cardiovascular risk factors), variations in the acute course of COVID-19 (mild disease or need for hospitalization/admission to an intensive care unit), the vaccination status of the participants, or the different viral strains responsible for the disease. Moreover, the literature review involved studies from only three databases and the absence of additional eligible studies cannot be excluded.

Funding

This work did not receive any grant from funding agencies in the public, commercial, or not-for-profit sectors.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.acvd.2022.09.001.

Disclosure of interest

The authors declare that they have no competing interest.

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Received 30 June 2022

Received in revised form 15 September 2022

Accepted 19 September 2022
Available online xxx