

Endothelial dysfunction in the post-COVID-19 period: a meta-analysis

P. Theofilis¹, E. Oikonomou², S. Lampsas², G. Siasos², K. Tsioufis¹, D. Tousoulis¹

¹Hippokraton General Hospital, Athens, Greece; ²Sotiria Regional Chest Diseases Hospital, 3rd Department of Cardiology, Athens, Greece

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Background: Coronavirus disease (COVID)-19 is an entity characterized by a cytokine storm and profound endotheliitis. Although several reports have pointed to the presence of endothelial dysfunction in the acute phase, data is accumulating regarding a possible prolonged adverse effect of COVID-19 on endothelial function.

Purpose: This systematic review and meta-analysis aims to evaluate the degree of endothelial impairment, assessed by flow-mediated dilation (FMD) of the brachial artery, in individuals recovering from COVID-19.

Methods: We conducted a systematic literature search for studies assessing FMD between in patients post-COVID-19 and controls. Exclusion criteria consisted of the absence of a control group, measurement of FMD only during the acute phase of the disease, and not reporting FMD in % change. Effect sizes were pooled via random-effect model and the results are expressed as uncorrected standardized mean difference (SMD), using the Cohen's d as the effect size metric, with 95% confidence intervals (CI). Between-study heterogeneity was assessed through the calculation

of I^2 . Subgroup analysis according to follow-up duration and the presence of cardiovascular risk factor-matched controls was also carried out.

Results: Database search identified 51 studies. Following the application of the exclusion criteria, 7 studies were included in the meta-analysis (post-COVID-19: 342 subjects, Control: 273 subjects). Compared to controls, patients post-COVID-19 had significantly lower FMD% values (SMD: -1.06 , 95% CI: -1.74 to -0.38 , $p < 0.01$, $I^2 = 86%$) (Figure 1). Results remained unaffected after exclusion of any single study using the leave-one-out method. Subgroup analysis revealed no significant differences in FMD between post-COVID-19 patients and controls according to follow-up duration or the presence of cardiovascular risk factor-matched control group.

Conclusion: Flow-mediated dilation of the brachial artery, indicative of endothelial dysfunction, was significantly reduced in post-COVID-19 subjects compared to non-infected controls. This finding may be an alarming sign towards a higher risk of incident cardiovascular events.

Study	Post-COVID-19			Control		
	Total	Mean	SD	Total	Mean	SD
Gao	86	3.40	1.8	30	7.30	2.9
Oikonomou	55	5.20	1.6	55	6.50	3.1
Ratchford	11	2.70	1.2	20	8.80	3.0
Riou	27	8.10	1.3	9	10.40	1.9
Nandadeva	16	5.20	2.5	12	6.80	1.8
Ambrosino	133	3.20	2.6	133	6.40	4.1
Jud	14	4.40	2.9	14	3.20	3.0
Random effects model	342			273		

Heterogeneity: $I^2 = 86%$, $\tau^2 = 0.7203$, $p < 0.01$
 Test for overall effect: $z = -3.07$ ($p < 0.01$)

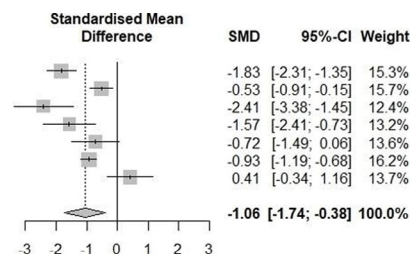


Figure 1