Post-COVID-19 illness trajectory: a multisystem investigation.

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Abstract

Background: The pathophysiology and trajectory of multiorgan involvement in post-COVID-19 syndrome is uncertain.

Methods: A prospective, multicenter, longitudinal, cohort study involving post-COVID-19 patients enrolled in-hospital or early post-discharge (visit 1) and re-evaluated 28-60 days post-discharge (visit 2). Multisystem investigations included chest computed tomography with pulmonary and coronary angiography, cardiovascular and renal magnetic resonance imaging, digital electrocardiography, and multisystem biomarkers. The primary outcome was the adjudicated likelihood of myocarditis.

Results: 161 patients (mean age 55 years, 43% female) and 27 controls with similar age, sex, ethnicity, and vascular risk factors were enrolled from 22 May 2020 to 2 July 2021 and had a primary outcome evaluation. Compared to controls, at 28-60 days post-discharge, patients with COVID-19 had persisting evidence of cardio-renal involvement, systemic inflammation, and hemostasis pathway activation.

Myocarditis was adjudicated as being not likely (n=17; 10%), unlikely (n=56; 35%), probable (n=67; 42%) or very likely (n=21; 13%). Acute kidney injury (odds ratio, 95% confidence interval: 3.40 (1.13, 11.84); p=0.038) and low hemoglobin A1c (0.26 (0.07, 0.87); p=0.035) were multivariable associates of adjudicated myocarditis. During convalescence, compared to controls, COVID-19 was associated with worse health-related quality of life (EQ5D-5L) (p<0.001), illness perception (p<0.001), anxiety and depression (p<0.001), physical activity (p<0.001) and predicted maximal oxygen utilization (ml/kg/min) (p<0.001). These measures were associated with adjudicated myocarditis.

Conclusions: The illness trajectory of COVID-19 includes persisting cardio-renal inflammation, lung damage and hemostasis activation. Adjudicated myocarditis occurred in one in eight hospitalized patients and was associated with impairments in health status, physical and psychological wellbeing during community convalescence.

Public registration: ClinicalTrials.gov identifier is NCT04403607.

Background

Self-reporting[1–4] and population studies[5–7] of post-COVID-19 illness trajectory have found that symptoms, such as fatigue, breathlessness, and exercise intolerance are common. At the outset of the COVID-19 pandemic, clinical studies lacked a prospective evaluation of disease pathogenesis and/or health status, and selectively recalled patients[3,7]. Few prospective studies have been reported[8–12], and multisystem imaging with clinical outcomes and contemporary controls were lacking. Pre-existing disease complicates attribution of causal inferences in COVID-19 and, since the heart, lungs and kidneys are deep organs, clinical evaluation is challenging. Accordingly, the pathophysiology and clinical significance of post-COVID-19 syndromes remain uncertain[9].

The pathogenesis of multiorgan inflammation in COVID-19 may involve direct virus invasion through binding angiotensin converting enzyme 2 (ACE2)[13,14], cardio-renal inflammation[15], endothelial dysfunction[15], thrombotic microvascular angiopathy[16], stress cardiomyopathy[15], and drug toxicity[15]. These distinct mechanisms define subgroups with multiorgan involvement (endotypes) in COVID-19. Myocarditis may cause longer-term morbidity and mortality[17]. Prior studies using cardiovascular magnetic resonance imaging in COVID-19 have reported imaging features of myocardial inflammation in 27%-60%[18,19] of patients. These studies involved case selection based on troponin elevation and retrospective recall[18,19]. Lack of coronary artery imaging is also a limitation for attributing the etiology of myocardial injury, which becomes susceptible to ascertainment bias.

Based on the cardiovascular tropism of SARS-CoV-2[15], we hypothesized, firstly, that the illness trajectory of post-COVID-19 syndromes involved hemostatic pathway activation and systemic inflammation during convalescence, second, cardio-renal involvement associates with pre-existing cardiovascular disease and, third, adjudicated myocarditis post-COVID-19 associates with persisting impairments in health status, physical and psychological wellbeing. Disease mechanisms were investigated using multisystem imaging and biomarkers and their changes over time. Health status and physical function were serially assessed using validated patient reported outcome measures.

Methods

Design

This study involved a prospective, observational, multicenter, longitudinal, secondary care cohort design to assess the time-course of multiorgan injury in survivors of COVID-19 during convalescence. Clinical information, a 12-lead digital ECG, blood and urine biomarkers, and patient reported outcome measures were acquired at enrolment (visit 1) and again during convalescence, 28–60 days post-discharge (visit 2). Chest computed tomography (CT), including pulmonary and coronary angiography, and cardio-renal MRI were acquired at the second visit.

Setting

The study involved three hospitals in the West of Scotland (population 2.2 million) - the Queen Elizabeth University Hospital, the Royal Infirmary in Glasgow, and the Royal Alexandra Hospital in Paisley.

Participant identification

Patients who received hospital care for COVID-19, with or without admission, and were alive, were prospectively screened in real time using an electronic healthcare information system (TrakCare®, InterSystems®, USA) and daily hospital reports identifying inpatients with laboratory-positive results for COVID-19.

Eligibility criteria

The inclusion criteria were: (1) age ≥18 years old; (2) history of an unplanned hospital visit e.g., emergency department, or hospitalization >24 hours for COVID-19 confirmed by a clinical diagnosis, laboratory test (e.g., polymerase chain reaction (PCR)), and/or a radiological test (e.g. CT chest or chest radiograph); (3) ability to comply with study procedures; and (4) ability to provide written informed consent. The imaging results were reported by accredited radiologists according to contemporary, national guidelines[20].

The exclusion criteria were: (1) contra-indication to magnetic resonance (MR) imaging (e.g., severe claustrophobia, metallic foreign body); and (2) lack of informed consent.

Screening

A screening log was prospectively completed. The reasons for being ineligible, including lack of inclusion criteria and/or presence of exclusion criteria, were recorded.

Diagnosis of COVID-19

A diagnosis of COVID-19 was based on either laboratory evidence of SARS-CoV-2 infection using a PCR test (Roche Cobas 6800 or Seegene SARS-CoV-2 PCR) on a biospecimen or a radiological and clinical diagnosis of COVID-19 but biospecimen negative [21].

Diagnosis of myocardial injury

The diagnosis of myocardial injury aligned with the Fourth Universal Definition of Myocardial Infarction[22]. Troponin I was measured in hospitalized patients using the Abbott Architect STAT TnI assay (sex-specific >99th percentile upper reference limit: female: >16 ng/L, male: >34 ng/L.

Diagnosis of acute kidney injury

Acute kidney injury (AKI) was defined as any stage of AKI (1-3) during COVID-19 hospitalization using categorization with the Kidney Disease: Improving Global Outcomes (KDIGO) criteria (Supplement) [23].

Research schedule

The protocol involved two visits. The first visit involved informed consent and baseline assessments during the initial hospitalization, or as soon as possible after discharge. The second visit occurred 28–60 days post-discharge. This window was positioned to reflect the convalescent phase and give sufficient scope to schedule the patients.

The procedures involved prospective collection of clinical data and a time-course of research investigations. Clinical data included demographics, medical and cardiovascular history, findings from clinical examinations, laboratory and radiological tests, cardiology tests (including an electrocardiogram (ECG) and an echocardiogram if available) and treatment. The research investigations at both visits included blood and urine samples, a 12-lead digital ECG (Beneheart R3, Mindray, Huntingdon, UK), health status questionnaires, and assessments of adverse events (Supplement). Heart, lung, and kidney imaging were acquired at the second visit.

Electrocardiology

SARS-CoV-2 infection and treatment may cause alterations in heart rate and rhythm, and ventricular repolarization. The changes may be specific for myocarditis e.g., concave ST-elevation, or non-specific e.g., ventricular arrhythmias. Digital ECGs were acquired, de-identified and provided to the University of Glasgow Electrocardiology Core Laboratory for automated analysis and adjudication. The ECG features of myopericarditis were predefined according to contemporary criteria[17].

Biomarkers

Blood and urine samples were collected at enrolment (visit 1) and 28–60 days post discharge (visit 2). Circulating biomarkers of cardiac injury (troponin I, N-terminal (NT)-pro hormone brain natriuretic peptide (NT-proBNP), inflammation (C-reactive protein, ferritin), thrombosis (TCT ratio, D-Dimer, fibrinogen, Factor VIII, antithrombin, protein C, protein S), endothelial activation (von Willebrand factor (vWF):GP1bR, VWF:Ag) and renal function (serum creatinine, glomerular filtration rate (GFR) was estimated using the Chronic Kidney Disease Epidemiology (CKD-EPI) equation[24]) and urinary albumin: creatinine ratio), and their

changes over time, were investigated. The measurements were undertaken in a central laboratory, blinded to the other clinical data. The methodology is described in the Supplement.

Multimodality imaging

CT

A 320-detector CT scanner (Aquilion ONE, Canon Medical Systems Corp.) provided full heart coverage within a single heartbeat. Intravenous metoprolol was used where required to control the heart rate (target 60 beats/min) and sublingual glyceryl trinitrate was given to all patients immediately before the scan acquisition. An initial low radiation dose helical scan of the thorax was acquired for comprehensive assessment of the lungs. A contrast bolus timing scan was acquired to provide information on cardiopulmonary transit times. Non-contrast and contrast-enhanced angiographic breath-hold ECG-gated volumes were acquired and timed for optimum pulmonary and systemic arterial (coronary) opacification. Patients with severe renal dysfunction underwent non-contrast CT.

Coronary CT angiography provided information on the presence and extent of coronary calcification (calcium score), coronary artery disease, and whether any coronary artery disease was obstructive (flow-limiting) including the Coronary Artery Disease - Reporting and Data System (CAD-RADS) score[25]. The functional significance of coronary artery disease was evaluated using fractional flow reserve CT (FFR_{CT}; HeartFlow, Redwood City, CA). A $FFR_{CT} \leq 0.80$ defined obstructive coronary artery disease, taking the lowest value in the vessel. FFR_{CT} measurements were taken at prespecified points using standard coronary segment definitions as a reference[26]. Median FFR_{CT} values were calculated for the left anterior descending, circumflex, and right coronary arteries, respectively, in combination with subsidiary vessels (i.e., diagonal arteries, obtuse marginal arteries). Patient-level FFR_{CT} values included all these coronary arteries.

Pulmonary vascular imaging assessed arterial thrombus (embolism)[27]. CT was used to delineate pulmonary features associated with COVID infection e.g., atelectasis, reticulation and/or architectural distortion, ground-glass opacity, and pre-existing lung damage e.g., emphysema. Cardiac and extra-cardiac incidental findings were reported and managed according to local standards of care.

Cardiovascular MRI

Cardiovascular MRI was undertaken to measure heart structure and function and assess for persisting evidence of myocardial injury and/or myocardial infarction using multi-parametric techniques[28]. MRI was acquired in a single reference site for all patients using a research-dedicated 3.0 Tesla (3T) scanner (MAGNETOM Prisma, Siemens Healthineers, Erlangen, Germany) with two 18-channel surface coils placed anteriorly and a 32-channel spine coil placed posteriorly. All patients underwent protocol-directed MRI in the convalescent phase, 28–60 days after discharge. The scan protocol included cine-imaging of cardiac anatomy and function and myocardial tissue characterization using multiparametric techniques. They included 1) mapping myocardial native longitudinal relaxation time (T1 in milliseconds) using the modified Look-Locker inversion recovery technique (T1-mapping) before and after intravenous administration of gadolinium contrast media (0.15 mmol/kg of Magnevist, Bayer Healthcare), 2) mapping transverse relaxation time (T2 in milliseconds), 3) first pass contrast-enhanced perfusion and 4) late gadolinium-enhancement imaging. Specific details on the MRI protocol are provided in the Supplement.

The expert consensus recommendations for the MRI diagnostic criteria of non-ischemic myocardial inflammation (modified Lake Louise criteria) were used to diagnose definite myocardial inflammation (abnormal T2 and T1 (native T1, late gadolinium enhancement or extracellular volume)) or probable myocardial inflammation (abnormal: T2 or T1)[17,29] (Supplement). Reference ranges derived from the UK Biobank were used to interpret cardiac structure and function[30], and contemporary local reference ranges specifically derived using the 3T MRI scanner (MAGNETOM Prisma) were used to define thresholds for localized abnormalities in myocardial T1- and T2- relaxation times. To limit selection bias, patients with severe renal dysfunction (GFR <45 ml/kg/m^2) were not excluded. They were eligible for MRI with or without contrast media according to the site Radiology protocol.

Renal MRI

Multi-parametric renal MRI included anatomical imaging and tissue characterization by measurement of native T1 and T2. The volume (ml), and native T1 (ms) and T2 (ms) in regions of interest obtained within the cortex and medulla of each kidney were recorded, and the averaged value of these parameters for both kidneys was then determined. Corticomedullary differentiation reflects a difference in tissue contrast on T1-weighted imaging due to a shorter T1 relaxation time of the cortex relative to the medulla, this being attributed to differences in water content between the two tissues[31,32]. Corticomedullary differentiation, reported here as a ratio of T1 cortex divided by T1 medulla[32], may diminish in kidney disease[31].

Blinding

The patients and the outcome assessors were blinded. Outcome assessments, including laboratory, MRI and CT analyses, and endpoint adjudication were undertaken by blinded researchers. The patients completed the health status questionnaires before undergoing the scans and they were unaware of the test results.

Outcomes

Primary outcome

The predefined primary outcome was a diagnosis of myocarditis (myocardial inflammation), an endotype of acute myocardial injury.

The diagnostic criteria for myocarditis included relevant clinical findings and test results (Supplement)[17]. Positive clinical findings included chest pain, pericarditic or pseudo-ischemic in nature, new onset breathlessness, subacute/chronic breathlessness, palpitations, unexplained arrhythmia, syncope, aborted sudden cardiac death, or unexplained cardiogenic shock. Positive test findings included 1) ECG features, 2) elevated troponin I (sex-specific >99th percentile upper reference limit: female: >16 ng/L, male: >34 ng/L; Abbott Architect STAT TnI assay); 3) functional and structural abnormalities on cardiac imaging (echocardiography, angiography, or MRI), and 4) tissue characterization MRI, including myocardial edema and late gadolinium enhancement with a distribution in alignment with the modified Lake Louise diagnostic criteria for myocarditis[29]. Acute and chronic myocardial pathology can be identified, discriminated, and quantified using MRI.

Myocarditis was clinically suspected if at least 1 clinical finding and at least 1 diagnostic test criterion from different categories, in the absence of: (1) angiographically detectable coronary artery disease (coronary stenosis ≥ 50%); (2) known pre-existing cardiovascular disease or extra-cardiac causes that could explain the syndrome (e.g., valve disease, congenital heart disease, hyperthyroidism, etc.). Suspicion increases with a rising number of fulfilled criteria. If the patient was asymptomatic, at least 2 diagnostic criteria were required.

Adjudication of the primary outcome

A diagnosis of myocarditis is susceptible to confounding through ascertainment bias. Recent studies in COVID-19 have not implemented the modified Lake Louise diagnostic criteria[18,19]. Accordingly, we pre-specified an adjudication procedure for the primary outcome, involving a panel of cardiologists with specialty accreditation. The reviews were undertaken according to a prespecified charter.

Consultant cardiologists (n=14) who were independent of the research team were invited as assessors. They were initially provided with information on the European Society of Cardiology Working Group on Myocardial and Pericardial Disease position statement on myocarditis[17], a charter, and training cases. The cardiologists were blind to the identity of the patients and independent of their clinical care. The adjudications were coordinated by a researcher (A.M.) using Teams (Microsoft, Seattle, USA) software.

Each cardiologist independently assessed the clinical data, including the medical history, biomarkers, ECG, and radiology reports for the CT chest, CT pulmonary angiogram, coronary CT angiogram, and cardiac MRI. Deidentified source clinical data e.g., scan images, were made available on request. The cardiologists determined the likelihood (not likely / unlikely / probable / very likely) of myocardial inflammation (myocarditis). The final diagnosis was based on the median likelihood based on the adjudications of 5 cardiologists. Their determinations were also categorized in binary form (not/unlikely = no; probable/very = yes).

Secondary outcomes

The differential etiology of myocardial injury/inflammation was adjudicated as a secondary outcome. The potential endotypes were:

1) SARS-CoV-2 myocarditis,

2) Acute stress cardiomyopathy,

3) Myocardial ischemia/impaired perfusion as a stressor of inflammation,

4) Infective myopericarditis (non-COVID infection),

5) Drug-induced (toxic) myocardial inflammation,

6) Idiopathic myocardial ± pericardial inflammation.

The endotypes of acute myocardial injury, including the type of myocardial infarction according to the 4th Universal Definition of MI[22], and myocarditis (myocardial inflammation, ischemia or stress cardiomyopathy)[17,29], were secondary outcomes.

Renal outcomes

Renal function was assessed using convalescent eGFR (CKD-EPI[24]) and albuminuria. Multi-parametric renal MRI at 28-60 days provided information on renal parenchymal disease.

Health status and patient reported outcome measures

Questionnaires were completed by participants at enrolment (visit 1) and 28–60 days after the last episode of hospital care (visit 2), blind to the other research data. Self-reported health status was assessed using the generic EuroQOL EQ-5D-5L questionnaire and the Brief Illness Perception Questionnaire (Brief-IPQ)[33,34]. The Patient Health Questionnaire-4 (PHQ–4) was utilized to assess for anxiety and depressive disorders[35]. The Duke Activity Status Index (DASI) was used to assess predicted maximal oxygen utilization (ml/kg/min), a measure of aerobic capacity, and functional capacity, a higher score reflects greater

physical function[36]. The International Physical Activity Questionnaire - Short Form (IPAQ-SF) measures the types and intensity of physical activity and sitting time that people do as part of their daily lives. The score reflects total physical activity in metabolic equivalent minutes per week[37].

Longitudinal follow-up

The participants were invited to give consent for clinical outcome assessment during follow-up using electronic health record linkage without direct contact.

Statistics

The statistical analyses were pre-defined in a Statistical Analysis Plan.

Sample size calculation

The primary outcome was myocarditis (myocardial inflammation), and the primary analysis determined the proportion of patients with the primary outcome by visit 2. The likelihood of myocarditis was determined based on the median likelihood from the clinical adjudication committee. To detect an association between a history of pre-existing cardiovascular disease and incident myocardial inflammation (myocarditis), we assumed a 25% prevalence of prior cardiovascular disease in the study population, and the incidence of myocardial inflammation in those with/without prior cardiovascular disease to be 33% and 10%, respectively[38]. To have 80% power to detect this difference we calculated that 140 participants (35 with cardiac problems, 105 without) with complete data would be required. Anticipating that 10-15% of the participants may have incomplete imaging e.g., artefact or claustrophobia, the target sample size was 160 to complete the imaging visit.

Cardiovascular disease status was prespecified and defined by (1) a prior history of cardiovascular disease, and (2) treatment. The associations between the circulating concentrations of mechanistic biomarkers, patient reported outcome measures, and their changes over time, and the primary and secondary outcomes were assessed. Missing data are reported. Significance tests with 2-sided p-values are accompanied by confidence intervals for estimated effect sizes and measures of association. The widths of the confidence intervals have not been adjusted for multiplicity. The p-values for subgroup differences were calculated using the Fisher Exact test and the Kruskal-Wallis test, for categorical and continuous data, respectively. A p-value of 0.05 was taken as statistically significant.

Trial management and timelines

The study was conducted in line with the current *Guidelines for Good Clinical Practice in Clinical Trials* and *STrengthening the Reporting of OBservational studies in Epidemiology* guidelines[39], and coordinated by a Study Management Group. A Scientific Steering Group had oversight of the study.

Ethics

The study was approved by the UK National Research Ethics Service (Reference 20/NS/0066).

Sources of Funding

This was an investigator-initiated clinical study that was funded by the Chief Scientist Office of the Scottish Government (COV/GLA/Portfolio project number 311300). The funder had no role in the design, conduct (non-voting TSC member), data analysis and interpretation, manuscript writing, or dissemination of the results. C.B, C.D., N.S., R.M.T. were supported by the British Heart Foundation (RE/18/6134217).

The MRI study involved technologies provided by Siemens Healthcare and the National Institutes of Health. HeartFlow (HeartFlow, Redwood City, CA) provided $FFR_{CT.}$ The study was co-sponsored by NHS Greater Glasgow & Clyde Health Board and the University of Glasgow.

Data and code availability

The datasets that support the findings of this study are available from the corresponding author upon reasonable request. Statistical code will be made available by the corresponding author upon reasonable request.

Registration

ClinicalTrials.gov: NCT04403607.

Results

One thousand three hundred and six patients were screened between 22 May 2020 and 16 March 2021 and 267 patients provided written informed consent. The flow diagram is shown in Figure 1 and clinical cases are illustrated in the Supplement.

One hundred and sixty-one patients were evaluated at 28-60 days after the last episode of hospital care. Their average age was 55 years, 88% were white, 43% were female, 47% had a history of cardiovascular disease or treatment, 40% were in the highest quintile of deprivation and 22% were healthcare workers (Table 1 and Supplement). Clinical disease severity scores are described in Table 1. Two (1.2%) patients had received a single dose of SARS-CoV-2 vaccine prior to hospitalization (Supplement, Table 2). Regarding COVID-19 therapy, 68.9% received oxygen, 55.3% received steroids, 26.1% received antiviral drug therapy, 19.3% received non-invasive respiratory support and 8.7% received invasive ventilation.

Comparison with controls

Twenty-seven control patients with similar age, sex, ethnicity, and cardiovascular risk factors underwent the same research procedures during a single visit between 13 April to 2 July 2021. Their characteristics are described in Table 1. Compared to controls, COVID-19 patients had multisystem differences in keeping with acute illness.

Multisystem investigations: comparisons with controls

In post-COVID-19 patients, compared to controls, the heart, lung and kidney imaging, electrocardiography and multisystem biomarkers revealed multiple persisting abnormalities (Table 2).

At 28-60 days post-discharge (visit 2), CT chest abnormalities were common: 44.7% had ground glass opacities and/or consolidation, 23.9% had ≥20% of the total lung area abnormal by visual estimation and 3.3% had pulmonary arterial thrombus. In the post-COVID-19 patients, the minimum patient-level FFR_{CT} was lower than in the control group (minimum FFR_{CT}: 0.80 (0.10) vs. 0.85 (0.08); p<0.001) consistent with flow-limiting coronary artery disease. MRI revealed persisting differences for left and right ventricular ejection fraction, contractility (strain), volumes, myocardial tissue characteristics, including late gadolinium enhancement in one in five patients mainly with a non-ischemic distribution, increased myocardial extracellular volume and pericardial thickening (Table 2). Renal MRI findings at 28-60 days post-discharge were similar between COVID-19 patients and controls (Table 2).

Circulating concentrations of C-reactive protein, ferritin, D-Dimers, fibrinogen, Factor VIII, and von Willebrand factor were higher in post-COVID-19 patients at enrolment compared to controls consistent with hemostatic pathway activation (Table 2). At 28-60 days post-discharge, Factor VIII concentration remained high. Circulating concentrations of NT-proBNP were higher in COVID-19 patients at enrolment and 28-60 days post-discharge. Urine albumin: creatine ratio and eGFR were not statistically different between the groups.

Primary outcome

A diagnosis of myocarditis was adjudicated as being not likely (n=17; 10%), unlikely (n=56; 35%), probable (n=67; 42%) or very likely (n=21; 13%). Adjudicated likelihood of myocarditis was associated with typical radiological features of COVID-19 (p=0.027), intensive care (p=0.045) and invasive ventilation (p=0.047), but there were no associations with demographic characteristics, cardiovascular history, or standard care blood results obtained during the index hospitalization (Table 1).

Multisystem phenotyping and adjudicated myocarditis

Electrocardiology

Premature ventricular contractions associated with the likelihood of myocarditis (Table 2).

CT chest, coronary and pulmonary angiography

Myocarditis did not appear to be associated with the extent or nature of lung involvement or coronary artery disease (Table 2).

Cardiovascular magnetic resonance imaging

Evidence was found of associations between the adjudicated likelihood of myocarditis and reduced left ventricular ejection fraction in females, myocardial inflammation, extracellular volume, late gadolinium enhancement (non-ischemic distribution) and the diagnostic criteria (Lake Louise) for myocardial inflammation (Table 2). Distinct patterns of myocardial pathology revealed by late gadolinium enhancement imaging are shown in the Supplement.

Renal magnetic resonance imaging

The adjudicated likelihood of myocarditis was associated with acute kidney injury during the initial admission. The average renal medulla T1 (ms), an imaging marker of inflammation in the left and right kidneys, associated with adjudicated myocarditis. No differences were observed for the averaged renal volumes, cortex tissue characteristics (T1, T2 ms), or renal function at 28-60 days.

Biochemical and hematological markers

At 28-60 days, protein S was inversely associated with the adjudicated likelihood of myocarditis. We found no other evidence of associations between the adjudicated myocarditis and biochemical and hematological markers of inflammation, hemostatic pathway activation, myocardial injury, or left ventricular dysfunction (Table 2).

Adjudicated cause of myocarditis

The etiology of myocardial inflammation was also adjudicated. SARS-COV-2 myocarditis was determined as being probable (66.7%) or very likely (33.3%) in all patients with adjudicated myocarditis (p<0.001) (Supplement, Table 3). Impaired myocardial blood flow as a stressor of inflammation was determined as probable in 6 (6.8%) patients with myocarditis adjudicated to be either probable or very likely (p<0.001).

Multivariable associates of adjudicated myocarditis

Univariate and multivariable associations between selected demographic and clinical measures at baseline (visit 1) and an adjudication of myocarditis being probable or very likely were assessed with logistic regression models (Table 3). Univariable associates of adjudicated myocarditis were female sex (odds ratio, 95% confidence interval: 1.92 (1.02, 3.70); p=0.045, healthcare worker (2.24 (1.03, 5.10); p=0.046), acute kidney injury (3.42 (1.25, 10.98); p=0.024), and hemoglobin A1c (per 1% difference: 0.25 (0.07, 0.77); p=0.020). After age and sex adjustment, acute kidney injury (3.40 (1.13, 11.84); p=0.038) and hemoglobin A1c (0.26 (0.07, 0.87); p=0.035) were multivariable associates of adjudicated myocarditis.

Health status

Compared to controls, at enrolment and 28-60 days post-discharge, post-COVID-19 patients had lower health-related quality of life, enhanced illness perception, higher levels of anxiety and depression, lower levels of physical activity and lower predicted maximal oxygen utilization (ml/kg/min) (Table 4).

The adjudicated likelihood of myocarditis associated with patient reported outcome measures at 28-60 days post-discharge, including lower health-related quality of life (p=0.005), enhanced illness perception (p=0.029), enhanced depression score (p=0.030), lower physical activity (p=0.014) and lower predicted maximal oxygen utilization (ml/kg/min) (p=0.014).

Serious adverse events

One patient died following consent, before discharge from hospital. A further patient died within 60 days of discharge (prior to visit 2). The causes of death and hospital readmission are listed in the Supplement.

Discussion

This prospective multicenter study characterized the illness trajectory of patients who survived hospitalization for COVID-19 during community convalescence. The study provided serial measurements of multisystem pathology coupled with patient-reported health status and aerobic exercise capacity.

Our results bridge a knowledge gap between post-COVID-19 syndromes and objective evidence of disease. We found that the illness trajectory of post-COVID-19 syndrome involved hemostatic pathway activation initially, including increases in circulating concentrations of fibrinogen and factor VIII and a reduction in protein S, and endothelial activation reflected by higher circulating concentrations of VWF:GP1bR and VWF:Ag. Most of these differences resolved by 28-60 days. This time-course of resolving hemostasis activation provides pathophysiological insights to explain the results of recent randomized clinical trials of antithrombotic therapy[40,41], including the efficacy of therapeutic anticoagulation with heparin in noncritically ill, hospitalized patients with Covid-19[40] (comparable to our population), and the lack of efficacy of aspirin or apixaban in community patients with milder illness[41] due to the low rate of cardiopulmonary thrombotic events. There was evidence of persisting systemic and renal inflammation and higher circulating concentrations of NTproBNP 28-60 days post-discharge. Post-COVID-19 status during convalescence associated with lingering impairments in health-related quality of life, illness perception, anxiety, depression, physical function, and predicted aerobic exercise capacity.

Incident myocarditis persisting 28-60 days post-COVID-19 affected approximately 1 in 8 patients (13%), which is lower than the percentages reported in other studies involving cardiovascular MRI (27%-60%)[18,19]. On the other hand, there is a knowledge gap on the incidence of myocardial inflammation in non-COVID infection, such as influenza, and new prospective studies are needed. The prevalence of obstructive coronary artery disease derived from FFR_{CT} was higher in the COVID-19 group than in the controls (Table 2). Notwithstanding, the etiology of myocarditis determined by the adjudication committee was predominately SARS-CoV-2 infection and less commonly, myocardial ischemia due to coronary artery disease (Supplement, Table 3).

Distinct from controls, one in five post-COVID-19 patients had imaging evidence of myocardial fibrosis indicative of distinct disease mechanisms, including myocarditis, microvascular thrombosis, myocardial infarction, and pre-existing scar (Supplement). Adjudicated myocarditis was also associated with premature ventricular contractions, myocardial fibrosis, pericardial thickening, and mild differences in left and right ventricular systolic function. On the other hand, hemoglobin A1c (%) was the only baseline characteristic associated with adjudicated myocarditis, but in the opposite direction to what may be expected, and so requiring validation in other cohorts. The mechanism may involve systemic inflammation leading microangiopathic hemolytic anemia and reduced red cell survival[42], although the lack of association with haptoglobin (Table 2) and other hematological parameters (Supplement, Table 1) does not support this possibility in our population. Reverse causality and residual confounding may be relevant.

Acute kidney injury portends mortality in COVID-19[43,44]. Adjudicated myocarditis was associated with acute kidney injury during admission and the averaged native T1 (ms) in the kidney medulla 28-60 days post-discharge, reflecting multiorgan inflammation during convalescence. These associations may be explained by systemic pathophysiology i.e. inflammation, hemostatic pathway activation, microvascular dysfunction, severe COVID-19 infection, or a combination of these pathologies[43]. Cardio-renal injury associated with persisting impairments in health-related quality of life, and poorer physical and psychological wellbeing during convalescence.

Post-COVID-19 syndrome ('long COVID') predominately affects females[1,6,12,45]. The proportion of women increased with the likelihood of myocarditis and female sex was a univariable associate of adjudicated myocarditis, which in turn was associated with lower mental and physical wellbeing. Adjudicated myocarditis was associated with left ventricular systolic dysfunction in females. Our findings provide a pathophysiological basis for symptoms burden and exercise limitation in some female patients with myocardial involvement post-COVID-19[45].

Our findings support clinical evaluation for myocarditis in patients who are hospitalized with COVID-19, especially in intensive care. Troponin is a cardiac protein that is ubiquitously released from injured cardiomyocytes. A rise in circulating troponin concentration is not cause-specific and troponin may increase due to hypoxia, hypotension, ischemia, and renal failure as well as from direct myocardial toxicity. On the other hand, cardiac biomarkers are a diagnostic criterion for myocarditis and are informative for prognostication[46]. Outside of intensive care, a selective approach for measuring cardiac biomarkers, informed by clinical findings, would seem appropriate.

Although there are no evidence-based treatments for the prevention or treatment of myocarditis in COVID-19, acute treatments, such as dexamethasone[47], should reduce the likelihood of myocarditis occurring. Since our findings identify myocarditis as an associate of worse physical and mental health post-COVID-19, cardio-renal involvement could be considered a therapeutic target (endpoint) in clinical trials to prevent post-COVID-19 syndrome. The RECOVERY Trial is currently investigating the effects of immunomodulatory therapies in acute COVID-19, including baricitinib and dimethyl fumarate, and the sodium-glucose cotransporter-2 inhibitor, empagliflozin, which reduces the progression of kidney disease and lower rates of clinically relevant renal events in patients with type 2 diabetes at high cardiovascular risk[48].

To our knowledge, the combination of systematic cardio-renal MRI and chest CT, including pulmonary and coronary angiography with FFR_{CT}, during the same visit, coupled with serial assessments of multisystem biomarkers and patient reported outcome measures, is novel. FFR_{CT} provided a high level of certainty for identifying flow-limiting coronary artery disease (myocardial ischemia) as a confounding associate for myocardial inflammation in this post-COVID-19 population.

Our study was designed to minimize selection bias excepting those who were unable to comply with the protocol. Use of hospital-level electronic health records in real-time facilitated an unbiased approach to screening. Troponin elevation was not an eligibility criterion and renal dysfunction was not an exclusion criterion. Our study stands apart from other studies, including those which had target populations with myocardial injury defined by troponin elevation (COVID-HEART[49] and COVIDsortium[50]), retrospective case selection[18,19] or a sample size limiting generalizable conclusions[11].

Our study minimized ascertainment bias which may have affected prior studies of myocarditis. The diagnosis of each patient was independently adjudicated by a committee of cardiologists and the statistical analysis was undertaken by biostatisticians independent of the research team. Since the study involved a single imaging reference center and central laboratories for biomarkers, measurement variations were minimized. The results may reasonably be considered as representative of post-COVID-19 populations who received hospital care.

This study was designed but not powered to assess clinical outcomes such as rehospitalization and death. In 47,780 individuals (mean age 65 years, 55% men) hospitalized with COVID-19 and discharged alive, during a mean follow-up of 140 days, nearly a third of individuals were readmitted (14,060 of 47,780) and more than one in ten (5875) died after discharge, with these events occurring at rates four and eight times greater, respectively, than in the matched control group[6].

Limitations

By designating imaging during the convalescent phase, the community-based participants were not anticipated to be infectious. This approach aligns with the International Severe Acute Respiratory and Emerging Infection Coronavirus Clinical Characterisation Consortium (ISARIC4C) study[51]. Since multi-organ imaging was not performed during the acute phase, some pathologies that might have been detected acutely may have resolved by 28 days. Our findings may therefore under-estimate disease burden. Most of the patients were unvaccinated. The incidence of myocarditis in hospitalized vaccinated patients warrants investigation. The definition of acute kidney injury was based on in-hospital blood tests. Endomyocardial biopsy (EMB) was not performed. Longer term follow-up is ongoing.

Conclusions

The illness trajectory of COVID-19 includes persisting cardio-renal inflammation, lung involvement, and hemostatic pathway activation. Adjudicated myocarditis occurred in one in eight patients and was associated with poorer health-related quality of life, psychological wellbeing, physical activity, and predicted aerobic exercise capacity. The results support the rationale for cardio-renal therapy development for prevention of post-COVID-19 syndromes.

Declarations

Disclosures

CB is employed by the University of Glasgow which holds consultancy and research agreements with Abbott Vascular, AstraZeneca, Boehringer Ingelheim, Coroventis, GSK, HeartFlow, Menarini, Novartis, Siemens Healthcare and Somalogic. These companies had no role in the design or conduct of the study, or in the data collection, interpretation, or reporting. HeartFlow derived FFR_{CT}. None of the other authors have any relevant disclosures.

Contributors

CB designed the study and wrote the first draft of the manuscript with KM. AMcI and AMcC developed the statistical analysis plan and performed the statistical analyses. The co-authors reviewed the manuscript drafts. Each author has individually contributed to either the delivery of the study or helped to devise aspects of the study protocol. All authors have given final approval for the current version to be published.

References

1. Carfì, A., Bernabei, R., Landi, F., & Gemelli Against COVID-19 Post-Acute Care Study Group. Persistent Symptoms in Patients After Acute COVID-19. *JAMA* **324**, 603–605 (2020).
2. Mandal, S. *et al.* 'Long-COVID': a cross-sectional study of persisting symptoms, biomarker and imaging abnormalities following hospitalisation for COVID-19. *Thorax* **76**, 396–398 (2021).
3. Dennis, A. *et al.* Multiorgan impairment in low-risk individuals with post-COVID-19 syndrome: a prospective, community-based study. *BMJ Open* **11**, e048391 (2021).
4. Cirulli, E. T. *et al.* Long-term COVID-19 symptoms in a large unselected population. *medRxiv* 2020. 10.07.20208702 (2020) doi:10.1101/2020.10.07.20208702.
5. Prevalence of ongoing symptoms following coronavirus (COVID-19) infection in the UK - Office for National Statistics. https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/conditionsanddiseases/bulletins/prevalenceofongoingsymptomsfollowin
6. Ayoubkhani, D. *et al.* Post-covid syndrome in individuals admitted to hospital with covid-19: retrospective cohort study. *BMJ* **372**, n693 (2021).
7. Daugherty, S. E. *et al.* Risk of clinical sequelae after the acute phase of SARS-CoV-2 infection: retrospective cohort study. *BMJ* **373**, n1098 (2021).
8. Group, P.-C. C. *et al.* Physical, cognitive and mental health impacts of COVID-19 following hospitalisation – a multi-centre prospective cohort study. *medRxiv* 2021.03.22.21254057 (2021) doi:10.1101/2021.03.22.21254057.
9. Raman, B. *et al.* Medium-term effects of SARS-CoV-2 infection on multiple vital organs, exercise capacity, cognition, quality of life and mental health, post-hospital discharge. *EClinicalMedicine* **31**, (2021).
10. Drake, T. M. *et al.* Characterisation of in-hospital complications associated with COVID-19 using the ISARIC WHO Clinical Characterisation Protocol UK: a prospective, multicentre cohort study. *Lancet* **398**, 223–237 (2021).
11. Singh, T. *et al.* MRI and CT coronary angiography in survivors of COVID-19. *Heart* (2021) doi:10.1136/heartjnl-2021-319926.
12. Blomberg, B. *et al.* Long COVID in a prospective cohort of home-isolated patients. *Nat Med* **27**, 1607–1613 (2021).
13. Zhou, P. *et al.* A pneumonia outbreak associated with a new coronavirus of probable bat origin. *Nature* **579**, 270–273 (2020).
14. Hoffmann, M. *et al.* SARS-CoV-2 Cell Entry Depends on ACE2 and TMPRSS2 and Is Blocked by a Clinically Proven Protease Inhibitor. *Cell* **181**, 271-280.e8 (2020).
15. Guzik, T. J. *et al.* COVID-19 and the cardiovascular system: implications for risk assessment, diagnosis, and treatment options. *Cardiovasc Res* doi:10.1093/cvr/cvaa106.
16. Varga, Z. *et al.* Endothelial cell infection and endotheliitis in COVID-19. *The Lancet* **395**, 1417–1418 (2020).
17. Caforio, A. L. P. *et al.* Current state of knowledge on aetiology, diagnosis, management, and therapy of myocarditis: a position statement of the European Society of Cardiology Working Group on Myocardial and Pericardial Diseases. *European Heart Journal* **34**, 2636–2648 (2013).
18. Puntmann, V. O. *et al.* Outcomes of Cardiovascular Magnetic Resonance Imaging in Patients Recently Recovered From Coronavirus Disease 2019 (COVID-19). *JAMA Cardiol* (2020) doi:10.1001/jamacardio.2020.3557.
19. Kotecha, T. *et al.* Patterns of myocardial injury in recovered troponin-positive COVID-19 patients assessed by cardiovascular magnetic resonance. *European Heart Journal* (2021) doi:10.1093/eurheartj/ehab075.
20. Hare, S. S. *et al.* The continuing evolution of COVID-19 imaging pathways in the UK: a British Society of Thoracic Imaging expert reference group update. *Clinical Radiology* **75**, 399–404 (2020).
21. Chung, M. *et al.* CT Imaging Features of 2019 Novel Coronavirus (2019-nCoV). *Radiology* **295**, 202–207 (2020).
22. Thygesen, K. *et al.* Fourth universal definition of myocardial infarction (2018). *Eur Heart J* **40**, 237–269 (2019).
23. Khwaja, A. KDIGO Clinical Practice Guidelines for Acute Kidney Injury. *NEC* **120**, c179–c184 (2012).
24. Levey, A. S. *et al.* A New Equation to Estimate Glomerular Filtration Rate. *Ann Intern Med* **150**, 604–612 (2009).
25. Cury, R. C. *et al.* CAD-RADS^{TM}: Coronary Artery Disease - Reporting and Data System: An Expert Consensus Document of the Society of Cardiovascular Computed Tomography (SCCT), the American College of Radiology (ACR) and the North American Society for Cardiovascular Imaging (NASCI). Endorsed by the American College of Cardiology. *J Am Coll Radiol* **13**, 1458-1466.e9 (2016).
26. Sianos, G. *et al.* The SYNTAX Score: an angiographic tool grading the complexity of coronary artery disease. *EuroIntervention* **1**, 219–227 (2005).

27. Qanadli, S. D. *et al.* New CT index to quantify arterial obstruction in pulmonary embolism: comparison with angiographic index and echocardiography. *AJR Am J Roentgenol* **176**, 1415–1420 (2001).
28. Kramer, C. M. *et al.* Standardized cardiovascular magnetic resonance imaging (CMR) protocols: 2020 update. *Journal of Cardiovascular Magnetic Resonance* **22**, 17 (2020).
29. Ferreira, V. M. *et al.* Cardiovascular Magnetic Resonance in Nonischemic Myocardial Inflammation: Expert Recommendations. *J. Am. Coll. Cardiol.* **72**, 3158–3176 (2018).
30. Petersen, S. E. *et al.* Reference ranges for cardiac structure and function using cardiovascular magnetic resonance (CMR) in Caucasians from the UK Biobank population cohort. *Journal of Cardiovascular Magnetic Resonance* **19**, 18 (2017).
31. Wolf, M. *et al.* Magnetic resonance imaging T1- and T2-mapping to assess renal structure and function: a systematic review and statement paper. *Nephrology Dialysis Transplantation* **33**, ii41–ii50 (2018).
32. Dekkers, I. A. *et al.* Consensus-based technical recommendations for clinical translation of renal T1 and T2 mapping MRI. *MAGMA* **33**, 163–176 (2020).
33. EQ-5D-5L – EQ-5D. https://euroqol.org/eq-5d-instruments/eq-5d-5l-about/.
34. Broadbent, E., Ellis, C. J., Thomas, J., Gamble, G. & Petrie, K. J. Further development of an illness perception intervention for myocardial infarction patients: a randomized controlled trial. *J Psychosom Res* **67**, 17–23 (2009).
35. Löwe, B. *et al.* A 4-item measure of depression and anxiety: validation and standardization of the Patient Health Questionnaire-4 (PHQ-4) in the general population. *J Affect Disord* **122**, 86–95 (2010).
36. Hlatky, M. A. *et al.* A brief self-administered questionnaire to determine functional capacity (the Duke Activity Status Index). *Am. J. Cardiol.* **64**, 651–654 (1989).
37. Lee, P. H., Macfarlane, D. J., Lam, T. & Stewart, S. M. Validity of the international physical activity questionnaire short form (IPAQ-SF): A systematic review. *International Journal of Behavioral Nutrition and Physical Activity* **8**, 115 (2011).
38. Docherty, A. B. *et al.* Features of 20 133 UK patients in hospital with covid-19 using the ISARIC WHO Clinical Characterisation Protocol: prospective observational cohort study. *BMJ* **369**, m1985 (2020).
39. von Elm, E. *et al.* The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *Lancet* **370**, 1453–1457 (2007).
40. REMAP CAP, ACTIV-4a & ATTACC investigators. Therapeutic Anticoagulation with Heparin in Critically Ill Patients with Covid-19. *New England Journal of Medicine* **385**, 777–789 (2021).
41. Connors, J. M. *et al.* Effect of Antithrombotic Therapy on Clinical Outcomes in Outpatients With Clinically Stable Symptomatic COVID-19: The ACTIV-4B Randomized Clinical Trial. *JAMA* (2021) doi:10.1001/jama.2021.17272.
42. Conway, E. M. & Pryzdial, E. L. G. Is the COVID-19 thrombotic catastrophe complement-connected? *J Thromb Haemost* **18**, 2812–2822 (2020).
43. Drake, T. M. *et al.* Characterisation of in-hospital complications associated with COVID-19 using the ISARIC WHO Clinical Characterisation Protocol UK: a prospective, multicentre cohort study. *The Lancet* **398**, 223–237 (2021).
44. Sullivan, M. K. *et al.* Acute kidney injury in patients hospitalised with COVID-19 from the ISARIC WHO CCP-UK Study: a prospective, multicentre cohort study. *Nephrology Dialysis Transplantation* (2021) doi:10.1093/ndt/gfab303.
45. Phillips, S. & Williams, M. A. Confronting Our Next National Health Disaster — Long-Haul Covid. *New England Journal of Medicine* **385**, 577–579 (2021).
46. Ukena, C. *et al.* Diagnostic and prognostic validity of different biomarkers in patients with suspected myocarditis. *Clin Res Cardiol* **103**, 743–751 (2014).
47. The RECOVERY Collaborative Group. Dexamethasone in Hospitalized Patients with Covid-19. *New England Journal of Medicine* (2020) doi:10.1056/NEJMoa2021436.
48. Wanner, C. *et al.* Empagliflozin and Progression of Kidney Disease in Type 2 Diabetes. *New England Journal of Medicine* **375**, 323–334 (2016).
49. Gorecka, M. *et al.* Demographic, multi-morbidity and genetic impact on myocardial involvement and its recovery from COVID-19: protocol design of COVID-HEART-a UK, multicentre, observational study. *J Cardiovasc Magn Reson* **23**, 77 (2021).
50. Joy, G., Artico, J., Kurdi, H., Seraphim, A. & Lau, C. Prospective case-control study of cardiovascular abnormalities six months following mild COVID-19 in healthcare workers. *JACC: Cardiovascular Imaging* (2021).
51. ISARIC 4C (Coronavirus Clinical Characterisation Consortium). *isaric4c.github.io* https://isaric4c.net/index.html.

Tables

Table 1. Clinical characteristics of the study population by likelihood of adjudicated myocarditis post-COVID-19.

	COVID-19	Controls		Myocarditis				
			p-value	Not likely	Unlikely	Probable	Very likely	p-value
	n = 161	n = 27		n = 17 (10%)	n = 56 (35%)	n = 67 (42%)	n = 21 (13%)	
Demographic								
Age ±SD, years	54.6±12.0	56.5±9.3	0.702	56.9±11.4	55.1±13.3	53.6±11.6	54.9±10.1	0.669
Male sex, n (%)	92 (57.1)	16 (59.3)	1.000	13 (76.5)	35 (62.5)	35 (52.2)	9 (42.9)	0.136
Female sex, n (%)	69 (42.9)	11 (40.7)		4 (23.5)	21 (37.5)	32 (47.8)	12 (57.1)	
Most deprived SIMD Quintile (Q1), n (%)	61 (40.1)	5 (18.5)	0.058	4 (25.0)	20 (37.0)	25 (40.3)	12 (60.0)	0.066
Healthcare worker, n (%)	36 (22.4)	5 (19.2)	1.000	1 (5.9)	10 (17.9)	18 (26.9)	7 (33.3)	0.132
Ethnicity, n (%)								
Arab	4 (2.5)	0 (0.0)	0.738	0 (0.0)	2 (3.6)	1 (1.5)	1 (4.8)	0.254
Black	2 (1.2)	0 (0.0)		0 (0.0)	0 (0.0)	2 (3.0)	0 (0.0)	
East Asian	4 (2.5)	0 (0.0)		0 (0.0)	2 (3.6)	2 (3.0)	0 (0.0)	
South Asian	8 (5.0)	2 (7.4)		0 (0.0)	0 (0.0)	6 (9.0)	2 (9.5)	
West Asian	2 (1.2)	1 (3.7)		1 (5.9)	1 (1.8)	0 (0.0)	0 (0.0)	
Latin American	0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
White	141 (87.6)	24 (88.9)		16 (94.1)	51 (91.1)	56 (83.6)	18 (85.7)	
Presenting characteristics, mean (SD)								
Body mass index, kg/m^2	30.5 (7.1)	30.6 (5.1)	0.701	30.9 (5.6)	29.6 (5.8)	31.1 (8.6)	30.6 (6.4)	0.804
Heart rate, bpm	**95 (19)**	**66 (11)**	**<0.001**	98 (19)	94 (20)	95 (17)	94 (25)	0.584
Systolic blood pressure, mmHg	**129 (20)**	**143 (19)**	**0.003**	122 (24)	135 (18)	127 (20)	124 (17)	0.150
Diastolic blood pressure, mmHg	**77 (13)**	**84 (14)**	**0.018**	74 (13)	79 (12)	77 (14)	74 (12)	0.441
Peripheral oxygen saturation, %	**93 (6)**	**98 (2)**	**<0.001**	91 (10)	94 (5)	94 (6)	94 (9)	0.758
Respiratory rate, min	**24 (12)**	**14 (2)**	**<0.001**	22 (5)	23 (11)	25 (16)	21 (6)	0.302
WHO clinical severity score, n (%)								
No evidence of infection	**0 (0.0)**	**27 (100.0)**	**<0.001**	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0.111
Hospitalized, no oxygen therapy	**50 (31.1)**	**0 (0.0)**		3 (17.6)	17 (30.4)	24 (35.8)	6 (28.6)	
Oxygen therapy by mask or nasal prongs	**76 (47.2)**	**0 (0.0)**		8 (47.1)	30 (53.6)	30 (44.8)	8 (38.1)	
Non-invasive ventilation	**20 (12.4)**	**0 (0.0)**		4 (23.5)	7 (12.5)	8 (11.9)	1 (4.8)	
Mechanical ventilation	**5 (3.1)**	**0 (0.0)**		0 (0.0)	0 (0.0)	3 (4.5)	2 (9.5)	
Ventilation with organ support	**10 (6.2)**	**0 (0.0)**		2 (11.8)	2 (3.6)	2 (3.0)	4 (19.0)	
COVID-19 diagnosis, n (%)								
PCR test	**158 (98.1)**	**-**	**<0.001**	17 (100.0)	56 (100.0)	65 (97.0)	20 (95.2)	0.388
Nosocomial	8 (5)	0	0.605	0 (0.0)	4 (7.1)	4 (6.0)	0 (0.0)	0.488
Antibody test*	-	27 (100.0)	**<0.001**					
Radiology, chest radiograph or CT scan, n (%)								
Typical features of COVID-19	**111 (75.0)**	**-**		**12 (75.0)**	**40 (78.4)**	**43 (69.4)**	**16 (84.2)**	**0.027**
Atypical features of COVID-19	**11 (7.4)**	**-**		**2 (12.5)**	**3 (5.9)**	**4 (6.5)**	**2 (10.5)**	
Unlikely	**4 (2.7)**	**-**		**2 (12.5)**	**0 (0.0)**	**1 (1.6)**	**1 (5.3)**	
Normal	**22 (14.9)**	**-**		**0 (0.0)**	**8 (15.7)**	**14 (22.6)**	**0 (0.0)**	
Acute COVID-19 therapy, n (%)								
Oxygen	111 (68.9)	-		14 (82.4)	39 (69.6)	43 (64.2)	15 (71.4)	0.558
Steroid	89 (55.3)	-		12 (70.6)	31 (55.4)	36 (53.7)	10 (47.6)	0.545
Antiviral	42 (26.1)	-		9 (52.9)	15 (26.8)	14 (20.9)	4 (19.0)	0.064
Non-invasive respiratory support	31 (19.3)	-		5 (29)	9 (16.1)	11 (16.4)	6 (28.6)	0.358
Intensive care	24 (14.9)	-		**5 (29.4)**	**5 (8.9)**	**8 (11.9)**	**6 (28.6)**	**0.045**
Invasive ventilation	14 (8.7)	-		**2 (11.8)**	**1 (1.8)**	**5 (7.5)**	**6 (28.6)**	**0.004**
Intravenous inotrope	7 (4.3)	-		1 (5.9)	2 (3.6)	1 (1.5)	3 (14.3%)	0.090
Cardiovascular history, n (%)								
Smoking: Never	107 (66.5)	17 (63.0)	0.826	12 (70.6)	38 (67.9)	45 (67.2)	12 (57.1)	0.512
Smoking: Former	44 (27.3)	9 (33.3)		4 (23.5)	17 (30.4)	17 (25.4)	6 (28.6)	
Smoking: Current	10 (6.2)	1 (3.7)		1 (5.9)	1 (1.8)	5 (7.5)	3 (14.3)	
Hypercholesterolemia	77 (47.8)	12 (44.4)	0.836	10 (58.8)	30 (53.6)	29 (43.3)	8 (38.1)	0.402
Hypertension	57 (35.4)	9 (33.3)	1.000	8 (47.1)	21 (37.5)	19 (28.4)	9 (42.9)	0.363
Diabetes mellitus	35 (21.7)	2 (7.4)	0.115	2 (11.8)	17 (30.4)	13 (19.4)	3 (14.3)	0.277
Chronic kidney disease	7 (4.3)	0 (0.0)	0.596	1 (5.9)	1 (1.8)	4 (6.0)	1 (4.8)	0.559
CCS Angina Class: No angina	156 (96.9)	27 (100.0)	1.000	16 (94.1)	55 (98.2)	66 (98.5)	19 (90.5)	0.177
CCS Angina Class I-IV	5 (3.1)	0 (0.0)		1 (5.9)	1 (0.6)	1 (0.6)	2 (3.5)	
Myocardial Infarction	17 (10.6)	0 (0.0)	0.138	3 (17.6)	6 (10.7)	6 (9.0)	2 (9.5)	0.719
Heart failure	6 (3.7)	0 (0.0)	0.596	0	2 (3.6)	3 (4.5)	1 (4.8)	1
Stroke or TIA	6 (3.7)	2 (7.4)	0.323	1 (5.9)	1 (1.8)	4 (6.0)	0 (0.0)	0.476
Peripheral vascular disease	1 (0.6)	0 (0.0)	1.000	1 (5.9)	0 (0.0)	0 (0.0)	0 (0.0)	0.106
Previous PCI	10 (6.2)	0 (0.0)	0.362	3 (17.6)	2 (3.6)	4 (6.0)	1 (4.8)	0.204
Previous CABG	2 (1.2)	0 (0.0)	1.000	0 (0.0)	1 (1.8)	1 (1.5)	0 (0.0)	1.000
Cardiovascular disease and / or treatment	75 (46.6)	13 (48.1)	1.000	8 (47.1)	29 (51.8)	27 (40.3)	11 (52.4)	0.575
Risk scores, mean (SD)								
ISARIC-4C in-hospital mortality risk, %	**12.3 (10.7)**	**5.4 (6.2)**	**0.0003**	14.0 (10.7)	13.2 (11.4)	10.9 (9.8)	12.8 (11.7)	0.575
Q-Risk 3, 10-year cardiovascular risk, %	13.7 (11.1)	12.5 (9.7)	0.757	12.5 (7.9)	15.5 (12.8)	12.3 (9.9)	14.3 (13.1)	0.794
Charlson Comorbidity Index	1.9 (1.8)	1.3 (1.1)	0.179	1.7 (1.9)	2.1 (2.0)	1.9 (1.8)	1.6 (1.2)	0.819
Pre-existing maintenance medication, n (%)								
Aspirin	12 (7.5)	0 (0.0)	0.221	3 (17.6)	4 (7.1)	4 (6.0)	1 (4.8)	0.426

Statin	46 (28.6)	10 (37.0)	0.372	7 (41.2)	20 (35.7)	13 (19.4)	6 (28.6)	0.129
Beta-blocker	20 (12.4)	2 (7.4)	0.746	3 (17.6)	7 (12.5)	5 (7.5)	5 (23.8)	0.181
Angiotensin converting enzyme inhibitor	36 (22.4)	3 (11.1)	0.303	6 (35.3)	11 (19.6)	14 (20.9)	5 (23.8)	0.566
Angiotensin receptor blocker	10 (6.2)	2 (7.4)	0.684	0 (0.0)	6 (10.7)	3 (4.5)	1 (4.8)	0.428
Oral anticoagulation	8 (5.0)	1 (3.7)	1.000	1 (5.9)	3 (5.4)	3 (4.5)	1 (4.8)	1.000
Laboratory results, index admission								
Initial hemoglobin, mean (SD), g/L	141 (16)	144 (12)	0.337	142 (15)	140 (17)	140 (15)	143 (16)	0.519
Initial platelet count, mean (SD), $x10^9$/L	236 (94)	266 (52)	0.002	264 (137)	217 (75)	242 (9)	248 (95)	0.395
Initial white cell count, mean (SD), $x10^9$/L	7.4 (5.6)	6.9 (2.0)	0.432	7.3 (4.8)	6.7 (2.6)	8.0 (7.8)	7.5 (3.0)	0.690
Initial lymphocyte count, mean (SD), $x10^9$/L	1.5 (4.6)	2.0 (0.6)	<0.001	1.0 (0.5)	1.1 (0.5)	2.1 (7.2)	1.4 (0.6)	0.250
Peak D-Dimer, mean (SD), ng/mL	1719 (5439)	245 (213)	0.006	2022 (4159)	916 (2132)	1704 (6489)	3127 (7431)	0.925
Peak creatinine, mean (SD), µmol/L	104 (95)	67 (12)	0.211	99 (54)	89 (57)	96 (78)	168 (187)	0.538
Minimum eGFR, ml/min/1.73m^2	81 (28)	90 (24)	0.536	80 (27)	85 (23)	83 (27)	69 (37)	0.486
Acute kidney injury, n (%)	21 (15)	-	1.000	3 (19)	2 (4)	10 (18)	6 (33)	0.008
Peak hs-troponin I, median (IQR), ng/L	4.0 (3.0,13.0)	4.0 (4.0, 4.0)	0.242	6.0 (4.0,11.0)	4.0 (3.0,10.0)	4.0 (3.0,11.2)	30.0 (3.5, 83.8)	0.157
Peak ferritin, mean (SD), mg/L	360 (182, 863)	106 (66, 164)	<0.001	454 (184, 835)	359 (212, 1082)	332 (159, 670)	562 (198, 1860)	0.414
Peak C-reactive protein, median (IQR), mg/L	128 (108)	17 (71)	<0.001	158 (132)	118 (92)	116 (91)	169 (159)	0.654
HbA1c, mean mmol/mol Hb, %	47.9 (18.3)	44.6 (22.5)	0.031	57.3 (32.3)	50.5 (18.1)	44.6 (13.4)	44.9 (19.2)	0.088
Initial albumin, mean, g/L	34.1 (5.3)	40.7 (4.4)	<0.001	32.1 (5.0)	35.0 (4.4)	33.7 (6.1)	34.8 (4.8)	0.267
Timelines								
Hospitalized, n (%)	145 (90)			16 (94)	53 (95)	56 (84)	20 (95)	0.194
Duration of admission, mean (SD), days	12 (21)			11 (13)	9 (12)	11 (16)	26 (44)	0.827
Symptom onset to primary outcome, mean (SD) days	65 (20)			66 (13)	62 (15)	65 (18)	73 (38)	0.850
Diagnosis to primary outcome, mean (SD) days	61 (20)			63 (14)	58 (15)	61 (18)	67 (37)	0.831

Ethnicity: Indian (0), Pakistani (0), Bangladeshi (0), Other Asian (3 (1.9%)), Black Caribbean (0), Black African (2 (1.2%), Chinese 1 (0.6%)), Other 13 (8.1%), White, n=142 (88.2%). Missing data in post-COVID-19 patients: D-Dimer, n=62; HbA1c, n=24; ferritin, n=19; troponin I, n=22. CCS – Canadian Cardiovascular Society; GFR - glomerular filtration rate was estimated using the Chronic Kidney Disease Epidemiology equation[24], ISARIC-4C - Coronavirus Clinical Characterisation Consortium; PCR – polymerase chain reaction; SD – standard deviation; SIMD - Scottish Index of Multiple Deprivation; TIA – transient ischaemic attack; WHO – World Health Organization. In the control group, the Abbott Architect CMIA SARS-CoV-2 IgG assay* was used to confirm absence of prior infection with COVID-19. The primary outcome evaluation (visit 2) was scheduled 28-60 days post-discharge.

Table 2. Multisystem phenotypying: serial electrocardiography, biomarkers of inflammation, metabolism, renal function, and hemostasis, and heart, lung, and kidney imaging at 28-60 days post-discharge.

				Myocarditis				
	COVID-19 (n = 161)	Controls (n = 27)	P-value	Not likely n = 17 (10%)	Unlikely n = 56 (35%)	Probable n = 67 (42%)	Very likely n = 21 (13%)	P-value
Electrocardiogram, n (%)								
Admission (n = 152)								
Myopericarditis criteria	32 (21.1)	0 (0)	0.005	3 (17.6)	9 (16.7)	14 (23.3)	6 (28.6)	0.635
Premature atrial contraction	2 (1.3)	0 (0)	1.000	0 (0.0)	0 (0.0)	2 (3.3)	0 (0.0)	0.716
Premature ventricular contraction	3 (2.0)	0 (0)	1.000	1 (5.9)	0 (0.0)	0 (0.0)	2 (9.5)	0.014
Atrial fibrillation or flutter, n = 9 missing	5 (3.3)	0 (0)	1.000	0 (0.0)	2 (3.6)	2 (3.3)	1 (4.8)	1.000
Enrolment (n = 148)								
Myopericarditis criteria	47 (31.8)	0 (0)	<0.001	3 (21.4)	16 (30.2)	20 (31.7)	8 (44.4)	0.586
Premature atrial contraction	7 (4.7)	0 (0)	0.596	1 (5.9)	3 (5.4)	2 (3.0)	1 (4.8)	0.792
Premature ventricular contraction	1 (0.6)	0 (0)	1.000	0 (0.0)	1 (1.8)	0 (0.0)	0 (0.0)	0.564
Atrial fibrillation or flutter	3 (2.0)	0 (0)	1.000	0 (0.0)	1 (1.8)	1 (1.6)	1 (5.9)	0.621
28-60 days post-discharge (n = 144)								
Myopericarditis criteria	33 (22.9)	0 (0)	0.003	2 (14.3)	10 (20.4)	14 (23.0)	7 (35.0)	0.539
Premature atrial contraction	8 (5.0)	0 (0)	0.605	1 (5.9)	3 (5.4)	3 (4.5)	1 (4.8)	1.00
Premature ventricular contraction	2 (1.2)	0 (0)	1.000	1 (5.9)	0 (0.0)	1 (1.5)	0 (0.0)	0.217
Atrial fibrillation or flutter	2 (1.3)	0 (0)	1.000	0 (0.0)	0 (0.0)	1 (1.6)	1 (5.0)	0.527
CT chest 28-60 days post-discharge								
Ground glass opacity and/or consolidation, n (%)	71 (44.7)	0 (0.0)	<0.001	10 (66.7)	26 (46.4)	25 (37.3)	10 (47.6)	0.210
Reticulation and/or architectural distortion, n (%)	47 (29.6)	1 (4.5)	0.010	6 (40.0)	15 (26.8)	18 (26.9)	8 (38.1)	0.566
Atelectasis, n (%)	13 (8.2)	0 (0.0)	0.372	1 (6.7)	7 (12.5)	4 (6.0)	1 (4.8)	0.601
Pulmonary arterial thrombus, n (%)	5 (3.3)	0 (0.0)	1.000	0 (0.0)	2 (3.6)	2 (3.1)	1 (5.3)	0.905
Visual estimate of % of total lung area abnormal, mean (SD)	14.4 (19.2)	0.1 (0.5)	<0.001	19.3 (22.5)	12.7 (17.60	12.7 (17.9)	21.1 (23.4)	0.299
<20%, n (%)	108 (67.9)	22 (100)	0.005	9 (60.0)	38 (67.9)	49 (73.1)	12 (57.1)	0.399
≥20%, n (%)	38 (23.9)	0 (0.0)		3 (20.0)	15 (26.8)	14 (20.9)	6 (28.6)	
≥50%, n (%)	13 (8.2)	0 (0.0)		3 (20.0)	3 (5.4)	4 (6.0)	3 (14.3)	
CT coronary angiogram 28-60 days post-discharge								
Coronary calcium - Agatston score, mean (SD)	146 (500)	75 (289)	0.077	44 (61)	253 (730)	98 (363)	91 (162)	0.124
CADS-RADS score, n (%)								
Level 0	77 (52.4)	12 (52.2)	0.940	3 (25.0)	23 (43.4)	40 (64.5)	11 (55.0)	0.068
Level 1	42 (28.6)	7 (30.4)		7 (58.3)	18 (34.0)	12 (19.4)	5 (25.0)	
Level 2	9 (6.1)	2 (8.7)		0 (0.0)	4 (7.5)	4 (6.5)	1 (5.0)	
Level 3	6 (4.1)	1 (4.3)		1 (8.3)	1 (1.9)	4 (6.5)	0 (0.0)	
Level 4	13 (8.8)	1 (4.3)		1 (8.3)	7 (13.2)	2 (3.2)	3 (15.0)	
Level 5	0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
Obstructive coronary artery disease, n (%)	21 (13.7)	1 (4.3)	0.316	3 (20.0)	7 (12.7)	7 (10.9)	4 (21.1)	0.526
FFR_{CT}, patient level (all coronary arteries)								
Median FFR_{CT}, mean (SD)	0.93 (0.03)	0.94 (0.02)	0.094	0.92 (0.03)	0.93 (0.04)	0.93 (0.03)	0.92 (0.04)	0.308
Minimum FFR_{CT}, mean (SD)	0.80 (0.10)	0.85 (0.08)	<0.001	0.82 (0.08)	0.79 (0.11)	0.80 (0.09)	0.76 (0.13)	0.578
Minimum FFR_{CT} ≤0.80, n (%)	52 (38.8)	5 (21.7)	0.159	5 (41.7)	16 (34.8)	22 (37.9)	9 (50.0)	0.731
Cardiovascular MRI 28-60 days post-discharge								
LV end-diastolic volume index, mean (SD), mL/m^2	76.3 (17.6)	71.1 (13.5)	0.165	77.2 (17.9)	74.1 (16.6)	78.3 (18.5)	75.2 (17.7)	0.831
LV end-systolic volume index, mean (SD), mL/m^2	35.6 (13.2)	27.8 (9.7)	0.001	34.6 (11.1)	33.7 (11.7)	37.0 (14.9)	36.6 (12.4)	0.743
LV ejection fraction, mean (SD), %	54.0 (9.6)	61.5 (8.8)	<0.001	54.8 (9.8)	55.1 (10.1)	53.8 (8.6)	51.3 (11.5)	0.416
LV ejection fraction reduced, males <48%, n (%)	20 (22.0)	1 (7.1)	0.292	2 (15.4)	6 (17.1)	9 (25.7)	3 (33.3)	0.655
LV ejection fraction reduced, females <51%, n (%)	12 (17.6)	0 (0.0)	0.346	1 (25.0)	0 (0.0)	6 (18.8)	5 (41.7)	0.012
LV mass index, mean (SD), g/m^2	92.2 (26.0)	119.5 (25.4)	<0.001	100.9 (18.9)	93.2 (21.5)	90.6 (28.7)	87.6 (31.6)	0.185
LV global longitudinal strain, mean (SD), %	-14.2 (3.0)	-14.5 (7.2)	0.017	-13.7 (3.1)	-13.9 (2.9)	-14.6 (3.0)	-14.1 (3.0)	0.402
LV global circumferential strain, mean (SD), %	-17.0 (3.3)	-18.2 (2.9)	0.050	-17.4 (3.6)	-17.0 (3.4)	-17.0 (3.1)	-16.6 (3.4)	0.834
LV global radial strain, mean (SD), %	28.2 (7.8)	31.3 (7.6)	0.054	29.3 (8.4)	28.4 (8.3)	28.1 (7.3)	27.1 (7.9)	0.806
RV end-diastolic volume index, mean (SD), mL/m^2	73.5 (17.7)	79.2 (14.6)	0.039	77.8 (18.7)	72.7 (19.7)	73.0 (16.9)	73.3 (13.9)	0.775
RV end-systolic volume index, mean (SD), mL/m^2	36.0 (11.3)	33.6 (10.1)	0.665	34.6 (12.4)	36.6 (11.9)	35.3 (11.4)	38.1 (8.3)	0.552
RV ejection fraction, mean (SD), %	51.1 (10.5)	58.3 (9.4)	<0.001	54.6 (15.9)	49.9 (9.5)	52.2 (9.1)	47.5 (11.4)	0.187
RV global longitudinal strain, mean (SD), %	-17.2 (5.9)	-19.4 (5.8)	0.086	-14.4 (9.5)	-17.5 (5.4)	-18.0 (5.3)	-15.6 (4.3)	0.153
Myocardial tissue characterization								
Increased global T1 (>1233 ms), n (%)	56 (35.0)	4 (16.7)	0.101	2 (12.5)	14 (25.0)	31 (46.3)	9 (42.9)	0.015
Increased global T2 (>44 ms), n (%)	10 (6.2)	0 (0.0)	0.364	0 (0.0)	0 (0.0)	6 (9.0)	4 (19.0)	0.007
T2 ratio (myocardium/ serratus anterior), n (%)	1.7 (0.2)	1.6 (0.1)	0.140	1.6 (0.2)	1.6 (0.2)	1.8 (0.2)	1.8 (0.3)	<0.001
Increased global extracellular volume (>27.4%), n (%)	72 (49.7)	4 (18.2)	0.006	1 (7.7)	22 (41.5)	36 (60.0)	13 (68.4)	<0.001
Late gadolinium enhancement								
Myocardial late gadolinium enhancement, n (%)	32 (20.0)	0 (0.0)	0.010	4 (25.0)	7 (12.5)	15 (22.4)	6 (28.6)	0.290
Ischemic distribution, n (%)	8 (5.4)	0 (0.0)	0.600	0 (0.0)	2 (3.9)	5 (7.8)	1 (5.6)	0.768
Non-ischemic distribution, n (%)	26 (17.4)	0 (0.0)	0.027	4 (28.6)	5 (9.8)	10 (15.6)	7 (35.0)	0.049

				Myocarditis				
	COVID-19 (n = 161)	Controls (n = 27)	P-value	Not likely n = 17 (10%)	Unlikely n = 56 (35%)	Probable n = 67 (42%)	Very likely n = 21 (13%)	P-value
Pericardial thickening, n (%)	**35 (22.0)**	**0 (0.0)**	**0.005**	1 (5.9)	10 (18.5)	17 (25.8)	7 (33.3)	0.168
Pericardial effusion, n (%)	17 (10.7)	0 (0.0)	0.134	0 (0.0)	5 (9.1)	8 (12.1)	4 (19.0)	0.277
Right atrial area, mean (SD), cm^2	18.8 (4.7)	19.5 (4.2)	0.399	19.2 (3.9)	18.8 (4.9)	18.3 (5.1)	19.9 (3.2)	0.253
Left atrial area, mean (SD), cm^2	20.7 (4.7)	21.8 (4.6)	0.231	22.3 (5.0)	19.9 (4.2)	20.7 (5.1)	21.9 (4.1)	0.214
Myocardial inflammation (Lake Louise criteria), n (%)								
No evidence (0/2)	**17 (10.6)**	**27 (100)**	**<0.001**	**12 (75.0)**	**5 (8.9)**	**0 (0.0)**	**0 (0.0)**	**<0.001**
Probable (1/2)	**75 (46.9)**	**0 (0)**	**<0.001**	**4 (25.0)**	**49 (87.5)**	**22 (32.8)**	**0 (0.0)**	**<0.001**
Definite (2/2)	**68 (42.5)**	**0 (0)**	**<0.001**	**0 (0)**	**2 (3.6)**	**45 (67.2)**	**21 (100.0)**	**<0.001**
Renal MRI, mean (SD)								
Average volume of right and left kidneys, ml	153 (31)	155 (34)	0.887	158 (37)	154 (25)	150 (33)	153 (38)	0.705
Average cortex T1 of right and left kidneys, ms	1545 (62)	1515 (68)	0.063	1548 (66)	1535 (58)	1543 (63)	1585 (60)	0.110
Average medulla T1 of right and left kidneys, ms	1934 (68)	1955 (60)	0.134	**1935 (66)**	**1924 (65)**	**1925 (66)**	**2008 (57)**	**0.003**
Average T1 corticomedullary differentiation of kidneys	**0.80 (0.03)**	**0.78 (0.03)**	**<0.001**	0.80 (0.03)	0.80 (0.03)	0.80 (0.03)	0.79 (0.02)	0.475
Biomarkers at enrolment, central laboratory								
eGFR, median [IQR], ml/min/1.73m^2	96 (85, 105)	88 (70, 100)	0.063	95 (88, 103)	94 (84, 103)	94 (84, 107)	96 (83, 105)	0.916
eGFR <60 ml/min/1.73m^2, n (%)	8 (5.3%)	1 (5.3%)	1.000	1 (6.2%)	1 (1.9%)	5 (7.9%)	1 (5.3%)	0.401
C-reactive protein, mean (SD), mg/L	**26.3 (50.5)**	**2.2 (2.1)**	**<0.001**	17.3 (37.1)	31.2 (60.1)	26.9 (51.0)	18.6 (24.8)	0.987
High sensitivity troponin I, median [IQR], ng/L	4 (2, 6)	4 (4, 5)	0.365	4 (3, 5)	4 (2, 7)	3 (2, 6)	4 (3, 8)	0.771
NT pro BNP, median [IQR], pg/mL	**115 (57, 265)**	**51 (37, 88)**	**<0.001**	108 (57, 246)	116 (65, 258)	99 (51, 288)	139 (65, 274)	0.690
Ferritin, median [IQR], ug/L	**366 (203, 680)**	**186 (106, 243)**	**<0.001**	428 (143, 576)	398 (281, 658)	319 (185, 685)	379 (187, 637)	0.579
Haptoglobin, mean (SD), g/L	**2.3 (1.2)**	**1.5 (0.5)**	**0.001**	2.3 (1.1)	2.3 (1.3)	2.3 (1.2)	2.5 (1.1)	0.845
Total cholesterol, mean (SD), mmol/L	4.8 (1.4)	4.9 (1.1)	0.500	4.8 (1.4)	4.6 (1.3)	4.9 (1.5)	5.0 (1.1)	0.460
Triglycerides, mean (SD), mmol/L	**2.2 (1.3)**	**1.9 (1.3)**	**0.038**	2.3 (1.3)	2.4 (1.4)	2.2 (1.2)	2.1 (0.8)	0.797
HDL cholesterol, mean (SD), mmol/L	**1.1 (0.3)**	**1.2 (0.24)**	**0.027**	1.0 (0.3)	1.0 (0.3)	1.1 (0.4)	1.1 (0.4)	0.601
Prothrombin time, mean (SD), s	12.2 (3.7)	11.1 (0.8)	0.051	12.1 (2.0)	12.7 (5.5)	11.8 (2.5)	12.0 (1.5)	0.097
D-Dimer, mean (SD), ng/mL	**329 (221)**	**195 (180)**	**<0.001**	336 (183)	317 (167)	334 (287)	339 (177)	0.864
Fibrinogen, mean (SD), g/L	**4.1 (1.6)**	**3.0 (0.8)**	**0.001**	3.9 (1.5)	4.1 (1.7)	4.0 (1.6)	4.5 (1.9)	0.697
Factor VIII, mean (SD), IU/dL	**185 (93)**	**99 (39)**	**<0.001**	208 (88)	183 (97)	184 (98)	173 (73)	0.595
Antithrombin, mean (SD), IU/dL	111 (18)	109 (14)	0.762	108 (18)	112 (18)	111 (18)	109 (20)	0.758
Protein C, mean (SD), IU/dL	123 (30)	118 (21)	0.431	120 (30)	125 (33)	123 (21)	123 (21)	0.741
Protein S, mean (SD), IU/dL	85 (28)	98 (26)	0.063	94 (33)	87 (32)	84 (25)	75 (23)	0.256
VWF:GP1bR, mean (SD), IU/dL	**239 (130)**	**126 (41)**	**<0.001**	257 (176)	241 (118)	230 (122)	246 (122)	0.838
VWF:Ag, mean (SD), IU/dL	**246 (150)**	**157 (56)**	**<0.001**	310 (235)	233 (118)	236 (148)	261 (140)	0.483
Biomarkers at 28-60 days post-discharge, central laboratory								
eGFR, median [IQR], ml/min/1.73m^2	95 (83, 105)	88 (70, 100)	0.103	91 (79, 103)	95 (82, 106)	94 (87, 105)	98 (79, 105)	0.975
eGFR <60 ml/min/1.73m^2, n (%)	7 (4.6%)	1 (5.3%)	1.000	1 (6.7%)	1 (1.9%)	4 (6.2%)	1 (5.3%)	0.509
C-reactive protein, mean (SD), mg/L	6.6 (23.3)	2.2 (2.1)	0.241	2.9 (3.4)	3.4 (5.5)	7.7 (22.1)	14.6 (50.6)	0.994
High sensitivity troponin I, median [IQR], ng/L	**2 (2, 5)**	**4 (4, 5)**	**0.007**	2 (2, 4)	3 (2, 7)	2 (2, 4)	3 (2, 5)	0.805
NT pro BNP, median [IQR], pg/mL	**84 (55, 202)**	**51 (37, 88)**	**0.003**	60 (30, 172)	112 (65, 207)	90 (67, 171)	75 (52, 213)	0.313
Ferritin, median [IQR], ug/L	144 (71, 283)	186 (106, 243)	0.578	145 (86, 299)	158 (94, 296)	129 (59, 215)	157 (99, 319)	0.390
Haptoglobin, mean (SD), g/L	1.3 (0.6)	1.5 (0.5)	0.170	1.3 (0.6)	1.2 (0.6)	1.3 (0.6)	1.4 (0.8)	0.714
D-Dimer, mean (SD), ng/mL	206 (254)	195 (180)	0.857	171 (111)	197 (198)	196 (192)	302 (558)	0.921
Fibrinogen, mean (SD), g/L	3.7 (2.8)	3.0 (0.8)	0.103	3.6 (2.4)	3.6 (1.4)	3.6 (1.4)	5.8 (7.2)	0.199
Factor VIII, mean (SD), IU/dL	**148 (66)**	**99 (39)**	**<0.001**	151 (96)	137 (50)	153 (73)	159 (52)	0.568
Protein S, mean (SD), IU/dL	99 (22)	98 (26)	0.656	**107 (21)**	**104 (22)**	**94 (21)**	**89 (16)**	**0.025**
VWF:GP1bR, mean (SD), IU/dL	145 (85)	126 (41)	0.669	138 (104)	133 (76)	150 (87)	167 (83)	0.350
VWF:Ag, mean (SD), IU/dL	173 (145)	157 (56)	0.775	151 (79)	155 (88)	179 (185)	231 (157)	0.165
Urine Biomarkers								
Albumin: creatinine ratio at enrolment, mean (SD)	3.2 (8.0)	1.1 (1.5)	0.101	1.6 (3.1)	4.5 (12.0)	2.3 (4.2)	4.1 (6.5)	0.764
Albumin: creatinine ratio at 28-60 days post-discharge, mean (SD)	4.7 (15.6)	1.1 (1.5)	0.156	5.1 (13.4)	5.1 (15.2)	4.6 (18.4)	3.8 (6.4)	0.949

Missing data in post-COVID-19 patients (admission, enrolment, 28-60 days) and controls – myopericarditis criteria – n=9, n=13, n=17, n=0; Missing data in post-COVID-19 patients at 28-60 days and controls – CT chest atelectasis, reticulation, ground glass – n=2, n=5; pulmonary arterial thrombus – n=8, n=6; CT coronary angiogram 28-60 days and controls: Agatston score – n=7, n=4; CAD-RADS score – n=5, n=4; FFR_{CT} – n=27, n=4; Cardiovascular magnetic resonance imaging 28-60 days post-discharge: left ventricular end-diastolic volume index, left ventricular end-systolic volume index, left ventricular ejection fraction, left ventricular strain – n=2, n=3; right ventricular end-diastolic volume index, right ventricular systolic volume index, right ventricular ejection fraction, n=4, n=3; Global T1 – n=1, n=3; global T2 – n=1, n=3; global extracellular volume – n=16, n=5; left ventricular mass – n=8, n=4; late gadolinium enhancement – n=1, n=3; ischemic distribution – n=14, n=4; non-ischemic distribution – n=12, n=4; mixed distribution – n=14, n=4; pericardial thickening – n=3, n=3; pericardial effusion – n=2, n=3; right and left atrial area – n=1, n=3; myocardial inflammation – n=1, n=0; Blood biomarkers, post-COVID-19 patients (enrolment and 28-60 days) and controls – eGFR – n=9, n=10, n= 8; C-reactive protein – n=7, n=7, n=2; High sensitivity troponin I – n=17, n=34, n=2; NT proBNP – n=6, n=10, n=2; Total cholesterol, triglycerides, HDL cholesterol – n=4, n=5, n=2; Fibrinogen – n=1, n=14, n=14; D-Dimer – n=13, n=13, n=11; Fibrinogen – n=1, n=14, n=2; Factor VIII – n=1, n=13, n=14; Antithrombin – n=1, n=N/A, n=15; Protein C – n=1, n=N/A, n=15; Protein S – n=1, n=14, n=3; VWF:GP1bR – n=1, n=13, n=2; VWF:Ag – n=1, n=13, n=2. Abbreviations – aPTT - activated partial thromboplastin time; CAD-RADS - Coronary Artery Disease - Reporting and Data System; ECV - extracellular volume; eGFR (CKD-EPI) – estimated glomerular filtration rate using the Chronic Kidney Disease Epidemiology (CKD-EPI) equation)[24]; EF – ejection fraction; EDV – end-diastolic volume; ESV – end-systolic volume; FFR_{CT} – fractional flow reserve computed tomography; HbA1c - hemoglobin A1c; HDL – high density lipoprotein; LV – left ventricle; MESA - Multi-ethnic study of atherosclerosis; NT-proBNP - N-terminal pro B-type natriuretic peptide; PT – prothrombin time; RV - right ventricle; T1 – longitudinal relaxation time; T2 – transverse relaxation time; TCT - thrombin clotting time; vWF:Ag - von Willebrand factor antigen.

Table 3. Univariable and multivariable associates of adjudicated myocarditis (primary outcome) including demographic characteristics (A), cardiovascular history (B), severity of COVID-19 (C), and biomarkers (D).

	Univariate Odds ratio (95% CI)	p-value	Multivariable Odds Ratio (95% CI)	p-value
Demographics				
Age (decades)	0.89 (0.68, 1.16)	0.398	0.99 (0.70, 1.40)	0.938
Sex: Female (*vs.* Male)	**1.92 (1.02, 3.70)**	**0.045**	1.75 (0.81, 3.85)	0.161
Ethnicity: Other (*vs.* white)	2.11 (0.79, 6.25)	0.147		
SIMD quintile 2 (*vs.* most deprived)	0.49 (0.19, 1.20)	0.120		
SIMD quintile 3 (*vs.* most deprived)	0.47 (0.16, 1.33)	0.159		
SIMD quintile 4 (*vs.* most deprived)	0.58 (0.19, 1.71)	0.319		
SIMD quintile 5 least deprived (*vs.* most deprived)	1.10 (0.44, 2.87)	0.838		
Healthcare worker	**2.24 (1.03, 5.10)**	**0.046**		
Body mass index, kg/m^2	1.02 (0.98, 1.07)	0.345		
Cardiovascular history				
Hypertension	0.71 (0.37, 1.35)	0.297		
Chronic kidney disease	2.14 (0.45, 15.25)	0.372		
Diabetes mellitus	0.63 (0.29, 1.34)	0.232		
Hypercholesterolemia	1.67 (0.90, 3.14)	0.108		
Smoking (former *vs.* never)	0.96 (0.48, 1.95)	0.911		
Smoking (current *vs.* never)	3.51 (0.83, 23.97	0.123		
History of cardiovascular disease	0.74 (0.40, 1.38)	0.343		
Q-Risk 3, 10-year cardiovascular risk, %	0.98 (0.95, 1.02)	0.311		
Medical history				
Charlson Comorbidity Index	0.96 (0.80, 1.14)	0.612		
ISARIC-4C in-hospital mortality risk, %	0.94 (0.86, 1.03)	0.231		
WHO Score: oxygen therapy (*vs.* hospitalized, no oxygen)	0.67 (0.32, 1.37)	0.272		
WHO Score: non-invasive ventilation (*vs.* hospitalized, no oxygen)	0.55 (0.19, 1.55)	0.257		
WHO Score: invasive ventilation (*vs.* hospitalized, no oxygen)	1.83 (0.54, 7.35)	0.352		
Acute kidney injury	**3.42 (1.25, 10.98)**	**0.024**	**3.40 (1.13, 11.84)**	**0.038**
Biomarkers (standard care)				
Hemoglobin, g/L	1.00 (0.98, 1.02)	0.872		
Platelet count, x10^9/L	1.82 (0.74, 4.60)	0.195		
Peak white cell count, x10^9/L	1.52 (0.75, 3.23)	0.256		
Lowest lymphocyte count, x10^9/L	1.69 (0.97, 3.13)	0.080		
Peak D-Dimer, ng/mL	1.02 (0.74, 1.42)	0.925		
Peak fibrinogen, g/L	1.25 (0.87, 1.90)	0.257		
HbA1c, %	**0.25 (0.07, 0.77)**	**0.020**	**0.26 (0.07, 0.87)**	**0.035**
Peak creatinine, mmol/L	1.43 (0.75, 2.87)	0.288		
Peak ferritin, mg/L	0.89 (0.67, 1.17)	0.397		
Peak high sensitivity troponin I, ng/L	1.11 (0.94, 1.33)	0.226		
Peak C-reactive protein, mg/L	0.87 (0.68, 1.09)	0.223		

Table 4. Health status, illness perception, anxiety and depression, and physical function.

					Myocarditis				
	Patients, n	All (n = 161)	Controls (n = 27)	P-value	Not likely n = 17 (10%)	Unlikely n = 56 (35%)	Probable n = 67 (42%)	Very likely n = 21 (13%)	P-Value
Health status, mean (SD)									
Health-related quality of life EQ-5D-5L score at enrolment	155	0.74 (0.22)	0.87 (0.20)	<0.001	0.80 (0.19)	0.78 (0.18)	0.73 (0.24)	0.66 (0.25)	0.154
Health-related quality of life EQ-5D-5L score 28-60 days post-discharge	156	0.77 (0.23)	0.87 (0.20)	0.003	0.85 (0.13)	0.81 (0.20)	0.75 (0.27)	0.64 (0.20)	0.005
Patient assessed EQ-5D-5L score at enrolment, EQ-5D-5L score	155	61.1 (22.0)	77.1 (18.4)	<0.001	71.2 (18.7)	64.2 (19.0)	56.4 (23.1)	59.9 (25.8)	0.065
Patient assessed EQ-5D-5L score at 28-60 days post-discharge,	156	72.4 (19.7)	77.1 (18.4)	0.179	75.3 (16.6)	74.8 (17.3)	72.5 (21.5)	63.0 (20.9)	0.134
Illness perception, mean (SD)									
Brief Illness Perception Questionnaire score at enrollment	155	42.4 (12.2)	32.4 (14.1)	<0.001	37.8 (12.0)	42.1 (11.3)	42.9 (12.5)	45.2 (13.4)	0.454
Brief Illness Perception Questionnaire score 28-60 days post-discharge	148	36.8 (14.7)	32.4 (14.1)	0.067	33.2 (12.2)	35.9 (14.3)	35.3 (15.5)	45.8 (11.5)	0.029
Anxiety and depression, mean (SD)									
PHQ-4 anxiety score at enrollment	153	2.11 (2.08)	0.70 (1.51)	<0.001	1.53 (1.74)	1.83 (1.83)	2.31 (2.23)	2.70 (2.36)	0.347
PHQ-4 anxiety score at 28-60 days post-discharge	146	1.81 (2.00)	0.70 (1.51)	0.002	1.20 (1.08)	1.43 (1.73)	2.09 (2.23)	2.45 (2.24)	0.196
PHQ-4 depression score at enrolment	153	2.18 (1.94)	0.44 (1.15)	<0.001	1.59 (1.87)	2.06 (1.79)	2.30 (2.01)	2.60 (2.16)	0.412
PHQ-4 depression score at 28-60 days	146	1.77 (1.90)	0.44 (1.15)	<0.001	1.07 (1.10)	1.34 (1.68)	2.06 (2.05)	2.55 (2.06)	0.030
PHQ-4 total score at enrolment	153	4.29 (3.77)	1.15 (2.60)	<0.001	3.12 (3.37)	3.89 (3.29)	4.61 (4.01)	5.30 (4.35)	0.346
PHQ-4 total score at 28-60 days post-discharge	146	3.58 (3.70)	1.15 (2.60)	<0.001	2.27 (2.02)	2.77 (3.11)	4.15 (4.17)	5.00 (3.97)	0.054
Physical function, mean (SD)									
IPAQ category at enrolment	142								
High		12 (8.5)	11 (42.3)	<0.001	2 (11.8)	3 (5.9)	4 (7.1)	3 (16.7)	0.441
Moderate		16 (11.3)	6 (23.1)		3 (17.6)	6 (11.8)	7 (12.5)	0 (0.0)	
Low		114 (80.3)	11 (42.3)		12 (70.6)	42 (82.4)	45 (80.4)	15 (83.3)	
IPAQ category at 28-60 days post-discharge, n (%)	133								
High		20 (15.0)	11 (42.3)		4 (33.3)	4 (8.2)	10 (18.9)	2 (10.5)	0.156
Moderate		45 (33.8)	6 (23.1)		5 (41.7)	18 (36.7)	18 (34.0)	4 (21.1)	
Low		68 (51.1)	9 (34.6)		3 (25.0)	27 (55.1)	25 (47.2)	13 (68.4)	
Duke Activity Status Index at enrollment	150	19.7 (18.2)	47.9 (17.5)	<0.001	25.7 (18.5)	19.9 (17.7)	18.1 (18.1)	19.2 (19.9)	0.250
Duke Activity Status Index at 28-60 days post-discharge	156	24.2 (17.6)	- (-)		33.6 (18.7)	25.1 (17.9)	23.9 (17.4)	14.6 (12.5)	0.014
Predicted maximal O_2 utilization (ml/kg/min) at enrollment	150	18.1 (7.8)	30.2 (7.5)	<0.001	20.6 (8.0)	18.1 (7.6)	17.4 (7.8)	17.8 (8.6)	0.250
Predicted maximal O_2 utilization (ml/kg/min) at 28-60 days post-discharge	156	20.0 (7.6)	- (-)		24.0 (8.0)	20.4 (7.7)	19.9 (7.5)	15.9 (5.4)	0.014

PHQ-4 - Patient Health Questionnaire-4 ; IPAQ - International Physical Activity Questionnaire.

Figures

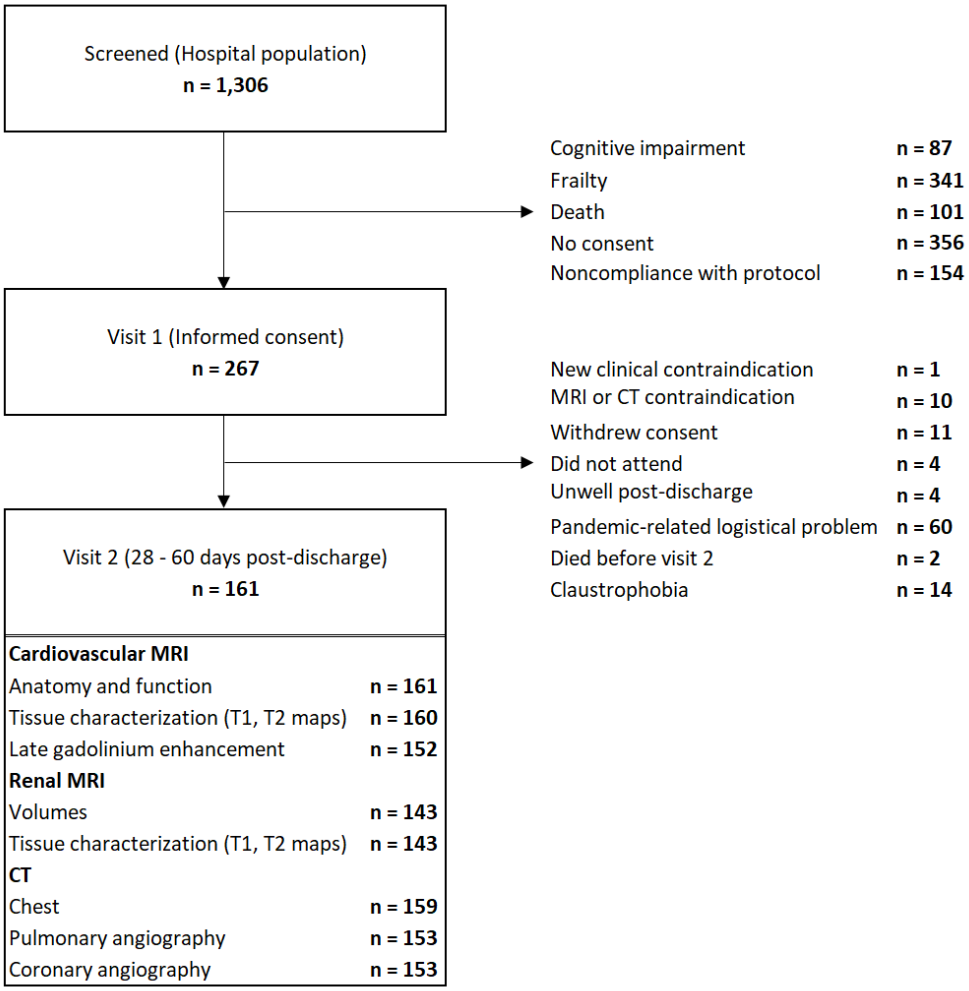

Figure 1

Flow diagram of the clinical study. The procedures involved screening hospitalised patients with COVID-19 and obtaining informed consent. Serial investigations were initiated in-hospital or early post-discharge (visit 1) and then repeated in association with multi-organ imaging at 28-60 days post-discharge (visit 2).

Supplementary Files

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