Atherosclerosis 407 (2025) 120389

Contents lists available at ScienceDirect

Atherosclerosis

journal homepage: www.elsevier.com/locate/atherosclerosis

Impact of severe COVID-19 infection on coronary microvascular dysfunction in ANOCA patients: A cross-sectional study☆

Ali Aldujeli [a,b,c,k,1], Tsung-Ying Tsai [c,d,1], Ayman Haq [e], Kamile Puipaite [a], Rima Braukyliene [a], Vacis Tatarunas [a], Diana Zaliaduonyte [a], Ramunas Unikas [a], Mick Renkens [c], Pruthvi C. Revaiah [c], Kotaro Miyashita [c], Akihiro Tobe [c], Asahi Oshima [c], Faisal Sharif [f], Vaiva Lesauskaite [a], John A. Spertus [g,h], Scot Garg [i,j], Yoshinobu Onuma [c,f], Emmanouil S. Brilakis [e], Patrick W. Serruys [c,*]

[a] Lithuanian University of Health Sciences, Kaunas, Lithuania
[b] Klaipeda University Hospital, Klaipeda, Lithuania
[c] CORRIB Research Centre for Advanced Imaging and Core Lab, University of Galway, Galway, Ireland
[d] Cardiovascular Center, Taichung Veterans General Hospital, Taichung, Taiwan
[e] Abbott Northwestern Hospital/Minneapolis Heart Institute Foundation, Minneapolis, MN, USA
[f] Department of Cardiology, University Hospital Galway, University of Galway, Galway, Ireland
[g] Cardiovascular Research Saint Luke's Mid America Heart Institute Kansas City, Missouri, USA
[h] Department of Biomedical and Health Informatics of Medicine University of Missouri-Kansas City, Kansas City, Missouri, USA
[i] Department of Cardiology, Royal Blackburn Hospital, Blackburn, United Kingdom
[j] School of Medicine, University of Central Lancashire, Preston, United Kingdom
[k] Bon Secours Hospital Limerick, Limerick, Ireland

ARTICLE INFO

Keywords:
COVID-19
Long COVID syndrome
Coronary microvascular dysfunction (CMD)
Angina without obstructive coronary artery disease (ANOCA)
Coronary flow reserve (CFR)
Index of microvascular resistance (IMR)
Seattle Angina Questionnaire (SAQ-7)
Quality of life
Invasive coronary physiology assessment
Exercise stress testing (EST)

ABSTRACT

Background and aims: Millions of survivors from severe COVID-19 infection suffer from residual symptoms including anginal chest pain. The pathophysiological mechanisms, particularly the role of coronary microvascular dysfunction (CMD), however, remain elusive. We compared the incidence and endotypes of CMD in patients with angina without obstructive coronary artery disease (ANOCA) between those who had a history of severe COVID-19 infection (COVID group, defined as COVID patients needing supplemental oxygen therapy with SpO2 < 90 % on room air), versus those who didn't (Control group).

Methods: This multicentre, prospective cohort study enrolled 117 ANOCA patients (COVID group n = 59, Control group n = 58). All participants underwent exercise stress testing and invasive coronary physiology assessment to measure coronary flow reserve (CFR), and the index of microvascular resistance (IMR). CMD was defined as CFR<2.0 or IMR≥25. Patients also completed the modified Seattle Angina Questionnaire (SAQ-7) after invasive functional assessment.

Results: CMD was diagnosed in 42 patients (35.9 %): 47.5 % in the COVID group and 24.1 % in the Control group ($p = 0.015$). The prevalence of structural CMD was significantly higher in the COVID group (28.8 % vs. 5.2 %, $p < 0.001$). The median IMR was significantly higher in the COVID versus the Control group (20.00 [15.00, 42.00] vs. 17.00 [12.00, 21.00], $p = 0.002$) while no significant differences were observed in CFR and FFR. The SAQ-7 summary scores (54.44 vs. 59.44, $p = 0.003$) and physical limitation and quality-of-life domain scores were all significantly lower in the COVID group.

Conclusions: The incidence of CMD, particularly structural CMD, was higher in ANOCA patients with a history of severe COVID-19 infection, suggesting a link between persistent angina and CMD in this population.

☆ This trial is registered at https://clinicaltrials.gov/study/NCT05841485.

* Corresponding author. Interventional Medicine and Innovation at the University of Galway, Ireland.Research Centre for Advanced Imaging and Core Lab (CORRIB) Research Centre, University Road, Galway, H91 TK33, Ireland.
E-mail address: patrick.serruys@universityofgalway.ie (P.W. Serruys).

[1] Both individuals contributed equally to this project and are considered co-first authors.

https://doi.org/10.1016/j.atherosclerosis.2025.120389
Received 30 March 2025; Received in revised form 13 May 2025; Accepted 30 May 2025
Available online 2 June 2025

1. Introduction

The post-acute sequelae of SARS-CoV-2 infection, otherwise known as “long COVID” syndrome or ‘Post COVID-19 condition’, as officially named by the World Health Organization, has been defined as the ‘continuation or development of new symptoms 3 months after the initial SARS-CoV-2 infection, with the symptoms lasting for at least 2 months with no other explanation’ [1]. Long COVID syndrome can affect up to 45 % of COVID survivors, especially those who require oxygen use during the disease course. These patients frequently report cardiovascular complaints, especially angina-like chest pain, the most common presentation [2,3].

The pathophysiological mechanisms underlying these cardiac symptoms however remain poorly understood, with hypotheses suggesting a complex interplay between the direct viral toxicity of SARS-CoV-2, genetic susceptibility, the patient’s immune and inflammatory response, and the patient’s own co-morbidities such as obesity, diabetes, and ischemic heart disease [4]. Microvascular thrombosis and/or endothelial dysfunction are among the most plausible pathophysiological processes [5]. It has also been reported that these patients exhibit significant capillary rarefication long after recovery from the infection [6]. Notably, there have been conflicting results from non-invasive imaging studies regarding the prevalence of coronary microvascular dysfunction (CMD) among patients with previously mild COVID-19 infection and those with severe COVID-19 infection history [7,8].

Thus, understanding the potential link between severe COVID-19 infection and CMD becomes crucial, especially since CMD is known to be strongly associated with adverse outcomes, such as persistent angina, heart failure, and mortality [9]. Invasive functional assessment with a pressure-temperature sensor wire is the most common modality to investigate coronary microvascular function and has been given a Class IB recommendation in relevant guidelines [10]. Furthermore, by investigating the indices of coronary physiology, such as the index of microvascular resistance (IMR) and coronary flow reserve (CFR), the endotypes of CMD can be elucidated [11].

In the Comparative Study of Microvascular Dysfunction in COVID-19 Survivors with Stable Angina COMET-19 study, we aimed to compare the incidence and endotypes of CMD in patients with angina without obstructive coronary artery disease (ANOCA) between those who had a history of severe COVID-19 infection versus those who didn’t.

2. Methods

2.1. Study design

The COMET-19 study was a multicentre, prospective cohort study which aimed to compare the prevalence of CMD in ANOCA patients between those who had a history of severe COVID-19 infection versus those who didn’t. The study was registered on clinicaltrial.gov [NCT05841485], and a detailed study protocol can be found in the Supplementary Material. The study was conducted at two university hospitals in the Republic of Lithuania: Klaipeda University Hospital and the Hospital of Lithuanian University of Health Sciences Kaunas Clinics.

Consecutive adult patients (aged 40–80 years) with a diagnosis of ANOCA, defined as patients presented with typical angina and have no coronary artery stenoses ≥50 % on quantitative coronary angiography. These patients underwent invasive testing to the left anterior descending artery (LAD) to assess the fractional flow reserve (FFR) and for the

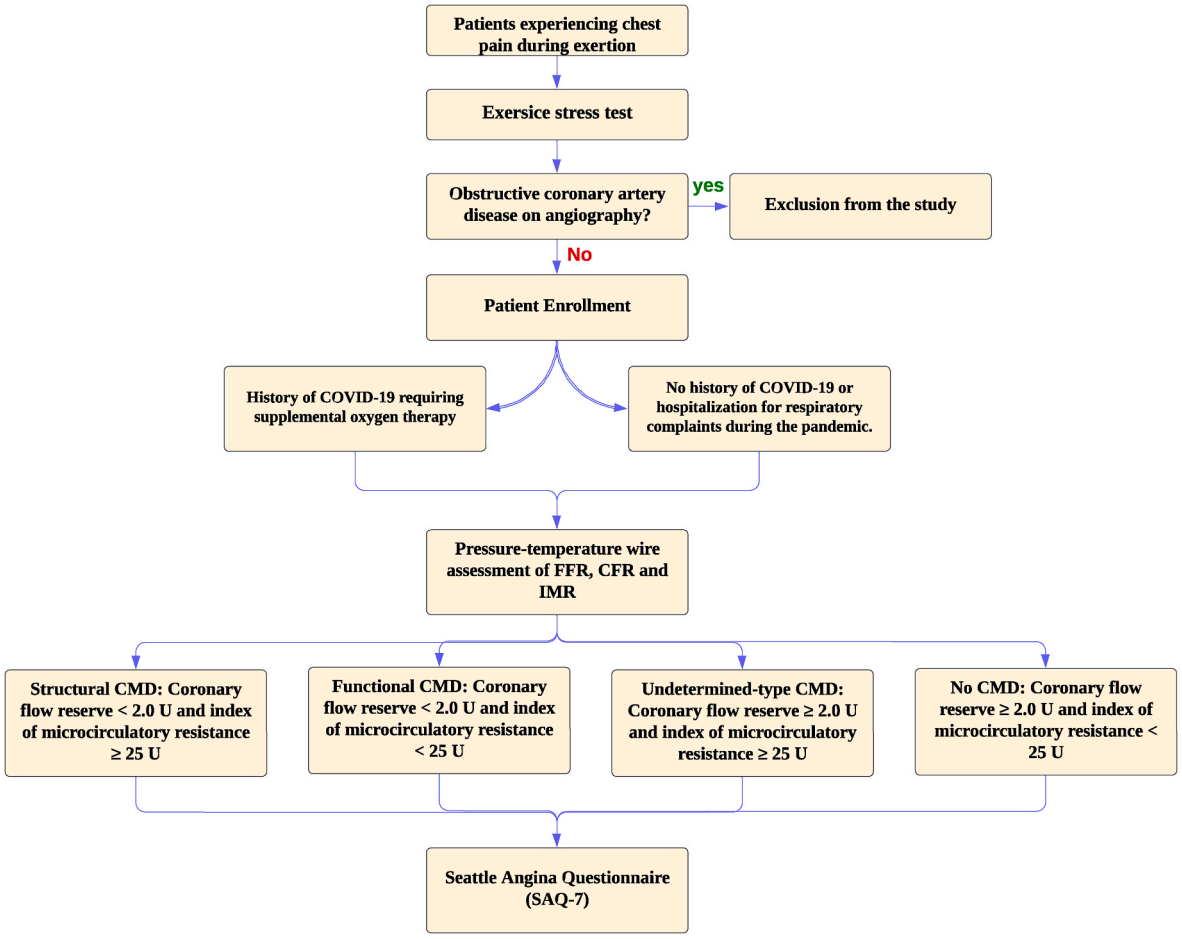

Fig. 1. Flowchart of patient enrollment and assessment process in the COMET-19 study.

presence or absence of CMD. Patients were stratified according to whether there was, or was not, a history of prior severe COVID-19 infection, defined as a positive polymerase chain reaction test for COVID-19 and the need for supplemental oxygen therapy due to a SpO2 < 90 % on room air whilst infected (Fig. 1). Patients with a history of severe COVID-19 infection were assigned to the COVID group, while those who never tested positive for COVID-19 via PCR and had no history of hospitalization for respiratory issues during the pandemic (from January 2020 until enrollment) were placed in the control group.

Patients were excluded if they presented with acute coronary syndromes (ACS), or if they had a history of myocardial infarction (MI), a left ventricular ejection fraction (LVEF) ≤40 %, obstructive coronary artery disease (CAD), or a history of coronary artery bypass graft surgery (CABG). Additional exclusion criteria included chronic kidney disease (eGFR <30 mL/min/1.73 m^2 at screening), active liver injury (aspartate aminotransferase or alanine aminotransferase levels >3 times the upper limit of normal at screening), significant valvular heart disease (defined as moderate or severe aortic or mitral valve stenosis or insufficiency), cardiomyopathy (e.g. hypertrophic cardiomyopathy), pregnancy or the use of chronic supplemental oxygen therapy prior to their diagnosis of COVID-19 (for COVID Group). Patients with physical limitations that prevented them from performing exercise stress testing (EST) were also excluded.

All patients completed the modified Seattle Angina Questionnaire (SAQ-7), underwent EST, and received an invasive coronary physiology assessment for CMD following the standardized protocols described below [12]. The clinicians performing the EST and physiology assessment were blinded to the patient's COVID-19 status, while the patients themselves were blinded to the results of their EST and physiology assessment.

2.2. Exercise stress testing

EST was conducted on the same day before the invasive physiology assessment, and followed the American College of Cardiology/American Heart Association (ACC/AHA) guidelines and the Bruce protocol [13,14]. A 12-lead ECG, heart rate, and blood pressure were recorded at regular intervals. The tests were supervised and evaluated by board-certified cardiologists, blinded to the patient's COVID-19 history. Exercise duration was timed from the start to the cessation of the protocol. Exercise-induced chest discomfort was documented when the patient reported chest tightness during exercise. Ischemic ECG changes were defined as ≥0.1-mV horizontal or down-sloping ST-segment depression 80 ms from the J-point (CardioSoft® v6.7 Diagnostic System, GE Healthcare, Illinois, U.S.A). Patients who developed ischemic ECG changes were classified as having a positive EST. Patients who did not develop ischemic ECG changes after reaching their target heart rate were classified as having a negative EST, while those who did not develop ischemic ECG changes but did not reach the target heart rate were classified as inconclusive.

2.3. Coronary physiology assessment

Coronary physiology assessments were conducted after confirming the absence of obstructive coronary artery disease with quantitative coronary angiography, thereby confirming the status of ANOCA. The Pressure Wire X (Abbott Vascular, Santa Clara, CA, USA) and the CoroFlow system (Coroventis Research AB, Uppsala, Sweden) were utilized for invasive functional assessments. FFR, CFR, and the IMR were measured for the left anterior descending artery (LAD) of all patients using the standard bolus thermodilution technique [15,16]. Due to institutional protocol regulation, Acetylcholine flow reserve (AChFR) was not performed in the current study. Coronary physiology assessments were conducted following an initial intracoronary nitroglycerin (100 or 200 μg) injection. The calibrated pressure wire was then positioned in the distal two-thirds of the LAD. Resting mean transit time (Tmn) was determined as the average of measurements obtained after three injections of 3 mL saline solution into the coronary artery. The measurement of distal coronary pressure and Tmn were repeated under steady state hyperemia, induced by continuous intravenous infusion of adenosine (140 μg/kg/min). The normal ranges for the measurements were FFR ≥0.80, CFR ≥2.0, and IMR <25 units [17].

2.4. Modified Seattle Angina questionnaire

After completing the EST and CMD assessment, all patients were asked to fill out the short version of the SAQ (SAQ-7), assisted by the trained study nurse. The SAQ-7 consists of seven questions divided into three domains: quality of life, physical limitation, and angina frequency [12,18]. The score of each domain, as well as the summary score, were calculated.

2.5. Study endpoints

The study's primary endpoint was the incidence of CMD, defined as a CFR<2.0 or IMR≥25 according to the European Society of Cardiology (ESC), the ACC/AHA guidelines and the European Association of PCI (EAPCI) definition [15,19,20]. Secondary endpoints included the severity of CMD in both groups, as indicated by CFR and IMR values. The prevalence of CMD endotypes (structural, functional, undetermined) was also investigated in both groups. Functional CMD was defined as CFR<2.0 in combination with IMR<25, structural CMD as CFR<2.0 with IMR≥25, and undetermined CMD as CFR>2.0 with IMR≥25 [9,11].

As a sensitivity analysis, CMD was also defined using a CFR<2.5, regardless of IMR, as per the British Heart Foundation (BHF)/National Institute for Health Research (NIHR) [21]. Functional CMD was defined as CFR<2.5 in combination with IMR<25, and structural CMD was defined as CFR<2.5 with IMR≥25. The correlation between COVID status and EST results, as well as anginal status as assessed by SAQ-7, were investigated.

2.6. Statistical analysis and sample size calculation

The detailed sample size calculation is described in the study protocol **(Supplemental material)**. In brief, to detect a difference of 15 % vs. 45 % [8,22] prevalence of CMD in ANOCA patients without vs. with a history of severe COVID-19 infection with a power of 90 % and a two-sided alpha of 0.05, a total of 94 patients (47 per study arm) were required. Additionally, assuming that the proportion of structural CMD is 36.7 % among those with CMD in the control group, the estimated prevalence of structural CMD in this group would be 5.5 % [9]. In contrast, we assume the proportion of structural CMD among patients with CMD in the COVID-19 group to be 50 %. Hence, the prevalence of structural CMD in this group would be 22.5 %. Therefore, to detect a difference in structural CMD prevalence of 5.5 % versus 22.5 % with 80 % power and a two-sided alpha of 0.05, a total of 116 patients would be required.

Shapiro-Wilk test was used to assess the distribution of continuous variables, which were expressed as mean ± standard deviation (SD) or as median with interquartile range as appropriate. Categorical variables were expressed as frequencies and percentages. The comparison between the COVID-19 and non-COVID-19 groups was performed using unpaired Student's T-test, Mann-Whitney *U* test, chi-square test, and Fisher's exact test as appropriate. To account for the possible interference of prior PCI, a sensitivity analysis excluding the patients with prior PCI history was conducted. The correlation between physiological indices, including FFR, CFR, and IMR, and COVID-19 severity parameters, including duration of symptoms and duration of oxygen therapy, were evaluated using the Spearman correlation coefficient. A two-sided p-value of <0.05 was considered statistically significant for all tests. Statistical analyses were performed using R statistical software (R

Foundation for Statistical Computing, Vienna, Austria)

2.7. Ethics approval and consent to participate

The study was carried out in accordance with the Declaration of Helsinki, and the study protocol received ethical approval from the Kaunas and Klaipeda Regional Biomedical Research Ethics Committees (Republic of Lithuania, nr: BE-3-7). All participants or their legal representatives provided written informed consent prior to the study.

3. Results

3.1. Study population

From June 2023 to June 2024, the study enrolled a total of 117 ANOCA patients, consisting of 59 patients in the COVID-19 group and 58 in the control group (Fig. 1). The mean patient age was 65.95 ± 11.43 years old, with well-balanced demographics (age, sex, height, and weight), clinical histories (arterial hypertension, diabetes, etc.), as well as baseline hemodynamic and laboratory data (Tables 1 and 2). The analysis of quantitative coronary angiography also showed similar diameter stenosis between the two groups in all three major coronary arteries (Table 3). In the COVID-19 group, 3 patients (5.1 %) had recovered from the infection less than 6 months prior, 17 patients (28.8 %) between 6 and 12 months, and 39 patients (66.1 %) more than 12 months ago. The median duration of COVID-19 symptoms was 14 [9.00, 18.00] days, and the median duration of oxygen therapy was 6 [4.00, 7.00] days. During the COVID disease course, 5 (8.5 %) patients required inotropic agent and 4 (6.8 %) required mechanical ventilation support.

3.2. COVID-19 status and coronary microvascular dysfunction

Among the 117 patients, 42 (35.9 %) were diagnosed with CMD, which consisted of 20 (17.09 %) structural CMD, 15 (12.8 %) functional CMD, and 7 (6.0 %) undetermined CMD. The prevalence of CMD was higher in the COVID-19 group than the control group (28 [47.5 %] vs. 14 [24.1 %], $p = 0.015$, Fig. 2a and Table 3). Interestingly, all patients who required mechanical ventilation during their COVID infection had CMD. Although the number of patients was too small for statistical significance, patients with less than 6 months after their COVID recovery appear to have a higher prevalence of CMD (Supplemental Fig. 1). In the sensitivity analysis using the BHF/NIHR definition of CMD (CFR<2.5), the prevalence of CMD was nearly identical between the two groups (25 [42.4 %] vs. 24 [41.4 %], p = 1.00, Supplemental Fig. 2A), contradicting the findings using the EAPCI definition of CMD [21].

Regardless of the definition, the distribution of CMD endotypes was significantly different between the two groups, with structural CMD being more prevalent in the COVID group (17 [28.8 %] vs. 3 [5.2 %]) and functional CMD more prevalent in the non-COVID group (11 [19.0 %] vs 4 [6.8 %], Fig. 2B). This relationship was also true in the sensitivity analysis, with structural CMD being more prevalent in the COVID group (19 [32.2 %] vs. 3 [5.2 %]) and functional CMD more prevalent in the non-COVID group (21 [36.2 %] vs 6 [10.2 %], Supplemental Fig. 2B). In another sensitivity analysis excluding patients with prior PCI history (n = 14), the results remain similar to the entire cohort (Supplemental Fig. 3).

3.3. COVID-19 status and coronary physiology indices

The coronary physiology results are presented in Table 3. The median FFR was 0.89 [0.86, 0.95], with no patients having an FFR ≤0.80. There was no significant difference in FFR (0.89 [0.84, 0.96] vs. 0.90 [0.87, 0.95]; $p = 0.327$) and CFR (2.74 [1.75, 2.94] vs. 2.68 [2.14, 2.90]; $p = 0.540$, Fig. 3A and B) between the groups. However, the COVID-19 group had a bimodal distribution of CFR values, with a second peak at a

Table 1
Characteristics of Angina with Non-Obstructive Coronary Arteries patients classified by COVID-19 status.

Characteristic	Overall (n = 117)	Control Group (n = 58)	COVID-19 Group (n = 59)	*P*-value
Female Sex, n (%)	56 (47.9 %)	30 (51.7 %)	26 (44.1 %)	0.520
Age±SD, years	65.95 ± 11.43	66.21 ± 12	65.69 ± 10.93	0.810
Weight [Q1, Q3],kg	80.00 [72.00, 87.00]	77.50 [69.25, 86.5]	81.00 [74.00, 87.00]	0.103
Height [Q1, Q3], meter	1.71 [1.64, 1.77]	1.71 [1.62, 1.77]	1.71 [1.66, 1.77]	0.329
Body Mass Index [Q1, Q3], kg/m^2	26.83 [25.15, 29.41]	26.41 [24.97, 29.63]	27.1 [25.48, 29.41]	0.324
Arterial hypertension, n (%)	64 (54.7 %)	32 (55.2 %)	32 (54.2 %)	1
History of PCI, n (%)	14 (12.0 %)	5 (8.6 %)	9 (15.3 %)	0.419
History of stroke, n (%)	8 (6.8 %)	2 (3.5 %)	6 (10.2 %)	0.272
History of diabetes mellitus, n (%)	22 (18.8 %)	9 (15.5 %)	13 (22.0 %)	0.506
History of dyslipidemia, n (%)	71 (60.7 %)	32 (55.2 %)	39 (66.1 %)	0.307
Smoker (former/current), n (%)	62 (53.0 %)	31 (53.5 %)	31 (52.5 %)	1
History of alcohol abuse, n (%)	7 (6.0 %)	1 (1.7 %)	6 (10.2 %)	0.114
Time since COVID recovery				<0.001
Less than 6 months, n (%)	3 (2.6 %)	NA	3 (5.1 %)	
6–12 months, n (%)	17 (14.5 %)	NA	17 (28.8 %)	
Over 12 months, n (%)	39 (33.3 %)	NA	39 (66.1 %)	
Use of inotrope during COVID infection	4 (3.4 %)	NA	4 (6.8 %)	
Use of mechanical ventilation during COVID infection	5 (4.3 %)	NA	5 (8.5 %)	
CCS				0.364
I, n (%)	28 (23.9 %)	13 (22.4 %)	15 (25.4 %)	
II, n (%)	65 (55.6 %)	30 (51.7 %)	35 (59.3 %)	
III, n (%)	24 (20.5 %)	15 (25.9 %)	9 (15.3 %)	
IV, n (%)	0 (0.0 %)	0 (0.0 %)	0 (0.0 %)	
On Admission Medication				
Beta-blockers, n (%)	48 (41.0 %)	25 (43.1 %)	23 (39.0 %)	0.791
ACEi/ARB, n (%)	55 (47.0 %)	28 (48.3 %)	27 (45.8 %)	0.931
Calcium channel blocker, n (%)	49 (41.9 %)	23 (39.7 %)	26 (44.1 %)	0.767
Mineralocorticoid receptor antagonist, n (%)	5 (4.3 %)	2 (3.5 %)	3 (5.1 %)	1
Statin, n (%)	73 (62.4 %)	33 (56.9 %)	40 (67.8 %)	0.305
Aspirin, n (%)	51 (43.6 %)	20 (34.5 %)	31 (52.5 %)	0.075
Trimetazidine, n (%)	52 (44.4 %)	26 (44.8 %)	26 (44.1 %)	1
Ranolazine, n (%)	29 (24.8 %)	12 (20.7 %)	17 (28.8 %)	0.422
Ivabradine, n (%)	11 (9.4 %)	7 (12.1 %)	4 (6.8 %)	0.362
Nitrates, n (%)	22 (18.8 %)	11 (19.0 %)	11 (18.6 %)	1

Values are presented as n (%) for categorical variables, and as mean ± standard deviation (SD) or median [1st quartile, 3rd quartile] for numeric variables. PCI = Percutaneous Coronary Intervention; CCS = Canadian Cardiovascular Society grading of angina pectoris.

Table 2
Baseline Hemodynamic, Laboratory, and echocardiographic parameters of patients Angina with Non-Obstructive Coronary Arteries, categorized by COVID-19 status.

Parameters	Overall (n = 117)	Control Group (n = 58)	COVID-19 Group (n = 59)	*P*-value
Resting Heart rate ±SD, beats per minutes	69.1 ± 8.63	69.45 ± 8.75	68.76 ± 8.58	0.670
Resting aortic pressure [Q1, Q3], mmHg	84 [74, 92]	85.5 [74, 95]	81 [74.5, 88.5]	0.341
Hemoglobin ±SD,g/l	135.51 ± 18.99	134.21 ± 19.87	136.80 ± 18.16	0.463
Red Cell Distribution Width [Q1, Q3],%	13.60 [13.10, 14.40]	13.65 [13.12, 14.88]	13.60 [13.10, 14.10]	0.262
White Blood Cell Count [Q1, Q3],10^9/l	8.94 [7.59, 11.25]	9.18 [7.85, 11.36]	8.63 [7.59, 11.10]	0.273
Neutrophils [Q1, Q3],10^9/l	6.98 [5.20, 8.75]	7.16 [5.28, 8.61]	6.46 [5.24, 8.82]	0.641
Lymphocytes [Q1, Q3],10^9/l	1.90 [1.27, 2.73]	1.84 [1.25, 2.56]	2.10 [1.27, 3.00]	0.204
Neutrophil/ Lymphocyte Ratio [Q1, Q3]	3.63 [2.19, 5.49]	3.80 [2.36, 6.04]	3.57 [2.08, 5.06]	0.291
Platelets [Q1, Q3],10^9/l	241.00 [200.00, 264.00]	246.00 [219.00, 273.00]	217.00 [194.00, 264.00]	0.076
International normalized ratio±SD	1.09 ± 0.17	1.11 ± 0.19	1.07 ± 0.15	0.234
Potassium ±SD, mmol/L	4.17 ± 0.65	4.28 ± 0.58	4.08 ± 0.69	0.125
Glucose [Q1, Q3], mmol/L	6.12 [5.14, 6.89]	6.06 [5.14, 6.92]	6.14 [5.14, 6.9]	0.952
Hs-CRP [Q1, Q3], mg/L	3.55 [2, 6.34]	3.55 [1.83, 6.44]	3.55 [2.18, 6.3]	0.946
Creatinine Clearance [Q1, Q3], mL/min)	46.10 [38.70, 54.70]	45.35 [38.78, 53.32]	47.1 [38.35, 57.2]	0.874
Left ventricular ejection fraction [Q1, Q3], %	55.00 [51.00, 55.00]	55.00 [52.25, 56.00]	55.00 [50.50, 55.00]	0.264

Values are presented as mean ± standard deviation (SD) or median [1st quartile, 3rd quartile] for continuous variables. Hs-CRP = Hight sensitivity C-reactive protein.

Table 3
Quantitative coronary angioraphy, coronary physiology parameters and interpretations in patients with angina and non-obstructive coronary arteries, categorized by COVID-19 status.

Parameters	Overall (n = 117)	Control Group (n = 58)	COVID-19 Group (n = 59)	*P*-value
RCA Quantitative Coronary Angiography				*0.750*
diameter stenosis <30 %, n (%)	*103(88.0 %)*	*50(86.2 %)*	*53(89.8 %)*	
diameter stenosis 30 % ~50 %, n (%)	*14(12 %)*	*8(13.8 %)*	*6(10.2 %)*	
diameter stenosis ≥50 %, n (%)	*0(0.0 %)*	*0(0.0 %)*	*0(0.0 %)*	
LAD Quantitative Coronary Angiography				*1*
diameter stenosis <30 %, n (%)	*96(82.1 %)*	*48(82.8 %)*	*48(81.4 %)*	
diameter stenosis 30 % ~50 %, n (%)	*21(17.9 %)*	*10(17.2 %)*	*11(18.6 %)*	
diameter stenosis ≥50 %, n (%)	*0(0.0 %)*	*0(0.0 %)*	*0(0.0 %)*	
LCX Quantitative Coronary Angiography				*1*
diameter stenosis <30 %, n (%)	*96(82.1 %)*	*48(82.8 %)*	*48(81.4 %)*	
diameter stenosis 30 % ~50 %, n (%)	*21(17.9 %)*	*10(17.2 %)*	*11(18.6 %)*	
diameter stenosis ≥50 %, n (%)	*0(0.0 %)*	*0(0.0 %)*	*0(0.0 %)*	
Coronary physiology				
Coronary flow reserve [Q1, Q3]	2.71 [1.95, 2.94]	2.68 [2.14, 2.90]	2.74 [1.75, 2.94]	0.540
Fractional flow reserve [Q1, Q3],	0.89 [0.86, 0.95]	0.90 [0.87, 0.95]	0.89 [0.84, 0.96]	0.327
Index of microvascular resistance [Q1, Q3]	19.00 [14.00, 24.00]	17.00 [12.00, 21.00]	20.00 [15.00, 42.00]	0.003
Coronary microvascular dysfunction and its endotypes				
Coronary microvascular dysfunction, n (%)	42 (35.9 %)	14 (24.1 %)	28 (47.5 %)	0.015
Coronary microvascular dysfunction endotypes				<0.001
Structural, n (%)	20 (17.1 %)	3 (5.2 %)	17 (28.8 %)	
Functional, n (%)	15 (12.8 %)	11 (19.0 %)	4 (6.8 %)	
Undetermined, n (%)	7 (6.0 %)	7 (6.0 %)	7 (11.9 %)	

Values are presented as n (%) for categorical variables, and as median [1st quartile, 3rd quartile] for numeric variables.

CFR of approximately 1.6 (Fig. 3). A Shapiro-Wilk test for normality confirmed a non-normal distribution (p-value = 0.0251) of CFR in the COVID group. In comparison, the control group had normally distributed CFR values by the Shapiro-Wilk test (p-value = 0.2214). Furthermore, the COVID group had a significantly higher IMR than the control group (17.00 [12.00, 21.00] vs. 20.00 [15.00, 42.00]; p = 0.002, Fig. 3C).

There was no significant association between physiological indices, i.e., FFR, CFR and IMR and the duration of COVID-19 symptoms or the duration of oxygen therapy (Supplemental Fig. 4).

3.4. COVID-19 status and anginal symptoms

The results of SAQ-7 are presented in Table 4. The mean SAQ-7 summary score was significantly lower in the COVID group than in the control group (62.5 [48.06, 70.42] vs. 68.89 [57.01, 72.5]; p = 0.003, Fig. 4A). Among the domain scores, the angina frequency scores trended to be lower in the COVID group (70.00 [60.00, 80.00] vs. 70.00 [70.00, 80.00]; p = 0.056, Fig. 4B), whilst physical limitation scores, which implies the functional status of the patients and the quality-of-life scores were significantly lower in the COVID group (Fig. 4C and D).

FFR was weakly associated with the SAQ summary score (r = 0.20, p = 0.033) and SAQ angina frequency score (r = 0.24, p = 0.009) and not associated with the SAQ physical limitation score (r = 0.11, p = 0.248) or the SAQ quality of life score (r = 0.16, p = 0.079). However, CFR and IMR were both significantly associated with the SAQ summary score (p < 0.001), and all the domain scores (p < 0.05 for all, Supplemental Fig. 5).

In comparison, the duration of COVID-19 symptoms and oxygen use were not related to the SAQ summary score, angina frequency score, physical limitation score, and quality of life score, as shown in Supplemental Fig. 6.

3.5. COVID-19 status and exercise test results

The ESTs were positive in 19 (32.2 %) and 10 (17.2 %) patients in the COVID and control groups (p = 0.056), respectively (Supplemental Table 1). Additionally, the prevalence of exercise-induced chest discomfort was 21 (35.6 %) and 4 (6.9 %), p < 0.001) respectively. The distribution of significant ST changes and T wave inversion during EST was also numerically higher in the COVID group. Interestingly, twenty-

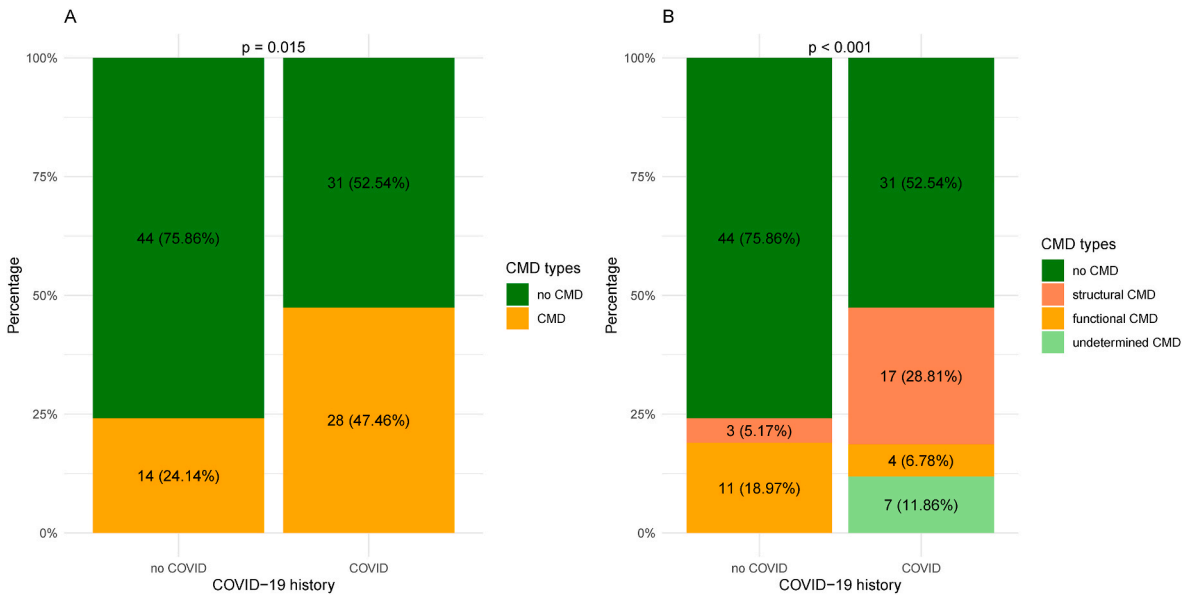

Fig. 2. Prevalence of CMD and CMD Endotypes in ANOCA patients with and without a history of severe COVID-19 (Defined According to EAPCI Criteria). Panel A shows the incidence of CMD while Panel B shows the CMD endotypes. CMD = coronary microvascular dysfunction, ANOCA = angina without obstructive coronary artery disease.

eight patients (96.6 %) with ischemic ECG changes had CMD. None of the seven (28.0 %) patients with chest pain without ischemic ECG changes had CMD, five of these patients were in the COVID group (Fig. 5).

4. Discussion

This prospective cohort study compared the prevalence of CMD in patients with ANOCA between those with, versus without, a history of severe COVID-19 infection. The main findings of the study are (Fig. 6).

1. The prevalence of CMD was significantly higher in the patients with a history of severe COVID-19, with the majority exhibiting structural CMD, while functional CMD was more common in those without a history of COVID-19.
2. While all patients reported similar anginal frequencies, those with a history of severe COVID-19 reported worse physical limitation and poorer quality of life with overall lower SAQ-7 scores.
3. There was a numerically higher incidence of positive EST and exercise-induced chest discomfort in those with a history of severe COVID-19, highlighting a potential link between COVID-19 and increased susceptibility to myocardial ischemia.

Collectively, these findings underscore the enduring and multifaceted impact of COVID-19 on coronary microvascular function, anginal symptoms, and potentially myocardial ischemia, highlighting the need for targeted management strategies in this patient population.

4.1. Prevalence of coronary microvascular dysfunction in patients with severe COVID infection history

In this cohort, patients with a history of severe COVID-19 infection exhibit a higher prevalence of CMD compared to controls, however, this difference was no longer seen when using the more lenient BHF/NIHR criteria of a CFR<2.5, irrespective of IMR values. This is largely attributed to the 12 patients with a CFR between 2.0 and 2.5 and a normal IMR —distributed as 10 in the control group and 2 in the COVID-19 group. A closer examination of the distribution of CFR values shows that the COVID-19 group included a subset of patients with a markedly low CFR, peaking at approximately 1.6, which is well below the established CFR cutoffs; notably, this subset was absent in the control group. Data cited by the BHF/NIHR guidelines indicate that a CFR <2.5 has only a mediocre specificity of 0.65 for CMD, with a much higher sensitivity of 0.95 [23]. More recent studies show that a CFR <2.0 is more specific for CMD than a CFR <2.5 (91.19 % vs 81.25 %), however it is less sensitive (57.61 % vs 75.54 %) for predicting a Doppler-based CFR<2.5 [24]. Thus, the varying results we observed may reflect differences in the diagnostic characteristics of the two criteria. Interestingly, the higher prevalence of around 40 % reported using the BHF criteria, corroborated better with the prevalence observed in studies using non-invasive ischemia tests (e.g, stress positron emission tomography (PET)) [25]. Furthermore, Rahman et al. have shown that patients having a CFR within the grey zone (i.e., 2.0–2.5) are physiologically indistinguishable from those with a CFR <2.0 [26]. Additionally, Demir et al. demonstrated that when compared with Doppler-derived CFR, the optimal thermodilution-derived CFR threshold for CMD was <2.5 [24]. However, to the best of our knowledge, there has been no direct comparison between the BHF/NIHR cut-off of CFR<2.5 and the EAPCI/AHA cut-off of CFR<2.0 or IMR≥25 in diagnosing CMD or predicting clinical prognosis. Therefore, our study presents the outcomes based on both sets of criteria. To eliminate confusion, the diagnostic threshold should be standardised, preferably using more reproducible parameters such as microvascular resistance reserve [27].

Despite these differences in the rates of CMD according to different diagnostic criteria, the prevalence of structural CMD was significantly higher in COVID-19 patients. This was primarily due to their elevated IMR, which ultimately did not correlate with the severity of their COVID-19 infection, as neither the total reported symptoms duration nor the total days of oxygen use were associated with IMR. Notwithstanding this, the duration of oxygen therapy and symptomatology are less objective markers than the clinical definition of severe COVID-19, which was based on an SpO2< 90 % on room air.

The prevalence of CMD in patients previously infected with COVID-19 has been previously investigated with studies using non-invasive imaging with PET and magnetic resonance imaging (MRI) yielding conflicting results. For example, Ahmed et al. reported that patients with prior COVID-19 infection exhibited poorer microvascular function and a higher rate of clinical events [8]. On the contrary, Karagodin et al. [7] observed that myocardial perfusion at rest or during stress, and therefore microvascular function, was comparable between patients

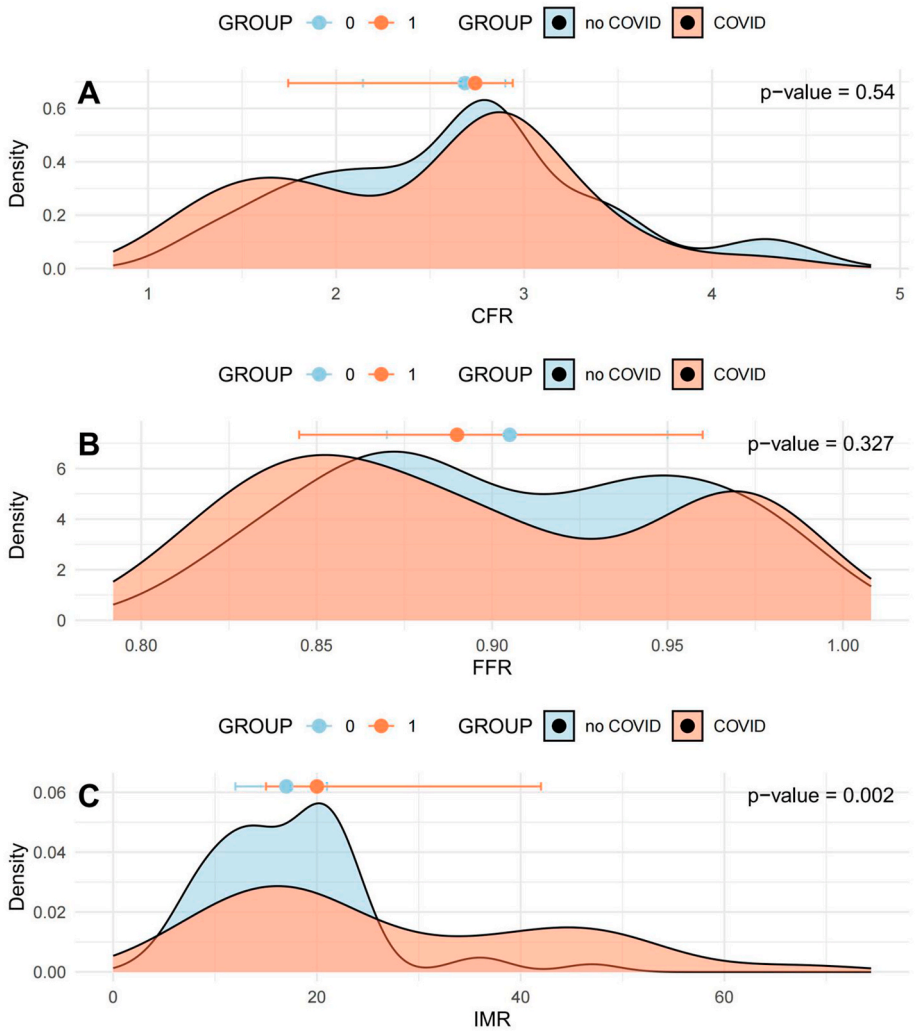

Fig. 3. Density Plots of Coronary Flow Reserve (CFR), Fractional Flow Reserve (FFR), and Index of Microvascular Resistance (IMR) in ANOCA patients with and without a history of severe COVID-19.

with-versus without prior mild COVID-19 history [7]. However, none of these studies elucidated the different endotypes and potential pathophysiological differences between COVID-19 and non-COVID-19 CMD. To our knowledge, the current study is the first to not only highlight these differences in CMD using invasive measurements, but also the first to detail the differences in coronary physiological indices and CMD endotypes between groups.

4.2. Pathophysiology of coronary microvascular dysfunction in patients with severe COVID infection history

The higher incidence of CMD following severe COVID-19 infection may be attributable to two major pathophysiological mechanisms, namely, endothelial dysfunction and microvascular thrombosis. Several studies have shown that other systemic viral infections, such as influenza, also share similar pathophysiological mechanisms [28]. However, although both COVID-19 and influenza are strongly associated with elevated myocardial infarction risk, the prevalence of CMD after influenza infection has not yet been reported [29,30]. Histopathological studies have demonstrated that SARS-CoV-2 viral particles can infiltrate and damage the vascular endothelium in organs like the kidney, lungs, and heart [31–33]. This resultant endothelial damage further initiates the prothrombotic pathways, evidenced by the elevated P-selectin and von Willebrand Factor levels in COVID-19 patients [34]. This hypercoagulable state leads to microvascular thrombosis, impaired capillary function, and eventually, microvascular dysfunction [35]. Moreover, severe COVID-19 infection can trigger cytokine storms, exacerbating the susceptibility and damage to the endothelium. These interwoven pathways contribute to CMD, supported by associations between coronary flow velocity reserve and biomarkers of fibrin turnover and inflammation [36]. It is hypothesized that these acute changes irreversibly damage the microcirculation, contributing to the high prevalence of CMD observed in COVID survivors. While early intervention with anticoagulants or anti-inflammatory agents may mitigate some effects, more research is needed to explore these treatments and their potential to reduce the incidence of CMD after COVID-19 infection.

In the current study, structural CMD, which encompasses alterations within the coronary microvasculature, such as arteriolar blockage, microvascular obstruction, and capillary depletion, predominated in COVID-19 patients [37]. Osiaevi et al. reported a significant decrease in vascular density that exclusively affected very small capillaries in long COVID syndrome patients as compared with healthy controls [6]. Autopsies have shown thrombi rich in fibrin, platelets, and leukocytes in the coronary microcirculation in 10–20 % of COVID-19 deaths [38,39]. A pathology study found intracoronary microthrombi in 35 % of COVID-19 deaths with myocardial necrosis, regardless of the presence of pre-existing coronary artery disease [40]. Analysis of thrombi retrieved from thrombo-aspiration in COVID-19 patients with ST-elevation myocardial infarction showed fibrin, leukocytes, a high density of neutrophil extracellular traps (NETs) and no plaque fragments [41].

Table 4
Modified Seattle Angina questionnaire responses and physical activity levels in patients with angina and non-obstructive coronary arteries, categorized by COVID-19 status.

Parameters	Overall (n = 117)	Control Group (n = 58)	COVID-19 Group (n = 59)	*P*-value
Modified Seattle Angina Questionnaire				
SAQ-7 (Question 1) [Q1, Q3]	4 [4, 5]	4 [4, 5]	4 [3, 4.5]	0.003
SAQ-7 (Question 2) [Q1, Q3]	4 [3, 4]	4 [4, 4]	4 [3, 4]	0.001
SAQ-7 (Question 3) [Q1, Q3]	4 [3, 4]	4 [3, 4]	3 [3, 4]	0.401
SAQ-7 (Question 4) [Q1, Q3]	4 [3, 4]	4 [3, 4]	3 [3, 4]	0.001
SAQ-7 (Question 5) [Q1, Q3]	6 [5, 6]	6 [5, 6]	6 [5, 6]	0.722
SAQ-7 (Question 6) [Q1, Q3]	5 [3, 5]	5 [3.25, 5]	4 [3, 5]	0.014
SAQ-7 (Question 7) [Q1, Q3]	2 [1, 2]	2 [1, 2]	2 [1, 2]	0.296
Modified Seattle Angina Questionnaire domain scores				
Angina Frequency [Q1, Q3]	70.00 [70.00, 80.00]	70.00 [70.00, 80.00]	70.00 [60.00, 80.00]	0.056
Physical limitation [Q1, Q3]	75.00 [58.33, 83.33]	75.00 [66.67, 83.33]	66.67 [50.00, 75.00]	0.002
Life Quality [Q1, Q3]	50.00 [25.00, 62.50]	62.5 [37.50, 62.50]	50.00 [25.00, 62.50]	0.023
***Modified Seattle Angina Questionnaire* summary score** [Q1, Q3]	65.00 [52.50, 71.94]	68.89 [57.01, 72.50]	62.50 [48.06, 70.42]	0.003

Values are presented as median [1st quartile, 3rd quartile] for numeric variables.

These findings suggest that micro-thromboembolisms and inflammation irreversibly damage the coronary microvasculature, leading to a high prevalence of structural CMD and contributing to long COVID syndrome. With the pathophysiological insights from these studies and the findings of our cohort, the logical next step is to investigate whether patients with COVID-19 history may also benefit from targeted medical treatments, as demonstrated in the CORonary MICrovascular Angina

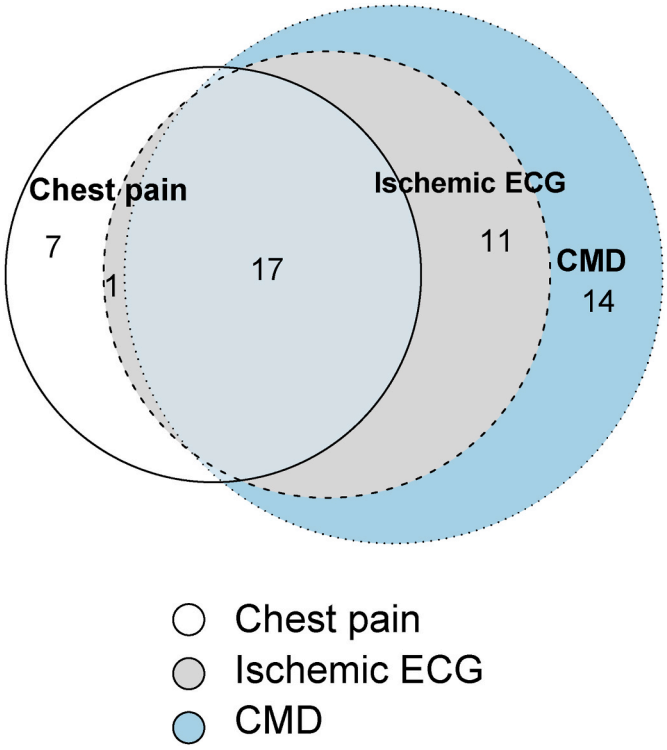

Fig. 5. Venn Diagram of Chest Pain, Ischemic ECG, and Coronary Microvascular Dysfunction in ANOCA patients.

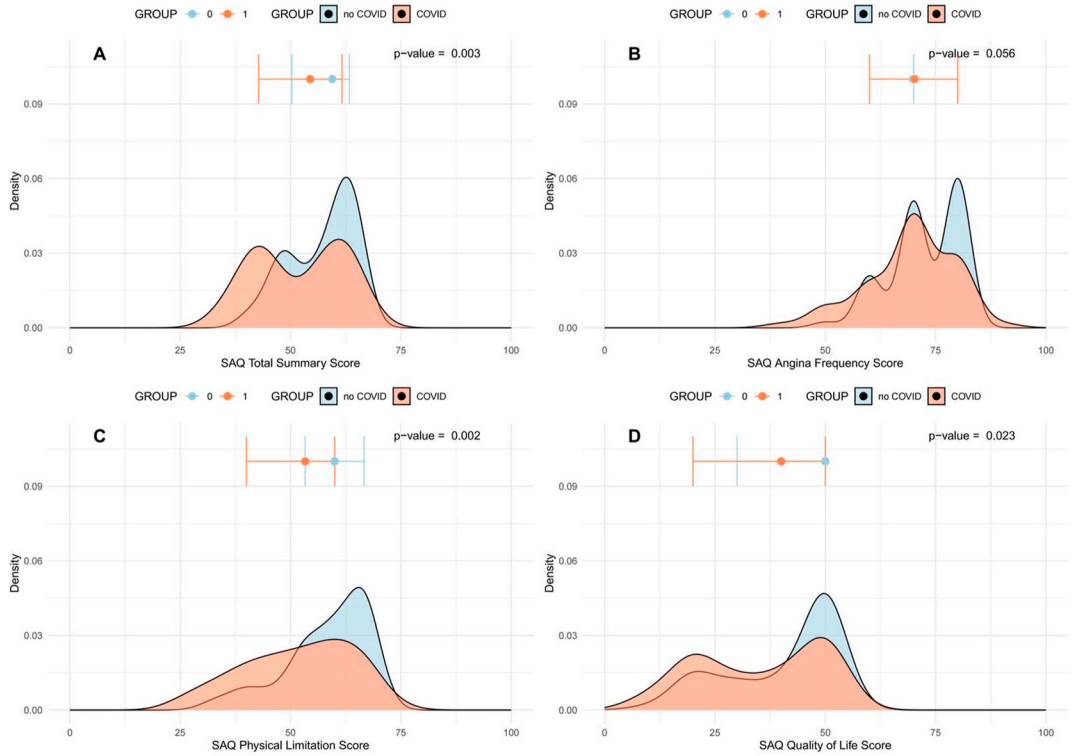

Fig. 4. Density Plots of Seattle Angina Questionnaire (SAQ) Scores in ANOCA patients with and without a history of severe COVID-19.

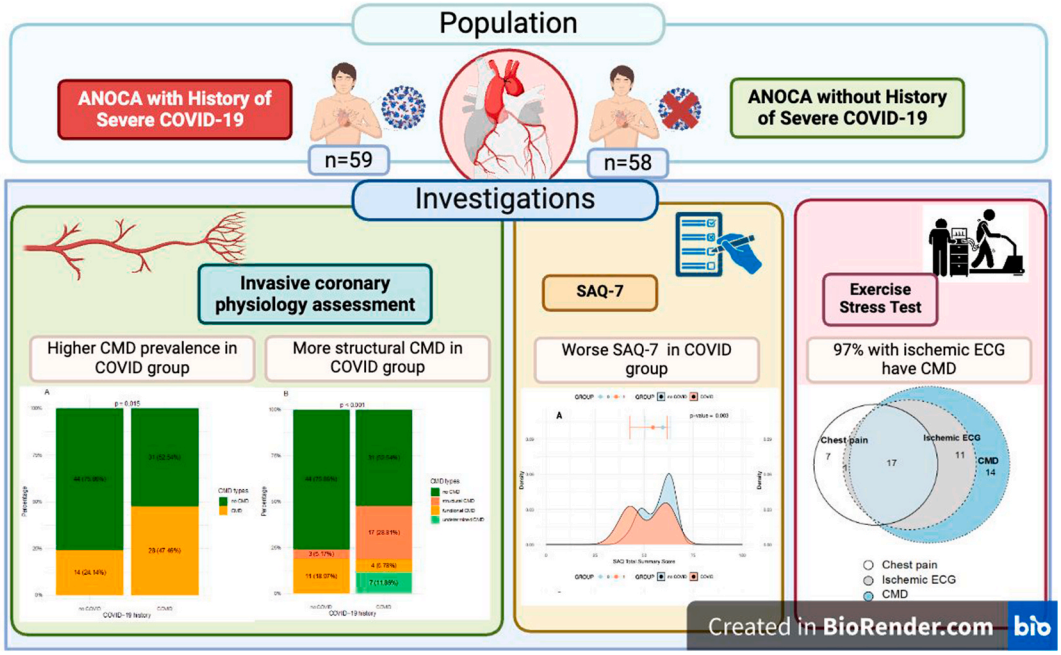

Fig. 6. Graphical abstract summarizing the main results of the study.

(CorMicA) trial [17,19].

4.3. Impact of severe COVID-19 infection on quality of life

The impact of severe COVID-19 on quality of life, especially in patients who developed long COVID syndrome, is profound and multifaceted. The OpenSAFELY study utilized patient-reported outcome measures (OpenPROMPT) to underline the substantial impact of long COVID, with symptoms reported in nearly a quarter of the 6070 participants [42]. Furthermore, these patients had 4.7 times higher odds of reduced health-related quality of life (HRQoL), quantified as a 0.37 loss in Quality-Adjusted Life Months (QALMs). The most significant predictor of HRQoL loss was disabilities related to physical activity. These patients also reported lower EQ-5D scores (mean 0.49) compared to those without long COVID (mean 0.71), a difference exceeding the minimally important difference of 0.063. This impact was worse than in patients with chronic conditions such as heart failure (mean 0.60), multiple sclerosis (mean 0.59), and end-stage renal disease (mean 0.68).

The baseline characteristics of patients in the Enhanced External Counterpulsation (EECP) study further illustrates the demographic and clinical profiles of long COVID patients [43]. This cohort had a mean age of 53.81 years, with high PROMIS Fatigue scores (mean 24.0 out of 52), indicating severe fatigue. SAQ scores showed considerable impairment in physical limitation (mean 44.1 out of 100) and quality of life (mean 40.3 out of 100). The Duke Activity Status Index (DASI) and 6-Minute Walk Test also reflected a severe impact on physical health. The COMET-19 study further highlighted these issues, showing that among ANOCA patients having comparable underlying disease, those with severe COVID-19 history had significantly lower SAQ-7 scores (median 62.50) compared to controls (median 68.89), underscoring the lasting reductions in quality of life due to persistent cardiovascular symptoms. These findings are consistent with the OpenPROMPT and EECP studies, emphasizing the profound and lasting impact of severe COVID-19 infection.

4.4. The impact of severe COVID-19 infection on myocardial ischemia

In the current study, positive EST test and ischemic ECG changes during EST were numerically more prevalent in COVID-19 patients, while exercise-induced chest discomfort was significantly more prevalent, indicating these patients might not only have a significantly higher incidence of CMD but also a higher incidence of myocardial ischemia. Sinha et al. showed that ischemic ECG changes are highly specific for an underlying ischemic substrate. There were no false positive results for ischemic ECG changes among ANOCA population, as all of them exhibited either endothelium-independent or endothelium-dependent microvascular dysfunction. Endothelium-independent dysfunction was characterized by an abnormal CFR, while endothelium-dependent dysfunction was indicated by abnormal acetylcholine flow reserve [44]. Our study corroborates these findings, showing that ECG changes correctly identified endothelium-independent CMD in 96.6 % of positive cases. In contrast with Sinha et al., where only 63 % of patients exhibited endothelium-independent CMD, all except one patient with an ischemic ECG in our cohort were diagnosed with endothelium-independent CMD. This suggests a fundamental difference between COVID-19-related CMD and CMD not associated with COVID-19.

5. Limitations

Despite the valuable insights provided by the COMET-19 study, several limitations must be acknowledged. The relatively small sample size of 117 patients may limit the generalizability of our findings, as does the focus on patients from two hospitals in Lithuania, which may not represent a broader population. Given the scale of the COVID-19 pandemic, it was impossible to entirely exclude patients with a history of mild COVID-19 infection. However, this is a common limitation in studies examining the impact of COVID-19. In the present study, we aimed to mitigate this limitation by rigorously excluding patients who had been hospitalized for respiratory symptoms at any point during the pandemic. While we demonstrated an association between severe COVID-19 history and CMD, given our cross-sectional design, we cannot establish causality, which, along with the temporal relationship between severe COVID-19 infection and the development of CMD, could only be established through longitudinal studies. It is entirely possible that patients with pre-existing CMD are more susceptible to severe COVID-19 infection. However, a substantial body of pathophysiological research suggests that the increased incidence of CMD is likely to be a direct consequence of COVID-19 infection. The use of bolus thermodilution for

invasive functional assessment introduces potential variability in the measurements of FFR, CFR, and IMR as compared with Doppler-based measurements or continuous thermal dilution methods [24]. Additionally, the assessment of endothelium-dependent CMD or coronary vasospasm via acetylcholine flow reserve testing was not performed in this study due to strict institutional regulations and ethical approval, which may have limited the ability to fully characterise the full scope of CMD. The differentiation of structural and functional CMD, while demonstrating fundamental pathophysiological differences, have not yet been shown to warrant specific therapeutic strategies. Furthermore, although we observed a trend toward more prevalent ischemic ECG changes in the COVID group, we did not have additional noninvasive imaging to demonstrate the true relationship between severe COVID-19 infection and the extent of myocardial ischemia. Given the low sensitivity of exercise stress tests, the inclusion of stress echocardiography or CMR should be considered in future trials. Despite efforts to control for baseline characteristics, the study was conducted in a consecutive, but neither matched nor randomised population. Thus, residual confounding factors, such as undiagnosed pre-existing conditions, variations in post-COVID-19 care, and the lack of longitudinal data may also have impacted the validity of our findings. Lastly, the exclusion of patients who are unable to perform exercise stress tests and those with severe renal dysfunction, while reasonable, may introduce a certain selection bias. This is because patients with the most severe sequelae after severe COVID infection, who are bedridden or suffer from end-organ failure, are excluded, which also explains the relatively low prevalence of mechanical ventilation in our COVID group. Hence, while we observed that all five mechanically ventilated patients exhibited CMD, the small number of observations is underpowered and should be treated as hypothesis-generating.

6. Conclusion

The COMET-19 study identifies a significant association between a history of severe COVID-19 infection and an increased prevalence of CMD in patients with ANOCA. Our findings demonstrate a higher incidence of structural CMD, suggesting that coronary microvascular impairment may be part of the pathophysiological mechanism for ANOCA in patients who had severe COVID-19 infection. The study highlights the persistent cardiovascular impact of severe COVID-19 infection, evidenced by elevated IMR and poorer anginal symptoms and quality of life in affected patients. Additionally, we showed that EST may be a valuable tool for predicting CMD, with ischemic ECG changes strongly correlating with the presence of CMD.

CRediT authorship contribution statement

Ali Aldujeli: MD., PhD.* contributed to, Conceptualization, Methodology, Investigation, Formal analysis, Data curation, Validation, Visualization, Writing – original draft, Writing – review & editing, and, Project administration. **Tsung-Ying Tsai:** MD * contributed to, Conceptualization, Methodology, Investigation, Formal analysis, Data curation, Validation, Visualization, Writing – original draft, and, Writing – review & editing. **Ayman Haq:** MD contributed to, Investigation, Data curation, and, Writing – review & editing. **Kamile Puipaite:** MD contributed to, Investigation, Data curation, and, Writing – review & editing. **Rima Braukyliene:** MD., PhD. contributed to, Investigation, Resources, and, Writing – review & editing. **Vacis Tatarunas:** PhD contributed to, Formal analysis, potentially, Software, and, Writing – review & editing. **Diana Zaliaduonyte:** MD., Ph.D contributed to, Investigation, Resources, and, Writing – review & editing. **Ramunas Unikas:** MD., Ph.D contributed to, Investigation, Supervision, and, Writing – review & editing. **Mick Renkens:** MD contributed to, Investigation, Data curation, and, Writing – review & editing. **Pruthvi C. Revaiah:** MD contributed to, Investigation, Data curation, and, Writing – review & editing. **Kotaro Miyashita:** MD contributed to, Investigation, Data curation, and, Writing – review & editing. **Akihiro Tobe:** MD contributed to, Investigation, Data curation, and, Writing – review & editing. **Asahi Oshima:** MD contributed to, Investigation, Data curation, and, Writing – review & editing. **Faisal Sharif:** MD, Ph.D contributed to. **Vaiva Lesauskaite:** MD., PhD. contributed to, Investigation, Resources, and, Writing – review & editing. **John A. Spertus:** MD, Ph.D contributed to, Conceptualization, input, Methodology, input, Funding acquisition, Supervision, and, Writing – review & editing. **Scot Garg:** MD, Ph.D contributed to, Conceptualization, input, Methodology, input, Funding acquisition, Supervision, and, Writing – review & editing. **Yoshinobu Onuma:** MD., Ph.D. contributed to, Conceptualization, Methodology, Supervision, Funding acquisition, Project administration, and, Writing – review & editing. **Emmanouil S. Brilakis:** MD., PhD contributed to, Conceptualization, Methodology, Supervision, and, Writing – review & editing. **Patrick W. Serruys:** MD., Ph.D. contributed to, Conceptualization, Methodology, Supervision, Funding acquisition, and, Resources.

Availability of data and materials

The datasets used in this study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

We conducted this study in compliance with the ethical standards of the Regional Bioethics Committee of Kaunas, Lithuania (the permission number is BE-3-7) and the World Medical Association Declaration of Helsinki on Ethical Principles for Medical Research Involving Human Subjects. Clinical Trials registration number: NCT05841485, prospectively registered. All subjects gave their informed consent to participate, and an information letter was given to them.

Consent to publication

Not applicable.

Funding

The study was sponsored by the Lithuanian University of Health Sciences.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

We would like to extend our gratitude to the dedicated Cath Lab staff for their unwavering support and assistance throughout this study. Their expertise and commitment have been invaluable to the success of our research.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.atherosclerosis.2025.120389.

References

[1] Soriano JB, Murthy S, Marshall JC, Relan P, Diaz JV. WHO clinical case definition working group on Post-COVID-19 condition. A clinical case definition of post-COVID-19 condition by a Delphi consensus. Lancet Infect Dis 2022;22:e102–7.
[2] O'Mahoney LL, Routen A, Gillies C, Ekezie W, Welford A, Zhang A, Karamchandani U, Simms-Williams N, Cassambai S, Ardavani A, Wilkinson TJ,

Hawthorne G, Curtis F, Kingsnorth AP, Almaqhawi A, Ward T, Ayoubkhani D, Banerjee A, Calvert M, Shafran R, Stephenson T, Sterne J, Ward H, Evans RA, Zaccardi F, Wright S, Khunti K. The prevalence and long-term health effects of long covid among hospitalised and non-hospitalised populations: a systematic review and meta-analysis. eClinicalMedicine 2023;55:101762.
[3] Cabrera Martimbianco AL, Pacheco RL, Bagattini ÂM, Riera R. Frequency, signs and symptoms, and criteria adopted for long COVID-19: a systematic review. Int J Clin Pract 2021;75:e14357.
[4] Tsampasian V, Bäck M, Bernardi M, Cavarretta E, Dębski M, Gati S, Hansen D, Kränkel N, Koskinas KC, Niebauer J, Spadafora L, Frias Vargas M, Biondi-Zoccai G, Vassiliou VS. Cardiovascular disease as part of long COVID: a systematic review. Eur J Prev Cardiol 2024:zwae070.
[5] Davis HE, McCorkell L, Vogel JM, Topol EJ. Long COVID: major findings, mechanisms and recommendations. Nat Rev Microbiol 2023;21:133–46.
[6] Osiaevi I, Schulze A, Evers G, Harmening K, Vink H, Kümpers P, Mohr M, Rovas A. Persistent capillary rarefication in long COVID syndrome. Angiogenesis 2023;26:53–61.
[7] Karagodin I, Wang S, Wang H, Singh A, Gutbrod J, Landeras L, Patel H, Alvi N, Tang M, Benovoy M, Janich MA, Benjamin HJ, Chung JH, Patel AR. Myocardial blood flow quantified using stress cardiac magnetic resonance after mild COVID-19 infection. JACC Adv 2024;3:100834.
[8] Ahmed AI, Al Rifai M, Alahdab F, Saad JM, Han Y, Alfawara MS, Nayfeh M, Malahfji M, Nabi F, Mahmarian JJ, Cooke JP, Zoghbi WA, Al-Mallah MH. Coronary microvascular health in symptomatic patients with prior COVID-19 infection: an updated analysis. Eur Heart J Cardiovasc Imaging 2023;24:1544–54.
[9] Boerhout CKM, Waard GA de, Lee JM, Mejia-Renteria H, Lee SH, Jung J-H, Hoshino M, Echavarria-Pinto M, Meuwissen M, Matsuo H, Madera-Cambero M, Eftekhari A, Effat MA, Murai T, Marques K, Appelman Y, Doh J-H, Christiansen EH, Banerjee R, Nam C-W, Niccoli G, Nakayama M, Tanaka N, Shin E-S, Beijk MAM, Knaapen P, Escaned J, Kakuta T, Koo B-K, Piek JJ, Hoef TP van de. Prognostic value of structural and functional coronary microvascular dysfunction in patients with non-obstructive coronary artery disease; from the multicentre international ILIAS registry. EuroIntervention J Eur Collab Work Group Interv Cardiol Eur Soc Cardiol 2022;18:719–28.
[10] Vrints C, Andreotti F, Koskinas KC, Rossello X, Adamo M, Ainslie J, Banning AP, Budaj A, Buechel RR, Chiariello GA, Chieffo A, Christodorescu RM, Deaton C, Doenst T, Jones HW, Kunadian V, Mehilli J, Milojevic M, Piek JJ, Pugliese F, Rubboli A, Semb AG, Senior R, Berg JM ten, Van Belle E, Van Craenenbroeck EM, Vidal-Perez R, Winther S, ESC Scientific Document Group. 2024 ESC guidelines for the management of chronic coronary syndromes: developed by the task force for the management of chronic coronary syndromes of the European Society of Cardiology (ESC) endorsed by the European Association for Cardio-Thoracic Surgery (EACTS). Eur Heart J 2024. ehae177.
[11] Hong D, Shin D, Lee SH, Joh HS, Choi KH, Kim HK, Ha SJ, Park TK, Yang JH, Song YB, Hahn J-Y, Choi S-H, Gwon H-C, Lee JM. Prognostic impact of coronary microvascular dysfunction according to different patterns by invasive physiologic indexes in symptomatic patients with intermediate coronary stenosis. Circ Cardiovasc Interv 2023;16.
[12] Chan PS, Jones PG, Arnold SA, Spertus JA. Development and validation of a short version of the Seattle angina questionnaire. Circ Cardiovasc Qual Outcomes 2014;7:640–7.
[13] null null, Gibbons RJ, Balady GJ, Beasley JW, Faafp null, Bricker JT, Duvernoy WFC, Froelicher VF, Mark DB, Marwick TH, McCallister BD, Thompson PD, Facsm null, Winters WL, Yanowitz FG. ACC/AHA guidelines for exercise testing: executive summary. Circulation 1997;96:345–54.
[14] null null, Gibbons RJ, Balady GJ, Timothy BJ, Chaitman BR, Fletcher GF, Froelicher VF, Mark DB, McCallister BD, Mooss AN, O 'Reilly Michael G, Winters WL, null null, Gibbons RJ, Antman EM, Alpert JS, Faxon DP, Fuster V, Gregoratos G, Hiratzka LF, Jacobs AK, Russell RO, Smith SC. ACC/AHA 2002 guideline update for exercise testing: summary article. J Am Coll Cardiol 2002;40:1531–40.
[15] Kunadian V, Chieffo A, Camici P, Berry C, Escaned J, Maas A, Prescott E, Karam N, Appelman Y, Fraccaro C, Buchanan G, Manzo-Silberman S, Al-Lamee R, Regar E, Lansky AJ, Abbott J, Badimon L, Duncker D, Mehran R, Capodanno D, Baumbach A. An EAPCI expert consensus document on ischaemia with non-obstructive coronary arteries in collaboration with european society of cardiology working group on coronary pathophysiology & microcirculation endorsed by coronary vasomotor disorders international study group. 3 June 2024. eurointervention.pcronline.com/article/an-eapci-expert-consensus-document-on-ischaemia-with-non-obstructive-coronary-arteries-in-collaboration-with-european-society-of-cardiology-working-group-on-coronary-pathophysiology-and-microcirculation-endorsed-by-coronary-vasomotor-disorders-international-study-group.
[16] Vranckx P, Cutlip DE, McFadden EP, Kern MJ, Mehran R, Muller O. Coronary pressure–derived fractional flow reserve measurements. Circ Cardiovasc Interv 2012;5:312–7.
[17] Ford TJ, Stanley B, Good R, Rocchiccioli P, McEntegart M, Watkins S, Eteiba H, Shaukat A, Lindsay M, Robertson K, Hood S, McGeoch R, McDade R, Yii E, Sidik N, McCartney P, Corcoran D, Collison D, Rush C, McConnachie A, Touyz RM, Oldroyd KG, Berry C. Stratified medical therapy using invasive coronary function testing in angina. J Am Coll Cardiol 2018;72:2841–55.
[18] Spertus JA, Winder JA, Dewhurst TA, Deyo RA, Prodzinski J, McDonell M, Fihn SD. Development and evaluation of the Seattle angina questionnaire: a new functional status measure for coronary artery disease. J Am Coll Cardiol 1995;25:333–41.
[19] Padro T, Manfrini O, Bugiardini R, Canty J, Cenko E, De Luca G, Duncker DJ, Eringa EC, Koller A, Tousoulis D, Trifunovic D, Vavlukis M, Wit C de, Badimon L. ESC working group on coronary pathophysiology and microcirculation position paper on 'coronary microvascular dysfunction in cardiovascular disease'. Cardiovasc Res 2020;116:741–55.
[20] Gulati M, Levy PD, Mukherjee D, Amsterdam E, Bhatt DL, Birtcher KK, Blankstein R, Boyd J, Bullock-Palmer RP, Conejo T, Diercks DB, Gentile F, Greenwood JP, Hess EP, Hollenberg SM, Jaber WA, Jneid H, Joglar JA, Morrow DA, O'Connor RE, Ross MA, Shaw LJ. AHA/ACC/ASE/CHEST/SAEM/SCCT/SCMR guideline for the evaluation and diagnosis of chest pain: a report of the American college of cardiology/american heart association joint committee on clinical practice guidelines. Circulation 2021;144:e368–454. 2021.
[21] Perera D, Berry C, Hoole SP, Sinha A, Rahman H, Morris PD, Kharbanda RK, Petraco R, Channon K. Invasive coronary physiology in patients with angina and non-obstructive coronary artery disease: a consensus document from the coronary microvascular dysfunction workstream of the British heart foundation/national institute for health research partnership. Heart 2023;109:88–95.
[22] de VA, Jansen TPJ, van 't Veer Marcel, Aukelien Dimitriu -Leen, Konst RE, Elias -Smale Suzette, Paradies V, Rodwell L, van den OS, Smits P, van RN, Pijls N, Damman P. Microvascular resistance reserve to assess microvascular dysfunction in ANOCA patients. JACC Cardiovasc Interv 2023;16:470–81.
[23] Rahman H, Demir OM, Ryan M, McConkey H, Scannell C, Ellis H, Webb A, Chiribiri A, Perera D. Optimal use of vasodilators for diagnosis of microvascular angina in the cardiac catheterization laboratory. Circ Cardiovasc Interv 2020;13:e009019.
[24] Demir OM, Boerhout CKM, de WGA, van de Hoef TP, Patel N, Beijk MAM, Williams R, Rahman H, Everaars H, Kharbanda RK, Knaapen P, van RN, Piek JJ, Perera D. Comparison of doppler flow velocity and thermodilution derived indexes of coronary physiology. JACC Cardiovasc Interv 2022;15:1060–70.
[25] Bradley C, Berry C. Definition and epidemiology of coronary microvascular disease. J Nucl Cardiol 2022;29:1763–75.
[26] Rahman H, Demir OM, Khan F, Ryan M, Ellis H, Mills MT, Chiribiri A, Webb A, Perera D. Physiological stratification of patients with angina due to coronary microvascular dysfunction. J Am Coll Cardiol 2020;75:2538–49.
[27] De Bruyne B, Pijls NHJ, Gallinoro E, Candreva A, Fournier S, Keulards DCJ, Sonck J, Veer M van't, Barbato E, Bartunek J, Vanderheyden M, Wyffels E, De Vos A, El Farissi M, Tonino PAL, Muller O, Collet C, Fearon WF. Microvascular resistance reserve for assessment of coronary microvascular function: JACC technology corner. J Am Coll Cardiol 2021;78:1541–9.
[28] Bauer L, Rijsbergen LC, Leijten L, Benavides FF, Noack D, Lamers MM, Haagmans BL, Vries RD de, Swart RL de, Riel D van. The pro-inflammatory response to influenza A virus infection is fueled by endothelial cells. Life Sci Alliance 2023;6:e202201837.
[29] Muscente F, De Caterina R. Causal relationship between influenza infection and risk of acute myocardial infarction: pathophysiological hypothesis and clinical implications. Eur Heart J Suppl J Eur Soc Cardiol 2020;22:E68–72.
[30] Hilser JR, Spencer NJ, Afshari K, Gilliland FD, Hu H, Deb A, Lusis AJ, Wilson Tang WH, Hartiala JA, Hazen SL, Allayee H. COVID-19 is a coronary artery disease risk equivalent and exhibits a genetic interaction with ABO blood type. Arterioscler Thromb Vasc Biol 2024;44:2321–33.
[31] Varga Z, Flammer AJ, Steiger P, Haberecker M, Andermatt R, Zinkernagel AS, Mehra MR, Schuepbach RA, Ruschitzka F, Moch H. Endothelial cell infection and endotheliitis in COVID-19. The Lancet 2020;395:1417–8.
[32] Bearse M, Hung YP, Krauson AJ, Bonanno L, Boyraz B, Harris CK, Helland TL, Hilburn CF, Hutchison B, Jobbagy S, Marshall MS, Shepherd DJ, Villalba JA, Delfino I, Mendez-Pena J, Chebib I, Newton-Cheh C, Stone JR. Factors associated with myocardial SARS-CoV-2 infection, myocarditis, and cardiac inflammation in patients with COVID-19. Mod Pathol Off J U S Can Acad Pathol Inc 2021;34:1345–57.
[33] Bösmüller H, Traxler S, Bitzer M, Häberle H, Raiser W, Nann D, Frauenfeld L, Vogelsberg A, Klingel K, Fend F. The evolution of pulmonary pathology in fatal COVID-19 disease: an autopsy study with clinical correlation. Virchows Arch 2020;477:349–57.
[34] O'Sullivan JM, Gonagle DM, Ward SE, Preston RJS, O'Donnell JS. Endothelial cells orchestrate COVID-19 coagulopathy. Lancet Haematol 2020;7:e553–5.
[35] Klok FA, Kruip MJHA, Meer NJM van der, Arbous MS, Gommers D, Kant KM, Kaptein FHJ, Paassen J van, Stals MaM, Huisman MV, Endeman H. Confirmation of the high cumulative incidence of thrombotic complications in critically ill ICU patients with COVID-19: an updated analysis. Thromb Res 2020;191:148–50.
[36] Çalışkan M, Baycan ÖF, Çelik FB, Güvenç TS, Atıcı A, Çağ Y, Konal O, İrgi T, Bilgili ÜZ, Ağırbaşlı MA. Coronary microvascular dysfunction is common in patients hospitalized with COVID-19 infection. Microcirc N Y; N 1994 2022,e12757.
[37] Mejía-Rentería H, Hoeven N van der, Hoef TP van de, Heemelaar J, Ryan N, Lerman A, Royen N van, Escaned J. Targeting the dominant mechanism of coronary microvascular dysfunction with intracoronary physiology tests. Int J Cardiovasc Imag 2017;33:1041–59.
[38] Basso C, Leone O, Rizzo S, De Gaspari M, Wal AC van der, Aubry M-C, Bois MC, Lin PT, Maleszewski JJ, Stone JR. Pathological features of COVID-19-associated myocardial injury: a multicentre cardiovascular pathology study. Eur Heart J 2020;41:3827–35.
[39] Halushka MK, Vander Heide RS. Myocarditis is rare in COVID-19 autopsies: cardiovascular findings across 277 postmortem examinations. Cardiovasc Pathol Off J Soc Cardiovasc Pathol 2021;50:107300.
[40] Pellegrini D, Kawakami R, Guagliumi G, Sakamoto A, Kawai K, Gianatti A, Nasr A, Kutys R, Guo L, Cornelissen A, Faggi L, Mori M, Sato Y, Pescetelli I, Brivio M, Romero M, Virmani R, Finn AV. Microthrombi as a major cause of cardiac injury in COVID-19: a pathologic study. Circulation 2021;143:1031–42.

[41] Blasco A, Coronado M-J, Hernández-Terciado F, Martín P, Royuela A, Ramil E, García D, Goicolea J, Del Trigo M, Ortega J, Escudier JM, Silva L, Bellas C. Assessment of neutrophil extracellular traps in coronary thrombus of a case series of patients with COVID-19 and myocardial infarction. JAMA Cardiol 2020;6:1–6.

[42] Carlile O, Briggs A, Henderson AD, Butler-Cole BFC, Tazare J, Tomlinson LA, Marks M, Jit M, Lin L-Y, Bates C, Parry J, Bacon SCJ, Dillingham I, Dennison WA, Costello RE, Walker AJ, Hulme W, Goldacre B, Mehrkar A, MacKenna B, Walker A, Green A, Mehrkar A, Schaffer A, Brown A, Goldacre B, Butler-Cole B, MacKenna B, Morton C, Walters C, Stables C, Cunningham C, Wood C, Andrews C, Evans D, Hickman G, Curtis H, Drysdale H, Dillingham I, Morley J, Massey J, Nab L, Hopcroft L, Fisher L, Bridges L, Wiedemann M, DeVito N, Macdonald O, Inglesby P, Smith R, Croker R, Park R, Higgins R, Bacon S, Davy S, Maude S, O'Dwyer T, Ward T, Speed V, Hulme W, Hart L, Stokes P, Bhaskaran K, Costello R, Cowling T, Douglas I, Eggo R, Evans S, Forbes H, Grieve R, Grint D, Herrett E, Langan S, Mahalingasivam V, Mansfield K, Mathur R, McDonald H, Parker E, Rentsch C, Schultze A, Smeeth L, Tazare J, Tomlinson L, Walker J, Williamson E, Wing K, Wong A, Zheng B, Bates C, Cockburn J, Parry J, Hester F, Harper S, O'Hanlon S, Eavis A, Jarvis R, Avramov D, Griffiths P, Fowles A, Parkes N, Perera R, Harrison D, Khunti K, Sterne J, Quint J, Herrett E, Eggo RM. Impact of long COVID on health-related quality-of-life: an OpenSAFELY population cohort study using patient-reported outcome measures (OpenPROMPT). Lancet Reg Health – Eur 2024;40.

[43] Sathyamoorthy M, Verduzco-Gutierrez M, Varanasi S, Ward R, Spertus J, Shah S. Enhanced external counterpulsation for management of symptoms associated with long COVID. Am Heart J Plus Cardiol Res Pract 2022;13:100105.

[44] Sinha A, Dutta U, Demir OM, De Silva K, Ellis H, Belford S, Ogden M, Li Kam Wa M, Morgan HP, Shah AM, Chiribiri A, Webb AJ, Marber M, Rahman H, Perera D. Rethinking false positive exercise electrocardiographic stress tests by assessing coronary microvascular function. J Am Coll Cardiol 2024;83:291–9.