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SYSTEMATIC REVIEW

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Clinical implications of vascular dysfunction in acute and convalescent COVID-19: A systematic review

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Abstract

Background: Accumulating evidence suggests that endothelial dysfunction is implicated in the pathogenesis and severity of coronavirus disease 2019 (COVID-19). In this context, vascular impairment in COVID-19 might be associated with clinical manifestations and could refine risk stratification in these patients.

Methods: This systematic review aims to synthesize current evidence on the frequency and the prognostic value of vascular dysfunction during acute and post-recovery COVID-19. After systematically searching the MEDLINE, clinicaltrials.gov and the Cochrane Library from 1 December 2019 until 05 March 2022, we identified 24 eligible studies with laboratory confirmed COVID-19 and a thorough examination of vascular function. Flow-mediated dilation (FMD) was assessed in 5 and 12 studies in acute and post-recovery phase respectively; pulse wave velocity (PWV) was the marker of interest in three studies in the acute and four studies in the post-recovery phase.

Results: All studies except for one in the acute and in the post-recovery phase showed positive association between vascular dysfunction and COVID-19 infection. Endothelial dysfunction in two studies and increased arterial stiffness in three studies were related to inferior survival in COVID-19.

Discussion: Overall, a detrimental effect of COVID-19 on markers of endothelial function and arterial stiffness that could persist even for months after the resolution of the infection and provide prognostic value was congruent across published studies. Further research is warranted to elucidate clinical implications of this association.

KEYWORDS
arterial stiffness, COVID-19, endothelial dysfunction, flow-mediated dilation, vascular function

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1 | INTRODUCTION

Coronavirus disease 2019 (COVID-19) is associated with a wide range of clinical presentations and is responsible for multitudinous deaths worldwide due to its rapid spread. Accumulating evidence suggests that endothelial dysfunction is a key player and mediator of the pathophysiologic pathways of COVID-19.[1–3] Notably, endothelial function and arterial stiffness leading to vascular alterations during the acute phase may persist even in the post-acute COVID-19 phase.[4,5]

Flow-mediated dilation (FMD) is a noninvasive tool which examines changes in brachial artery diameter in response to ischemia through ultrasound,[4] thus identifying endothelial dysfunction, whereas pulse wave velocity (PWV) is another noninvasive and reproducible technique considered the gold standard method for assessing aortic stiffness.[5] Both FMD and PWV are of high clinical value aiming to detect subjects at increased risk not only for future cardiovascular (CV) events but also for all-cause mortality.[4,5] Herein, the aim of this review was to critically summarize current evidence on COVID-19 related alterations in vascular function alongside their prognostic implications for acute and long-term adverse effects.

2 | METHODS

This review study was reported according to the Synthesis without meta-analysis in systematic reviews (SWiM) and conformed to the broad EQUATOR Reporting Guidelines where applicable.[6,7] Two independent researchers (GM and MD) performed a systematic review of the MEDLINE, clinicaltrials.gov and the Cochrane Library for relevant articles in humans, published from 1 December 2019 to 5 March 2022. Eligible studies had laboratory confirmed COVID-19 diagnosis and vascular assessment performed either on the acute phase of the infection or post-acute COVID-19. The latter was defined as the recovery phase after a time period of at least 4 weeks after acute COVID-19 infection.

Details of search strategy, eligibility, data extraction, synthesis and heterogeneity in reported effects, quality assessment and certainty of evidence are provided in **Supporting information**.

3 | RESULTS

Overall, we retrieved 24 studies that assessed vascular function during acute and post-acute COVID-19. Table 1 displays the main clinical characteristics of the population along with main findings from each study.

Key messages

- COVID-19 is associated with vascular dysfunction in the acute phase which persists following recovery.
- Endothelial dysfunction and increased arterial stiffness are related to inferior survival in the acute phase of COVID-19.
- Vascular dysfunction in the acute phase is associated with the presence of long COVID-19 symptoms.
- Endothelial dysfunction may serve as an emerging therapeutic target in COVID-19.

3.1 | Endothelial dysfunction

Seventeen studies have examined the association of COVID-19 with endothelial function.[8–24] Notably, it should be acknowledged that of the 16 studies assessing endothelial dysfunction through FMD, only four studies clearly adjusted FMD measurement for shear stress indices. Thus, residual confounding regarding the association between endothelial dysfunction and outcomes in acute and post-recovery COVID-19 cannot be excluded.[25] In the acute phase, endothelial dysfunction was documented in patients with COVID-19 compared with controls as shown by lower FMD values.[12,22]

In the recovery phase, patients with prior COVID-19 infection had also significantly lower values of FMD compared with controls (range of FMD 2.7%–8.2% in COVID-19 group compared with 6.5%–10.3% in patients without COVID-19) (Table 1).[8–11,13,16,22] FMD was lower in patients with COVID-19 than controls except for two studies, but this lack of association could be attributed to small sample size and cross-sectional design of both studies.[17,19] Importantly, endothelial dysfunction in recovered patients with COVID-19 was evident across a wide age range (8.9–57 years) since relevant studies included children, young and older adults. Similarly, results did not differ between male and female subjects.[10] Furthermore, children with multisystem inflammatory syndrome (MIS-C) after COVID-19 diagnosis had also impaired endothelial function assessed through FMD.[13]

In the study by Nandadeva et al.[19], FMD was lower in symptomatic recovered patients with COVID-19 compared with asymptomatic individuals and controls.[19] Moreover, the presence of post COVID-19 symptoms such as dyspnoea, cough and chest pain was associated with impaired endothelial function.[11] FMD values were also associated with measures of pulmonary dysfunction and were significantly lower in patients with reduced cognitive efficiency

TABLE 1 Studies assessing vascular function in patients with COVID-19.

Author	Population/setting	Age (years)	Study description	Marker of vascular function	Results
Acute phase of COVID-19					
Bianconi et al. (2021)	408 hospitalized patients	72	Prospective	FMD	FMD < 4.4%➔1.52–1.66x↑risk for ICU admission/ in-hospital death
Cristina-Oliveira et al. (2022)	211 hospitalized patients	58	Prospective cohort	FMD, carotid IMT	cIMTmean and cIMTmax predicted mortality and thrombotic events in the univariate but not multivariate analysis FMD% not associated with any outcome
Oliveira et al. (2021)	98 patients vs. 82 controls/ward or ICU	61 vs. 63	Prospective observational	FMD	↓FMD ($p < .01$) in the COVID-19 group FMD ≤ 3.43%➔mortality/hospital stay
Heubel et al. (2021)	109 noncritically hospitalized patients	51	Cross-sectional study	FMD	BMI: major factor associated with FMD Others: creatinine level baseline artery diameter
Rodilla et al. (2021)	12,170 hospitalized patients	67.5	Observational, retrospective, cohort study	AS as pulse pressure ≥ 60 mm Hg	Pulse pressure ≥ 60 mm Hg ➔ all-cause mortality
Stamatelo-poulos et al. (2021)	737 hospitalized patients vs. 934 nonhospitalized controls	72	Retrospective, longitudinal cohort study	ePWV	ePWV (controls < survivors with COVID-19 < deceased patients) (↑ per group = 1.89 m/s, $p < .001$)
Kumar et al. (2021)	23 (mild) vs. 21 (moderate) vs. 20 (severe) hospitalized patients	37.9 vs. 45.3 vs. 50.5	Non-randomized observational	cfPWV	cfPWV ↑ depending on severity: Mild (829.1 cm/s), Moderate (1067 cm/s) Severe (1416 cm/s) ($p < .0001$)
Schnaubelt et al. (2021)	22 patients (ward) vs. 22 age- and sex-matched patients	76.5 vs. 76.5	Case–control	baPWV, cfPWV	↑PWV in patients with COVID-19 ($p < .01$) ↑PWV in nonsurvivors ↑PWV➔ longer hospital stay
Post-acute phase of COVID-19					
Zanoli et al. (2022)	90 patients previously hospitalized for COVID-19 and 180 matched controls	55 vs. 55	Observational cross-sectional study	PWV	PWV remained significantly higher (+6%; $p = .04$) in patients with COVID-19 than in controls, 48 weeks after COVID-19 onset
Lambadiari et al. (2021)	70 patients 4 months after COVID-19 vs. 70 age- and sex-matched hypertensive controls vs. 70 healthy controls	54.5 vs. 54.5 vs. 54.8	Case–control, prospective study	FMD, cfPWV	↓FMD (5.8% vs. 9.06%, $p = .002$) and ↑cfPWV (12.09 vs. 10.04 m/s, $p = .036$) in patients with COVID-19 compared with healthy controls
Ambrosino et al. (2021)	133 patients after severe/critical COVID-19, after 2 negative swab tests vs. 133 age-, sex- and CV-profile-matched controls	61.6 vs. 60.4	Prospective	FMD	↓FMD in convalescent patients with COVID-19 (3.2% vs. 6.4%, $p < .001$) Recent COVID-19➔ predictor of FMD ($\beta = -0.427$, $p < .001$)

(Continues)

TABLE 1 (Continued)

Author	Population/setting	Age (years)	Study description	Marker of vascular function	Results
Gao et al (2022)	86 patients after hospitalization for COVID-19 vs. 28 age- and sex-matched healthy controls and 30 risk factor-matched patients	58 vs. 56 vs. 62	Prospective observational	FMD	↓FMD in survivors of COVID-19 (3.5%) than healthy controls (7.7%) and risk factor-matched controls (6.9%) ($p < .001$) FMD inversely correlated with TNF-α
Küçük et al (2022)	50 patients 3–6 months after COVID-19 vs. 50 age- and gender-matched healthy volunteers	No info	No info	Aortic stiffness index	↑Aortic stiffness index in patients with prior COVID-19 (2.82 vs. 2.46, $p < .001$)
Ambrosino et al. (2021)	82 patients with persistent clinical manifestations after severe or critical COVID-19 and 2 negative swab tests	60.4	Prospective	FMD	After pulmonary rehabilitation FMD 2.48% ➔ 4.24% ($p < .001$) ↑ change in FMD in patients without history of vascular events FEV1%, FVC% and DLCO% correlated with FMD
Ciftel et al. (2021)	38 patients with MIS-C vs. 38 age-, sex- and BMI-matched controls	8.9 vs. 8.9	Prospective	FMD, aortic strain	↓FMD in MIS-C (9.20 ± 3.81) < controls (12.10 ± 3.80, $p < .01$)
Ergül et al. (2021)	63 patients recovered from COVID-19 vs. 29 age- and sex- matched controls	44.4 (whole population)	Prospective, observational cross-sectional cohort study	FMD	ED➔ ↑COVID-19 rate (84.8 vs. 59.3%; $p = .009$) ↓FMD% in patients with COVID-19 (17.4 vs. 28.8, <0.001)
Moretta et al (2022)	55 convalescent patients with COVID-19 within two months from swab test negativization	60.1	Pilot	FMD	↓FMD in RCE patients compared with non-RCE (2.25% vs. 3.90%, $p = .006$) FMD negatively correlated with the number of impaired scores on neuropsychological tests FMD positively correlated with FEV1, FVC and DLCO
Jud et al. (2021)	14 patients post-COVID-19 vs. 14 age- and sex-matched controls with vs. 14 without ASCVD	68.7, vs. 31 vs. 67	Cross-sectional	FMD, PWV	No difference for FMD ↑ rate of aortic PWV > 10 m/s ($p = .001$) and ↑values of aortic PWV in patients post-COVID-19
Riou et al. (2021)	27 patients 3 months after hospitalization vs. 9 controls	57 vs. 59	Prospective	FMD	↓FMD in patients with COVID-19 (8.2 vs. 10.3, $p = .002$)
Ratchford et al. (2020)	11 patients 3–4 weeks after COVID-19 vs. 20 controls	20.2 vs. 23	Cross-sectional	FMD, cfPWV	↓FMD in patients with COVID-19 (2.71% vs. 8.81%) ($p < .01$) ↑cfPWV in patients with COVID-19 (5.83 m/s vs. 5.17 m/s) ($p < .01$)
Szeghy et al. (2021)	15 patients post-COVID-19 vs. 15 BMI-matched controls	20 vs. 23	Cross-sectional	AIx	↑Carotid stiffness, ↑aortic AIx and ↑aortic AIx@ HR75 in patients with COVID-19 ($p < .05$)

TABLE 1 (Continued)

Author	Population/setting	Age (years)	Study description	Marker of vascular function	Results
Nandadeva et al. (2021)	16 patients (8 symptomatic, 8 asymptomatic) at least 4 weeks after COVID-19 vs. 12 controls	22 vs. 24 vs. 23	Cross-sectional	FMD, peak blood velocity	↓FMD in symptomatic (3.8%) < asymptomatic (6.8%) and controls (6.8%) ($p < .05$) ↓Peak blood velocity in symptomatic <asymptomatic and controls ($p < .05$)
Willems et al (2022)	203 patients 3 months after COVID-19 disease vs. 312 controls	62.7	Cross-sectional observational cohort study	Carotid artery reactivity test	No difference in prevalence of macrovascular dysfunction (18.6% vs. 22.5%, risk difference − 4%, $p = .49$)
Both acute and post-acute phase of COVID-19					
Oikonomou et al (2022)	73 patients with COVID-19 (37% in ICU) vs. 73 controls at acute phase, 1 month and 6 months post-hospital discharge	No info	Prospective cohort	FMD	↓FMD in the COVID-19 group (1.65%) compared with the control (6.51%) ($p < .001$) ↓FMD in ICU-treated than medical ward- treated subjects ($p = 0.001$) During hospitalization, FMD inversely associated with IL-6 and troponin I ($p < .05$) ↓FMD in patients with COVID-19 compared with controls at 1 month and 6 months post-hospital discharge ($p < .05$)
Mejia-Renteria et al (2021)	20 patients with acute COVID-19 vs. 52 patients past COVID-19 vs. 72 matched controls	54 vs. 59, s 53.9	Prospective, observational, case–control and blinded study	LnRHI	↓LnRHI in patients post COVID-19 ($p < .0001$) ↓LnRHI from acute COVID-19 to post infection (0.73 vs. 0.42, $p = .0042$)

Abbreviations: AIx, aortic augmentation index; AIx@HR75, aortic AIx standardized to 75 beats/min; AS, arterial stiffness; ASCVD, atherosclerotic cardiovascular disease; BMI, body mass index; cfPWV, carotid-femoral pulse wave velocity; cIMTmax, maximum carotid intima media thickness; cIMTmean, mean carotid intima media thickness; COVID-19, coronavirus disease 2019; CV, cardiovascular; DLCO, diffusion lung capacity for carbon monoxide; ED, endothelial dysfunction; ePWV, estimated pulse wave velocity; FEV1, forced expiratory volume in 1 s; FMD, flow-mediated dilation; FVC, forced vital capacity; ICU, intensive care unit; IMT, intima media thickness; LnRHI, logarithmic scaled reactive hyperemia index; MIS-C, multisystem inflammatory syndrome in children; RCE, reduced cognitive efficiency; TNF-α, tumour necrosis factor α.

after COVID-19.[20] In children with MIS-C after COVID-19, the degree of endothelial dysfunction correlated with reduced left ventricular ejection fraction.[13] Whether endothelial function plays a causative role in the presence of these symptoms or they simply co-exist remains to be clarified. Table 2 summarizes current evidence regarding the association of endothelial dysfunction with COVID-19-related system dysfunction during acute and convalescent COVID-19.

Regarding prognosis, significantly lower FMD values were measured in patients with acute COVID-19 and radiographic signs of pneumonia, respiratory distress and need for noninvasive ventilation compared with their counterparts with less impaired respiratory profiles.[14] In addition, lower FMD values were detected in intensive care unit (ICU)-admitted patients in comparison to those treated in medical wards.[22] Both studies which assessed FMD during acute COVID-19 demonstrated that endothelial dysfunction was independently and incrementally associated with higher rate of mortality[12,14] and increased risk for ICU admission.[14] In contrast, impaired FMD in convalescent COVID-19 was not associated with severe or critical severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection in the acute phase.[8]

During hospitalization, FMD was inversely associated with interleukin-6 and troponin I.[22] In contrast, a potential link between inflammatory markers during hospitalization such as C-reactive protein, monoclonal antibodies like tocilizumab, lipid lowering drugs or those modulating blood pressure and FMD at post-recovery phase was not established.[8,9]

3.2 | Arterial stiffness

Eleven studies examined the potential link between COVID-19 and arterial stiffness.[10,11,17,19,26–32] Patients with acute COVID-19 had increased arterial stiffness compared with their counterparts without COVID-19.[27,28] In most studies[10,11,17,29] which assessed arterial stiffness, reflected either as PWV[10,11,17] or as aortic augmentation index,[29] in the recovery phase of COVID-19, patients of different age groups with prior SARS-CoV-2 infection had higher PWV values and aortic augmentation index in comparison to controls, even 48 weeks after COVID-19 onset.[32] Only one study yielded the opposite results,[19] where symptomatic and asymptomatic patients during acute COVID-19 infection had comparable PWV with controls at recovery phase. Of note, patients presenting with fatigue 4 months after COVID-19 infection had more impaired values of PWV compared with those without this symptom.[11]

PWV values in the acute phase raised progressively depending on severity of the infection with higher values observed in patients with severe COVID-19 disease.[30] On the contrary, there was no correlation between severity of acute COVID-19 and PWV measurements in post-recovery phase.[11,19] However high-sensitivity C-reactive protein at hospitalization and mean blood pressure at time of examination were associated with impaired arterial stiffness, depicted as higher PWV values, at least 12 weeks after COVID-19 onset. Importantly, a higher number of persistent symptoms such as loss of smell/taste at the time of the vascular examination was also associated with higher PWV values.[32]

Stamatelopoulos et al. used a readily calculated proxy of PWV (i.e., estimated PWV [ePWV]) to demonstrate increased arterial stiffness during COVID-19. By using machine-learning algorithms, they derived an optimal cut-off point for ePWV equal to 13.0 m/s that could discriminate patients at high risk for 28-day death.[28] Importantly, ePWV provided additive discrimination and reclassification value over the 4C Mortality score, a validated score for prediction of mortality in COVID-19 and the Charlson comorbidity index.[28] Moreover, higher ePWV values were

TABLE 2 Association of endothelial dysfunction with COVID-19-related system dysfunction during acute and convalescent COVID-19.

Association of endothelial dysfunction with COVID-19-related system dysfunction	
System	**Related dysfunction**
Cardiovascular	• Dyspnoea • Fatigue • Chest pain • Reduced ejection fraction
Respiratory	• Radiographic signs of pneumonia and respiratory distress (acute) • Impaired values of FEV1%, FVC% and DLCO% • Cough
Nervous	• Neuropsychological manifestations • Reduced cognitive efficiency

Abbreviations: DLCO, diffusion lung capacity for carbon monoxide; FEV1, forced expiratory volume in 1 s; FVC, forced vital capacity.

detected in deceased patients[28] compared with survivors with COVID-19 and controls, whereas in survivors higher PWV was associated with increased length of hospital stay.[27] In the same direction, in the largest study to date, increased arterial stiffness defined as admission pulse pressure ≥60 mmHg was associated with higher risk for all-cause mortality in hospitalized patients with COVID-19.[26]

Available evidence on the prevalence of impaired endothelial function and increased arterial stiffness in acute and convalescent COVID-19 alongside their prognostic implications are synthesized in Figure 1.

4 | DISCUSSION

Our systematic review confirms that COVID-19 is associated with impaired endothelial function and arterial stiffness during the acute and the post COVID-19 phase. Notably, this association was consistent across different age groups and different subgroups of disease severity. Moreover, FMD and PWV, as surrogate markers of endothelial function and arterial stiffness respectively, are associated with mortality and risk of ICU admission in hospitalized patients with COVID-19.

4.1 | Epidemiology and pathophysiology of COVID-19 related vascular dysfunction

Given the wide range of clinical presentations of SARS-CoV-2 infection, prevalence of COVID-19 related vascular dysfunction is difficult to be estimated. Increased body mass index and renal disease have been both associated with endothelial dysfunction in noncritically hospitalized patients with COVID-19.[18] Additionally, patients with type 2 diabetes and under treatment with beta blockers or angiotensin receptor blockers (ARBs) presented significantly lower FMD values.[14] Importantly, higher values of interleukin-6 and troponin I during hospitalization were also associated with impaired endothelial function at the acute phase.[22] Notably, patients of older age and male gender, with presence of CV risk factors and severe symptoms during the acute phase of the disease, extensive pulmonary lesions and reduced left ventricular global longitudinal strain had significantly higher odds to present impaired endothelial function in the post-recovery phase of the disease.[33]

4.1.1 | Endothelial dysfunction

Endothelial cells consist a preferential target for SARS-CoV-2 which directly invades these cells after binding the angiotensin-converting enzyme 2 (ACE2) receptor, whereas transmembrane serine protease 2 (TMPRSS2), a serine protein, also mediates the cleavage of the viral spike (S) protein.[34,35] The subsequent endocytosis of the complex of ACE2 receptor along with the virus reduces the number of ACE2 receptors available on the cell surface.[36] Consequently, this induces the dysregulation of ACE2 receptors expression, leading to endothelial dysfunction and activation of prothrombotic state commonly seen in COVID-19.[37]

Impaired endothelial function in patients with COVID-19 is not only a consequence of viral infiltration but can also be attributed to increased systemic inflammation.[1] Inflammatory cytokines, such as interleukin 1, interleukin 6 and tumour necrosis factor α, target specific receptors on the surface of endothelial cells, inducing the activation of numerous mediators which results in platelet activation as well as leukocyte adherence and release into circulation.[38] Moreover, nitric oxide (NO) deficiency may exaggerate endothelial dysfunction in patients with COVID-19 resulting in impaired vascular smooth muscle relaxation along with increased oxidative stress.[1,39] Importantly, it has been shown that patients with severe COVID-19 have systemic microcirculatory alterations indicative of endothelial dysfunction and the extent of these alterations was correlated with the severity of acute respiratory distress syndrome.[40]

4.1.2 | Arterial stiffness

The deficit of NO, due to the cytokine storm during acute systemic inflammation, may account for increased arterial stiffness in patients with COVID-19.[41] Alterations in NO bioavailability combined with the direct impact of SARS-CoV-2 on endothelial cells after binding at ACE2 receptors, may impair vascular smooth muscle cell function and induce structural changes of the extracellular matrix of the vascular wall favouring increased arterial stiffness.[42] Overactivation of the renin–angiotensin–aldosterone system (RAAS) is known to mediate increased arterial stiffness and has been linked to clinical deterioration of hospitalized patients with COVID-19.[43,44] Of note, uncontrolled systemic inflammation commonly seen in severe COVID-19 infection, may directly trigger arterial remodelling or result in adrenoceptor hyporeactivity which may contribute to acute impairment of vascular response.

4.2 | Vascular function and risk stratification in COVID-19

4.2.1 | Prognostic value of vascular markers for acute COVID-19 sequelae

Impaired FMD has been associated with worse in-hospital prognosis in patients with acute COVID-19 and confers

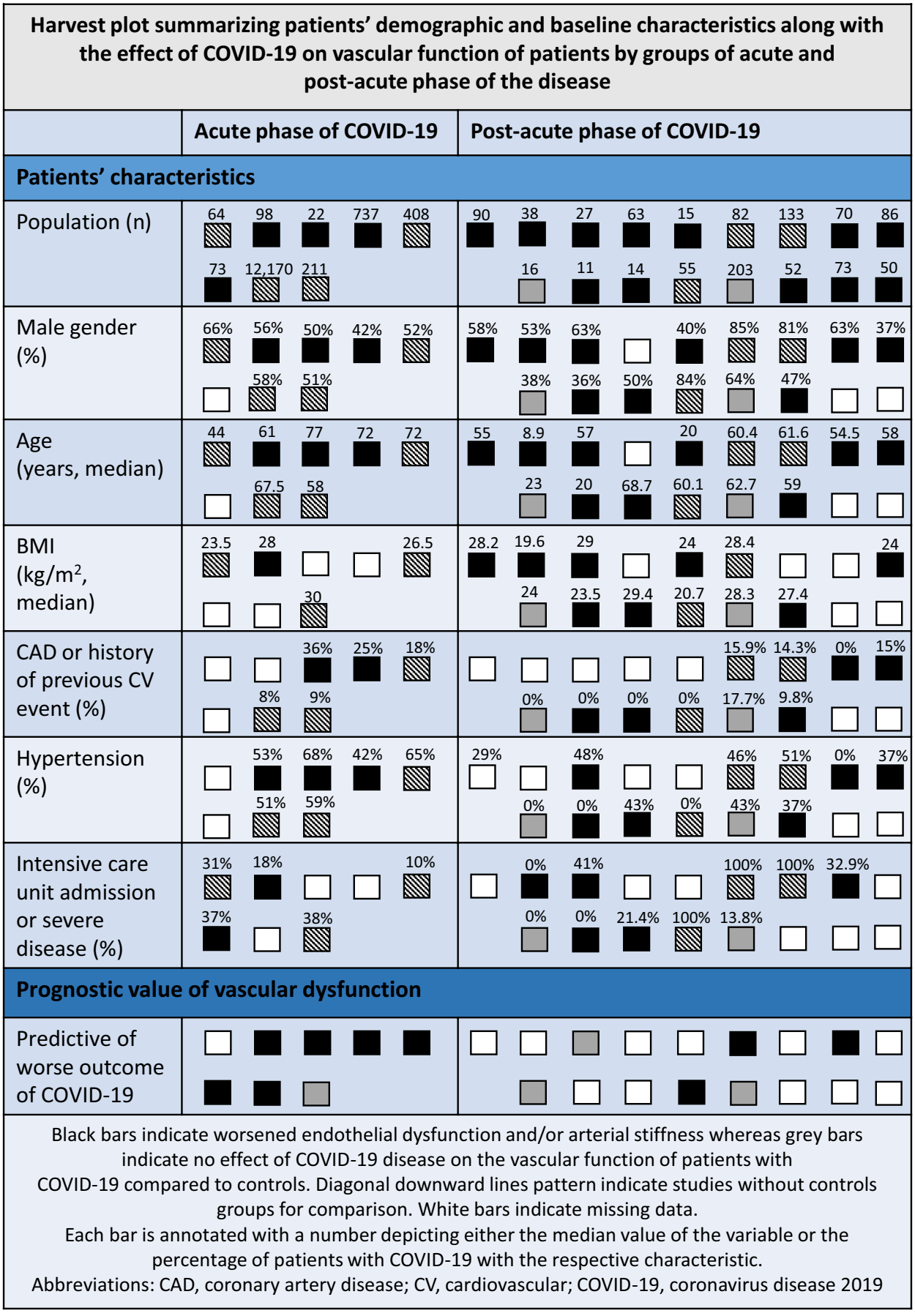

FIGURE 1 Harvest plot summarizing (i) the effect of COVID-19 (i.e., left column acute phase; right column convalescent disease) on vascular function according to patients' characteristics (rows 1–7) and (ii) the prognostic value of impaired vascular function during acute (left column) and convalescent (right column) COVID-19 (row 8).

increased risk for ICU admission and/or in-hospital death.[14] More precisely, FMD ≤ 0.26 mm was shown to accurately predict mortality risk in a 10-day hospitalization period due to COVID-19.[12] Respectively, increased arterial stiffness independently predicted 28-day all-cause mortality beyond established risk factors and risk scores in patients with COVID-19,[26,28] with ePWV providing incremental prognostic value over pulse pressure.[28] In the same direction, PWV correlated with severity as well as prolonged hospital stay in acute COVID-19,[27,30] whereas pulse pressure was prognostic of all-cause mortality in hospitalized patients.[26]

4.2.2 | Prognostic value of vascular markers for long-term COVID-19

Endothelial dysfunction during the acute phase of COVID-19 infection may discriminate patients at high risk for persistent symptoms of long COVID-19 syndrome, including fatigue, chest pain, pulmonary dysfunction and neurocognitive difficulties, since preliminary data suggest the causative role of persistent endothelial dysfunction in long COVID-19 syndrome.[20,33]

4.3 | Clinical implications—Future perspectives

Our systematic review highlights potential clinical implications. First, the more severe the clinical manifestations of COVID-19 at hospital admission the lower the values of FMD and subsequently the higher the degree of endothelial dysfunction.[14] Interestingly, unfavourable in-hospital prognosis of patients with vascular dysfunction was independent of pre-existing medical conditions.[14] Hence, FMD measurement at hospital admission may identify patients with COVID-19 more likely to suffer from severe clinical manifestations. Moreover, critical COVID-19 infection implies a markedly impaired endothelial function which may not be fully recovered 3 months after disease onset, identifying a group of patients at very high risk for CV complications.[45] Hence, assessment of endothelial function has been recommended in patients with convalescent COVID-19 for early detection of long-term CV complications.[46] In this direction, Green et al have previously showed that 1% decrease in FMD is associated with a 9% increase in the risk of CV events.[47] Similarly, ePWV conferred additive prognostic value for future CV events over traditional risk factors.[48]

It should be noted that cutoff points with clinical significance have been proposed for FMD and ePWV in patients with COVID-19. Indeed, optimization of risk stratification in acute phase of COVID-19 infection is of utmost importance to detect early high-risk patients and to guide critical treatment decisions.[49,50] Single or combined use of these markers could discriminate patients at high risk for acute and long-term complications, including transition to long COVID-19. The latter is a term commonly used to describe signs and symptoms such as dyspnoea, fatigue and anxiety that continue or develop at least 4 weeks after acute COVID-19 infection[51] and persist in a substantial proportion of patients at 12 months,[52] posing a remarkable issue of public health concern by increased healthcare burden and productivity losses.

Finally, the utilization of vascular markers in clinical routine could prioritize patients of higher risk for COVID-19-related complications that would benefit the most by the administration of advanced treatment regimens such as monoclonal antibodies and oral antiviral drugs.

4.4 | Vascular function as a therapeutic biomarker

Therapeutic interventions aiming to prevent or even improve endothelial dysfunction may attenuate progression of disease in patients with COVID-19 and might confer a survival benefit. Given the interplay between TMPRSS2 and SARS-CoV-2 cell entry, inhibitors of this serine protease may at least partially counteract systemic spread of the virus.[34] In addition, ACE2 receptor is a preferential target for SARS-CoV-2 and accumulating evidence suggests that administration of ACE inhibitors and ARBs has a beneficial effect on COVID-19 sequelae. Treatment with angiotensin-converting enzyme (ACE) inhibitors or ARBs can reduce mortality of COVID-19[53,54] with concomitant salutary antithrombotic effects.[55] Moreover, statins ameliorate endothelial function through a variety of mechanisms such as reduction of oxidized low-density lipoprotein cholesterol, increased expression of endothelial nitric oxide synthase (eNOS), suppression of pro-oxidant enzymes and have direct anti-inflammatory impact through inhibition of pro-inflammatory transcriptional and signal transduction pathways.[2,56] Notably, statin use was associated with a reduction of inflammatory biomarkers along with lower rate of mortality in patients with COVID-19.[57] Another treatment known to mitigate endothelial dysfunction through anti-inflammatory pathways in COVID-19 patients is corticosteroids.[58] Finally, cytokine-directed therapies such as the interleukin-6 antagonist tocilizumab may also ameliorate endothelial function but to date only scarce data is available from patients with COVID-19.[1]

5 | CONCLUSIONS

Vascular dysfunction underlies various manifestations of acute and long-term COVID-19. Assessment of vascular function in patients with COVID-19 could improve risk stratification and identify high yield therapeutic targets. Further research is warranted to delineate the molecular pathways and clinical correlates of vascular dysfunction in acute and convalescent COVID-19. This could be translated to early identification of high-risk patients and novel therapeutic strategies.

AUTHORS' CONTRIBUTIONS

G. Georgiopoulos, K. Stamatelopoulos and G. Mavraganis contributed significantly to the conception and design of the study, analysis, interpretation and the final approval of the version to publish. G. Mavraganis and M. Dimopoulou performed the systematic review of the MEDLINE, clinicaltrials.gov and the Cochrane Library for relevant studies. G. Georgiopoulos and G. Mavraganis prepared the original manuscript. K. Stamatelopoulos, D. Delialis, D. Bampatsias, A. Sianis and E. Maneta provided critical revision. R. Patras contributed significantly to the revised manuscript, including interpretation and synthesis of new data and appraisal of important intellectual content. All authors gave final approval and agree to be accountable to all aspects of work ensuring integrity and accuracy.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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