

STUDY PROTOCOL

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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

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Abstract

Background: Although coronavirus disease 2019 (COVID-19) is primarily a respiratory illness, myocardial injury is increasingly reported and associated with adverse outcomes. However, the pathophysiology, extent of myocardial injury and clinical significance remains unclear.

Methods: COVID-HEART is a UK, multicentre, prospective, observational, longitudinal cohort study of patients with confirmed COVID-19 and elevated troponin (sex-specific > 99th centile). Baseline assessment will be whilst recovering in-hospital or recently discharged, and include cardiovascular magnetic resonance (CMR) imaging, quality of life (QoL) assessments, electrocardiogram (ECG), serum biomarkers and genetics. Assessment at 6-months includes repeat CMR, QoL assessments and 6-min walk test (6MWT). The CMR protocol includes cine imaging, T1/T2 mapping, aortic distensibility, late gadolinium enhancement (LGE), and adenosine stress myocardial perfusion imaging in selected patients. The main objectives of the study are to: (1) characterise the extent and nature of myocardial involvement in COVID-19 patients with an elevated troponin, (2) assess how cardiac involvement and clinical outcome associate with recognised risk factors for mortality (age, sex, ethnicity and comorbidities) and genetic factors, (3) evaluate if differences in myocardial recovery at 6 months are dependent on demographics, genetics and comorbidities, (4) understand the impact of recovery status at 6 months on patient-reported QoL and functional capacity.

Discussion: COVID-HEART will provide detailed characterisation of cardiac involvement, and its repair and recovery in relation to comorbidity, genetics, patient-reported QoL measures and functional capacity.

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Keywords: COVID-19, Coronavirus, Cardiovascular magnetic resonance, Myocarditis, Myopericarditis, Myocardial infarction, myocardial injury, Myocardial inflammation, Myocardial repair, Cardiovascular disease

Background

The coronavirus disease 2019 (COVID-19) severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic [1] was initially recognised as a primarily respiratory illness with a severe acute respiratory syndrome, but it is now known that it can affect multiple organs with a wide spectrum of disease severity [2, 3].

The direct cardiovascular impact of COVID-19 is three-fold. Firstly, underlying cardiovascular disease (CVD) can predispose patients to the infection and is associated with an increased illness severity. Secondly, COVID-19 may exacerbate underlying cardiovascular co-morbidities leading to symptom destabilisation and potentially acute admission to hospital. Thirdly, de novo cardiac complications of COVID-19 may occur [4], with SARS-CoV-2 infection being implicated in acute myocarditis, pericarditis, prothrombotic complications, left ventricular (LV) and/or right ventricular (RV) dysfunction, arrhythmia and ischaemic sequelae in the presence or absence of underlying coronary artery disease (CAD) [1, 4–6].

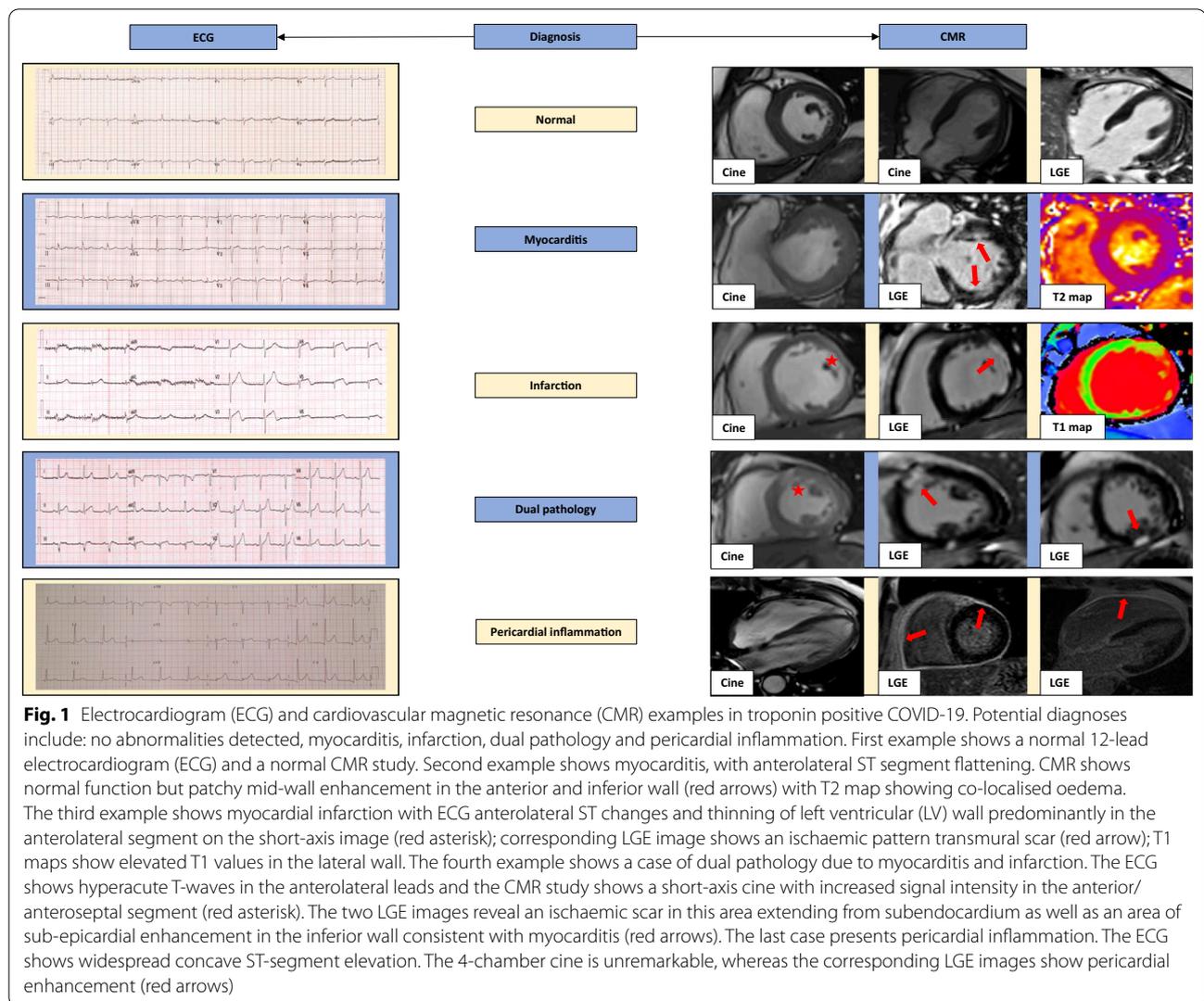
Multiple studies have demonstrated that myocardial injury, characterised by elevation in serum cardiac biomarkers, is common in COVID-19. The prevalence of myocardial injury, however, is variably reported, with early studies quoting a prevalence of 8–12% in hospitalised patients, whilst more recent data suggest that it is possibly much higher [4, 7]. Subsequently, a larger multicentre study of 305 patients identified an elevated troponin in more than half of the hospitalised patients [8]. A recent German cohort study reported imaging evidence of myocardial injury defined by cardiovascular magnetic resonance (CMR) in over 70%, although whether this was pre-existing or consequence was unclear with single time-point imaging [9]. The underlying mechanism of cardiac injury and troponin elevation remains unclear, but there are several potential explanations. Troponin T release is commonly seen in critically ill patients because of oxygen supply–demand mismatch and cytokine release, acute heart failure, RV strain (secondary to pneumonia, hypoxia and increased pulmonary artery pressure) and acute arrhythmia [10–12]. Furthermore, the acute-phase response to severe coronavirus infection can lead to coagulopathy and microvascular thrombosis, for example in the pulmonary and coronary circulations [13, 14]. Pre-existing coronary risk factors, such as hypertension and diabetes also predispose patients with COVID-19

to myocardial infarction in the acute setting, possibly implicating it as another potential disease mechanism [15]. On a cellular level, however, direct myocardial injury may occur due to viral angiotensin-converting enzyme-2 transmembrane receptor mediated damage, microvascular dysfunction or increased vessel wall permeability [16].

Troponin elevation in hospitalised COVID-19 patients is associated with higher morbidity and increased short-term mortality [4, 8, 17–21], particularly in those who also have underlying CVD [16]. Those with CV comorbidities (diabetes, hypertension, heart failure or CAD/peripheral artery disease) are heavily over-represented in both severe COVID-19 and mortality [22, 23].

An elevated troponin should prompt a search for causation, and particularly imaging, as structural abnormalities are likely to be found in this cohort and further predict adverse outcomes (Fig. 1) [4, 8, 17–20, 24]. In patients with an elevated troponin and non-obstructive coronary arteries, CMR can provide the diagnosis in up to 90% of cases [25], and is the imaging modality of choice for diagnosis of acute myocarditis [26]. The diagnostic performance of the CMR-Lake Louise imaging criteria to identify acute myocarditis has been reported to have an overall diagnostic accuracy of around 83% (sensitivity 78–80% and specificity ~87–88%) [27, 28]. CMR can also identify persistent inflammation and the presence of fibrosis in patients recovered from COVID-19 [9, 29], which may have long-term clinical implications. Furthermore, CMR is the reference standard method for assessing LV and RV pathology, whilst regional perfusion defects consistent with obstructive CAD can be accurately identified using CMR perfusion [30].

Based on the possibility that myocardial injury may be relatively common in COVID-19 patients, and has been shown to be a marker of poor prognosis, further studies are required to clarify the pathophysiology of SARS-CoV-2 related myocardial injury. In particular, the nature of injury may suggest the need for therapeutic intervention, which may be specific (e.g. antithrombotic, anti-inflammatory), or non-specific e.g. heart failure treatment. Importantly, the nature and extent of myocardial injury may also help risk stratify patients both acutely and chronically, and for this, multi-time-point imaging is required to separate out cause and effect. Finally, the underlying risk factors for myocardial involvement and the impact on long-term clinical outcomes need to be investigated.



Methods

Objectives

The primary objectives of COVID-HEART are, for a hospitalised-recovering patient population (or those recently discharged), to: (1) characterise the nature and extent of myocardial involvement in COVID-19 patients with an elevated troponin; (2) assess how cardiac involvement and clinical outcome associate with recognised risk factors for mortality in COVID-19 (age, sex, ethnicity and comorbidities) and with genetic factors; (3) evaluate if differences in myocardial recovery at 6-months are dependent on demographics, genetics and CVD comorbidities (diabetes, hypertension, heart failure and CAD/peripheral vascular disease); (4) understand the impact of recovery status at 6-months on patient-reported quality of life (QoL) and functional capacity.

The secondary objectives include: (a) to examine whether there are characteristic electrocardiogram (ECG) findings specific for SARS-CoV-2 myocarditis that are distinct from acute myocardial infarction which could minimise the requirement for invasive cardiac catheterisation and, (b) to establish the nature and prevalence of myocardial ischaemia and microvascular dysfunction (coronary vascular sub-study).

Study design

A longitudinal, multicentre, observational cohort study of UK patients presenting with COVID-19 and elevated serum troponin, who are either recovering in hospital or were recently discharged.

Ethics and registration

Ethical approval for the COVID-HEART study has been granted by the UK National Research Ethics Service (20/NW/0292). COVID-HEART is registered on the 'International Standard Randomised Controlled Trial' registry (ISRCTN 5866,920) <https://doi.org/10.1186/ISRCTN58667920>.

Funding, sponsorship and prioritisation

COVID-HEART is funded by the National Institute for Health Research (NIHR) and UK Research and Innovation (UKRI) COVID-19 Rapid Response Rolling Call (grant number COV0254), and sponsored by the University of Leeds, UK. The study has been endorsed by the British Society of Cardiovascular Magnetic Resonance (BSCMR) Research Group, and nationally prioritised, and received both BHF-NIHR Cardiovascular Partnership Flagship Status, and the NIHR Urgent Public Health Group identified it as an Urgent Public Health (UPH) study. Funding for the translation of the patient information leaflets into non-English languages was provided by the West Yorkshire and Humber Clinical Research Network (CV070).

Study population

Inclusion criteria include—hospitalised-recovering patient population (age ≥ 18 years), or those recently discharged from hospital, with a diagnosis of COVID-19 based upon either a pathology or radiology diagnosis, with cardiac biomarkers (troponin I or T) increased above the sex-specific upper reference limit of the local laboratory range. Exclusion criteria include being unable or unwilling to consent, contraindication to CMR, pregnancy or breast-feeding.

Contemporary patient cohorts acting as control data will be acquired for comparative CMR analysis. These will be derived from ethically approved local research studies from the recruiting centres for COVID-HEART using the same CMR scanners (vendor and field strength). As the patients in COVID-HEART are COVID(+) and Troponin(+), control populations will include:

- 1) A population matched for age and CVD risk factors, who have been hospitalised and are COVID(+) and Troponin(−) [e.g. Capturing MultiORgan Effects of COVID-19 (C-MORE) cohort, Oxford, UK; NCT04510025].
- 2) A population matched for age and CVD risk factors, who have tested COVID(−) and Troponin(−).

Setting

Recruitment will take place in 25 participating secondary or tertiary care hospitals across the UK, all of whom have access to well-established local CMR services.

Recruitment process and data collection

Screening will be performed at an individual hospital level, with participating hospitals cross-referencing all admissions with a positive COVID-19 status (pathology/radiology diagnosis), with serum troponin results. This study will integrate two key aspects. Work package-1 will establish a national image repository for patients with COVID-19 who have CMR for clinical reasons. Work package-2 (objectives as outlined above) will use CMR to characterise the nature and extent of myocardial injury in a hospitalised but recovering patient population, who are serum biomarker (troponin) positive for myocardial damage.

The source data will include hospital records, National Health Service (NHS) health and social care records, clinical and office charts, laboratory and pharmacy records as well as digital images from radiology (chest X-ray/computed tomography/CMR) and cardiology (echocardiography/angiography/CMR). Patients in work package-1 who have a clinically indicated CMR and are troponin positive will be invited to join work package-2 for a follow-up CMR scan and assessment at 6 months. Clinical follow up for vital status and cardiovascular events at 12 months (and up to 5-years) will be performed by recruitment sites via local hospital electronic patient records, primary care records and by national data-linkage for other NHS databases.

Co-enrolment of patients in existing registries will be encouraged (e.g. ISARIC-4c and CAPACITY: Cardiac complications in Patients with SARS Corona vIrus 2 regisTrY; NCT04325412). Also, as this is a longitudinal, observational study, co-enrollment with other UK COVID-19 studies/trials will be permitted.

Consent procedures

All recruited patients will provide written informed consent as per the international ethical and scientific quality standard of Good Clinical Practice (GCP). Patient information sheets for COVID-HEART will be provided in English, and also in up to 10 other languages commonly spoken in the UK, including: French, Portuguese, Polish, Urdu, Bengali, Punjabi, Gujarati, Hindi, Somali and Arabic.

When eligibility criteria are confirmed, medical staff or appropriately trained support staff will seek consent from patients after allowing as much time as necessary to consider the study, or at least 24 h, whilst the patient

is either an in- or out-patient. Consent for participation in the coronary vascular sub-study (ethics reference: 19/EM/0295) will be sought at the time of consent for work package-2.

All participants will have the right to withdraw from the study at any point. Moreover, the investigator may discontinue a participant from the study at any time if it is considered necessary for any reason including ineligibility, significant protocol deviation or loss to follow-up. The reason for withdrawal will be recorded. If consent is withdrawn before data are used in any research analyses, then data relating to that participant could be removed, if the participant explicitly requests that their data are not used. In general, if consent is withdrawn, or if the patient were to become incapacitated, any data collected up to that point will remain on file and will be included in the final study analysis.

Research investigations

All recruited patients will be offered CMR imaging, digital 12-lead ECG, validated quality of life questionnaires, 6 min walk test (6MWT), and additional blood sampling for genetic analysis/immunological responses/T-cell function and cardiovascular biomarkers, if not already acquired. See study flow diagram (Fig. 2) and below for detailed description of research investigations.

1) *CMR Scans* will ideally be performed pre-discharge or within 28 days of discharge, and then repeated at 6 months (± 4 weeks) from the date of admission and on the same scanner wherever possible. Scans will be performed on either a 1.5 T or a 3 T CMR system using multi-channel phased-array chest coils of any vendor, depending upon local availability. ECG gating will be employed for all cardiac gated sequences to ensure appropriate triggering. The main CMR protocol is in keeping with Society for Cardiovascular Magnetic Resonance (SCMR) recommended CMR protocols for scanning patients with active or convalescent phase COVID-19 [6], and it will take approximately 50 min to acquire, with an optional shortened and extended protocol dependent of patient preference and ability. An estimated glomerular filtration rate (eGFR) and haematocrit will be measured prior to each CMR scan. For patients with significant renal failure (eGFR < 30 ml/min/1.73 m²), late gadolinium enhancement (LGE) and post-contrast T1-mapping can be omitted and a contrast-free CMR scan performed.

The main CMR study protocol includes the following components and typical parameters, which may vary by vendor and field strength, but remain comparable overall (Fig. 3):

- A. Localiser sequences and breath-hold transverse Half-Fourier Acquisition Single-shot Turbo spin Echo (HASTE) imaging stacks covering lung and abdomen to 1–2 cm below the kidneys. Typical sequence parameters: TE 1.33 ms, TR 700 ms, slice thickness 8 mm, FOV = 400 mm, FOV phase 100%, flip angle 10°.
- B. Cine images acquired with breath-hold balanced steady-state free precession (bSSFP) sequence. Long-axis views of the LV: 4-chamber, 2-chamber, and 3-chamber views. Sequence parameters: TE 1.05 ms, TR 40.29 ms, slice thickness 8 mm, 25% distance factor, FOV = 500 mm, FOV phase 75%, flip angle 50°.
- C. Native (pre-contrast) T1-mapping: acquired using a single breath-hold shortened modified Look-Locker inversion (ShMOLLI) 5(1)1(1)1 technique [31], where available. Shimming will be performed to avoid artefacts. Native T1-mapping will be acquired in 3 short-axis cuts of the LV (basal, mid-ventricular, apical) to match the locations of segments 1–16 of the American Heart Association 17-segment model [32]. The apical segment 17 is omitted. Each acquisition will be verified against an R² map (according to vendor availability). Typical pulse sequence parameters: TE 1.07 ms, TR 379 ms, slice thickness 8 mm, FOV = 360 mm (can be adjusted according to size), FOV phase 75%, flip angle 35°, distance factor 25%, generalised auto-calibrating partially parallel acquisition (GRAPPA) 2 with 24 reference lines.
- D. Native (pre-contrast) T2-mapping: matching in slice location to the T1 maps, will be acquired using either a T2-prepped b-SSFP sequence with a minimum of 3 source images (e.g. MyoMaps T2-mapping for Siemens scanners), or a black-blood prepared, navigator-gated, free-breathing hybrid gradient (echo planar imaging, EPI) and spin-echo multi-echo sequence (GRASE). Typical sequence parameters: TE 1.3 ms, TR 222.43 ms, slice thickness 8 mm, FOV = 360 mm, FOV phase 80%, flip angle 20°.
- E. Rest myocardial perfusion imaging: obtained using pixel-wise perfusion mapping (or locally available pulse sequence) following administration of 0.05 mmol/kg of gadolinium based contrast agent (GBCA) at 4 ml/s with 20 ml flush at 4 ml/s via a power injector. Immediately after rest perfusion image acquisition, 0.1 mmol/kg top-up (giving a total dose of 0.15 mmol/kg) of GBCA will be given. Accepted GBCA agents include: gadobutrol and gadoteric acid. Sequence parameters: TE 1.04 ms, TR 143.04 ms, slice thickness 8 mm, FOV = 380 mm, FOV 75%, flip angle 50°.
- F. Ventricular short-axis stack. Sequence parameters will match the cine image acquisition in long-axis.

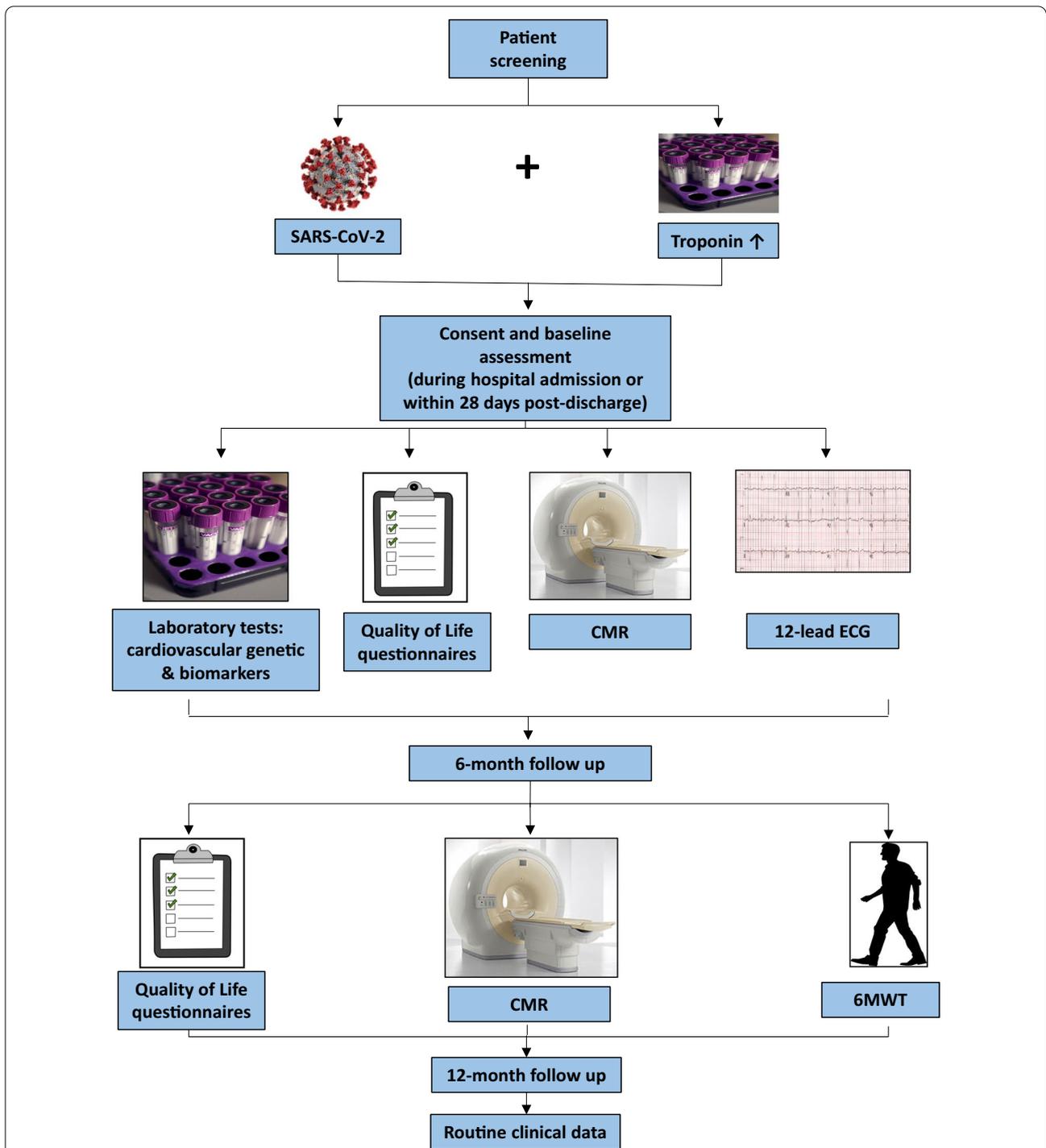
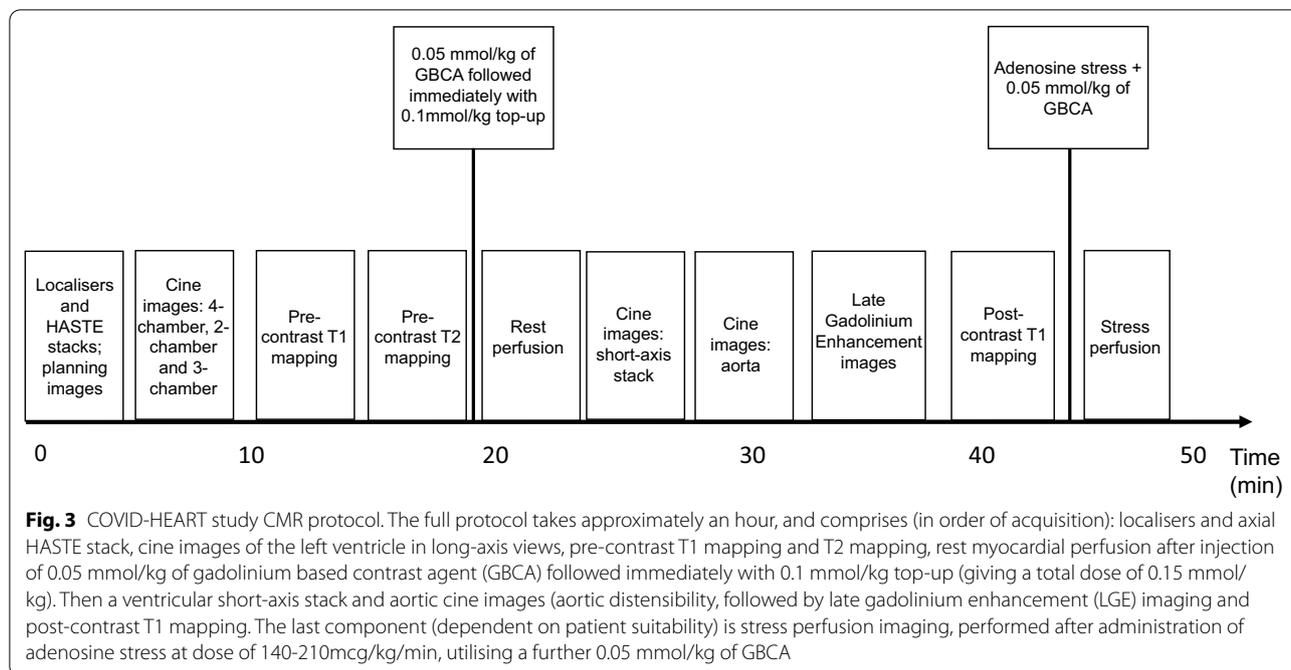


Fig. 2 Study flow diagram. COVID-19 patients, who have an elevated troponin, will be invited to participate in the study. Patients who are recruited undergo multimodality assessment at index visit: either during their hospital admission or within 28 days of discharge. Assessment includes a 12-lead ECG, CMR study, genetic and immunological blood tests, and Quality of Life questionnaires. Patients are subsequently invited for a second visit at 6 months. At this point they undergo a repeat CMR scan, quality of life assessments and 6-min walk test. Further follow up at 12 months will be conducted via examination of routine clinical data, available through general practitioners, electronic hospital records, NICOR and NHS Digital, and in collaboration with other nationally recognised COVID-19 studies



G. Aortic distensibility imaging: planned using bSSFP cine sequence of the thoracic aorta in sagittal oblique view and then acquired transverse to the ascending/descending thoracic aorta (at pulmonary artery bifurcation level). Blood pressure will be recorded whilst in the scanner to allow calculation of aortic distensibility. Sequence parameters: TE 1.25 ms, TR 43.35 ms, slice thickness 6 mm, FOV = 380 mm, FOV phase 100%, flip angle 55°, 50 phases.

H. LGE images will be acquired ~5–15 min after intravenous injection of 0.1–0.15 mmol/kg of GBCA with a free-breathing phase-sensitive motion correction bSSFP or breath-hold, segmented inversion-recovery sequence. Contiguous stack of LV short-axis images and single long-axis slices in 2-chamber, 4-chamber and 3-chamber at the same slice locations as obtained for cine imaging will be acquired. A Look-Locker sequence will be used to determine the appropriate inversion time (TI) [33]. Example parameters are: TI will be adjusted as per Look-Locker sequence, TE 1.14 ms, TR 411.48 ms, matrix 128 × 256, 8 mm slice thickness with 2 mm inter-slice gap, FOV = 400 mm, FOV phase 75%, flip angle 47°.

I. Post-contrast T1 measurements will be acquired at the exact same locations as the native T1-maps and performed at least 10 min after injection of GBCA, using the same pulse sequence and parameters as the native T1-maps.

J. A subset of patients eligible for coronary vascular assessment will undergo an extended protocol at baseline to include stress-perfusion imaging. Adenosine stress perfusion imaging will be acquired after post-contrast T1 mapping using an adenosine dose of 140–210 mcg/kg/min for 3–5 min, whilst monitoring symptoms, heart rate and blood pressure to assess an adequate response. Subsequently, GBCA will be given at a dose of 0.05 mmol/kg at 4 ml/s followed by a 20 ml flush at 4 ml/s, giving a total dose of 0.2 mmol/kg. Stress perfusion imaging will be acquired in the same slice locations as the rest perfusion images. Sequence parameters will match the resting scan.

2) *Digital 12-lead ECG*. A 12-lead ECG will be performed either as part of routine clinical assessment or as an additional research test during the index admission and again at 6 months follow up. In selected centres (which will be provided with an identical study-specific digital ECG machine), a full 12-lead digital ECG from COVID-19 patients will be recorded daily, if possible dependent on clinical status, for up to 7 days, whilst an in-patient. Digital ECGs in patients with CMR-proven myocarditis will be compared to a reference dataset of acute ST-elevation myocardial infarction patients already available from the

NIHR-Efficacy and Mechanism Evaluation Programme funded T-TIME randomised controlled trial [34].

3) *Functional assessment by 6-min walk test.* Participants will be asked to perform a standard 6MWT at the 6-month visit following the American Thoracic Society guidelines [35]. Patients will be instructed to walk along a corridor and turn at 15 m in order to cover the maximum distance in 6 min under the supervision of study investigators. The investigators will tell the participant how much time had elapsed every 2 min and encourage participants to continue at intervals of between 30 s and 1 min. At the end of 6 min, participants will be asked to stop, and the distance walked will be measured in metres.

4) *Quality of life questionnaires.* All participants will be asked to complete patient-reported health status questionnaires (36-Item Short Form Health Survey; SF-36v2) and a health-related QoL questionnaire (EQ-5D-5L) at baseline and 6 months. These will be performed either face to face, by telephone or by post, depending on local site and individual patient circumstances and preferences. These questionnaires were chosen to align with other UK national COVID-19 research studies (e.g. C-MORE/P-HOSP-COVID).

5) *Laboratory investigations.* As part of clinical routine, patients will undergo routine laboratory testing, including full blood count, renal and liver profile, inflammatory markers, and cardiovascular biomarkers (e.g. troponin and brain natriuretic peptide (BNP)). Additional research blood sampling for genetic analysis/inflammatory markers will be performed, if not already acquired from participation in other UK COVID-19 research studies. 10 ml of blood will be drawn into an ethylenediaminetetraacetic acid (EDTA) bottle. The tube will be inverted 5 times and transferred on ice. The sample will be centrifuged for 20 min at 2000G at 4 °C. The sample will be divided into 6 × 1 ml Thermo Matrix tubes. Subsequently a pipette will be used to provide 5 aliquots. Plasma will be taken from the centre of each sample avoiding the buffy coat layer, which will be retained separately. Samples will be labelled with a unique study ID and stored locally on-site, pending batch transfer for analysis at Leicester University and the University of Glasgow.

Follow-up

Patients will be followed up at 6 months (± 4 weeks) from date of the diagnosis of COVID-19, and invited to have a second CMR scan, ECG, QoL assessment (SF-36v2 and EQ-5D-5L) and functional assessment (6MWT). In addition, routine clinical outcome data will be collated up to 5 years post-infection from: electronic patient records,

general practice information systems, National Institute for Cardiovascular Outcomes Research (NICOR) and NHS Digital (eDRIS in Scotland).

Study outcomes

Main outcomes

- 1) Presence, extent, distribution of LGE
- 2) CMR biventricular volumes and function
- 3) Functional capacity (6MWT) and QoL measures
- 4) Long-term clinical outcomes

Exploratory outcomes

- 1) CMR: T1, T2 mapping indices, myocardial strain, myocardial perfusion, aortic distensibility measures.
- 2) ECG indices
- 3) Biomarker and genetic analyses
- 4) Coronary atheroma extent (coronary vascular sub-study)

Analysis plan

The prevalence and extent of cardiac involvement in patients with COVID-19 and raised troponin will be described by CMR. Predictors of cardiac dysfunction and recovery such as: blood biomarkers, the severity of the acute infection, genetics, and comorbidities will be identified. The determinants of adverse clinical outcome in this population will also be examined. Outcome assessments (clinical event adjudication) will be undertaken at individual hospital sites according to a pre-specified standard definition set (Appendix 1) contained within a signed clinical outcome charter.

1) *CMR data:* All quantitative analyses will be performed blinded to participant status. CMR data sets will be analysed by a disseminated core-lab technique as previously used in the BSCMR UK valve consortium [36]. LV structure and function including mass and wall thickness will be analyzed using a clinically validated artificial intelligence (AI) analysis platform [37]. Left atrial area and global longitudinal shortening will be similarly analyzed by further validated artificial intelligence approaches [38]. LGE patterns will also be classified into patterns reflecting likely aetiology and quantitative assessment will be performed by semi-automated signal intensity analysis according to the full width at half maximum technique and other thresholds where appropriate [36]. Evidence of pericarditis will be assessed on cine, LGE and tissue characterisation images. T1 and T2 mapping will be quality-assured and analysed to establish the

global and segmental T1 and T2 values, using standardised approaches developed by the Oxford group [39, 40]. Myocardial perfusion assessment for the coronary vascular sub-study will be carried out by segmental and global quantitative myocardial blood flow calculation during rest and adenosine stress; it will be calculated from fully automated in-line quantification [41, 42]. In addition, visual perfusion defects will be scored semi-quantitatively by 2 observers as previously described [43] with disagreement resolved by a third reader. The likelihood of microvascular disease (patchy perfusion defects not following the distribution of a coronary distribution or circumferential defects not affecting apical segments) will be recorded. Circumferential strain and strain rates will be generated by automated tissue tracking software (cvi42, Circle Cardiovascular Imaging, Alberta, Calgary, Canada) as previously described [44]. Aortic distensibility will be assessed using blood pressure assessments and measurements of the cross-sectional area of the ascending aorta in systole and diastole on axial cine slices at the level of the right pulmonary artery. $\text{Distensibility} = (\text{aortic max lumen area} - \text{aortic min lumen area}) / (\text{aortic min lumen area} * [\text{systolic blood pressure} - \text{diastolic blood pressure}])$.

2) *ECG data*: The standard and digital 12-lead ECGs will be electronically transferred via the study portal into the image repository at the coordinating centre in Glasgow, Scotland. Digital ECGs will be analysed in the University of Glasgow ECG core lab utilising the previously validated Glasgow ECG analysis software [45]. A full set of measurements plus interpretation will be extracted for analysis of ECG changes and statistical processing, with the aim of determining sensitive and specific criteria for diagnosing myocarditis from the ECG, and prognostic ECG findings in this population [46]. ECGs available in printed form will also be electronically transmitted in pdf format to the ECG Core Lab for standardised review based on the same criteria as used in the Glasgow program. Manually classified changes will also be subject to statistical analysis.

3) *Laboratory data*: All blood samples will be transferred to the central coordinating centre in Leicester, England and analysed in the University of Leicester Cardiovascular Research Centre and the BHF Glasgow Cardiovascular Research Centre, University of Glasgow. Analysis will entail novel cardiovascular biomarkers (e.g. vascular cell adhesion molecule, interleukin-6) and markers of genetic susceptibility to COVID-19. The genetic analysis will be used to explore links specifically in the black and minority ethnic populations and linked in with existing cohorts for genotyping (The Genetics and Vascular Health Check

study, The Biomedical Research Informatics Centre for Cardiovascular Science and UK Biobank).

4) *6MWT*: As per the American Thoracic Society guidelines, the distance walked (measured in meters) in 6 min will be recorded by the investigator supervising the test. Symptoms of perceived breathlessness will be recorded on the Borg scale and if the test was stopped early, the reason will be recorded.

5) *Quality of life questionnaires*: Patients' responses to the 36-Item Short Form Health Survey and the health-related QoL questionnaire (EQ-5D-5L) will be recorded in the eCRF by the investigators. Each of the 8 health domains measured by the SF-36v2 will be given a combined percentage score, with higher percentage scores representing a better level of functioning. Each of the 5 domains of the EQ-5D-5L will be scored on a 1–5 scale, with level 1 indicating no problems with a particular domain and level 5 indicating extreme problems. Health state of an individual patient will be determined by combining the levels from all the domains.

Statistical considerations

Sample size considerations

Patients in work package-1 will originate from the open national image repository for all UK CMR centres, and therefore no sample size calculation is required. For work package-2, based on the assumption that the mean prevalence of myocardial involvement was 12% (mid-range) from previous studies, a precision of 3.5% and 95% confidence level, a sample size of $333 \pm 3.5\%$ would be required. To account for a 10% drop out rate, it was calculated that 370 patients are needed.

Statistical analysis

Statistical analyses will be conducted after production of a signed statistical analysis plan and once baseline and follow-up data collection has been completed. Broadly, the statistical methods for each study objective will be as follows:

- 1) to characterise the nature and extent of myocardial involvement in COVID-19 patients with an elevated troponin, analyses will be descriptive, and will involve estimation of prevalence with 95% confidence intervals (CIs);
- 2) to assess how cardiac involvement and clinical outcomes associate with recognised risk factors for mortality in COVID-19 (age, sex, ethnicity and comorbidities) and with genetic factors, we shall present tabular and graphical descriptive summaries within

- subgroups, and use logistic regression to test for associations and provide estimates with 95% CIs;
- 3) to evaluate if differences in myocardial recovery at 6 months are associated with demographics, genetics and CV comorbidities (diabetes, hypertension, heart failure and CAD/peripheral vascular disease), descriptive summaries, and linear and logistic regression methods will be applied;
 - 4) to understand the association between recovery status at 6 months and patient-reported QoL and functional capacity, descriptive methods, and linear regression will be used.

To assess whether there are characteristic ECG findings specific for SARS-CoV-2 myocarditis, measures of diagnostic performance will be calculated, and ROC analyses will be used.

In the coronary vascular sub-study, descriptive methods will be used to establish the nature and prevalence of myocardial ischaemia and microvascular dysfunction, and linear regression methods, including mixed effects methods for modelling myocardial blood flow within segments 1–16 of the American Heart Association 17-segment model, will be used to assess risk factors.

Throughout these analyses, levels of missing data will be reported, and regression models will be fitted using multiple imputation of missing predictor variables. Where appropriate, data from other cohorts will be used as control populations.

Data monitoring and linkage

The University of Glasgow will be coordinating centre for data and analysis and will hold identifiable data in secured databases to permit record linkage. The Universities of Leicester and Glasgow and NHS Laboratory Medicine (including the Biorepository) will undertake storage and/or analysis of blood samples (DNA, RNA, and small molecules).

As part of the patient consent process, it will be explicitly requested that anonymised data and images can be shared with other national and global research initiatives, for efficiency in data collection and sharing across other nationally prioritised UK COVID studies (e.g. C-MORE, P-HOSP-COVID and CISCO-19 [Cardiovascular and Pulmonary Imaging in SARS Coronavirus disease-19]) [47], as well as with other international CMR studies and registries e.g. the international SCMR COVID-19 registry. The principles set out in the 2016 Statement on data sharing in public health emergencies will be followed and it will be ensured that the World Health Organization (WHO) has rapid access to the emerging findings that could aid the global response.

As this is an observational study only serious adverse events (SAEs) that relate directly to the participation in the study procedures and sample collection will be reported to the sponsor and Ethics committee. All hospitalisations and deaths will be recorded as study outcomes.

The management of incidental findings of the research CMR scans will be performed at the individual site level according to the normal local practice and procedures.

Discussion

The COVID-HEART study is a longitudinal, multicentre, observational cohort study of UK patients presenting with COVID-19 infection and positive troponin, who are either recovering in hospital or were recently discharged. It aims to utilise CMR in evaluation of the nature and extent of myocardial injury and subsequently, myocardial recovery in these patients, and to examine the impact of myocardial recovery status on quality of life and functional capacity. Additional investigations include laboratory testing, which will encompass routine tests, novel cardiac biomarkers, and genetic analysis. These results will be shared with other global initiatives to address genetic susceptibility to COVID-19. Furthermore, ECGs will be investigated with the aim of identifying sensitive and specific changes that would allow diagnosis of myocarditis without the need for invasive testing.

As COVID-19 is an unprecedented global health emergency and previous studies showed that a significant proportion of patients had myocardial injury, it is important to further understand the underlying pathophysiology, risk factors and long-term outcomes. Therefore, the results of the COVID-HEART study, and the results of other registries examining myocardial injury (e.g. PHOSP-COVID, ISRCTN10980107; MOIST, NCT04525404; MYOCOVID, NCT04375748; MIIC-MI, NCT04412369; CARDOVID, NCT04455347; CISCO-19, NCT04403607), may have significant clinical implications on the assessment and management of these patients. Furthermore, the new knowledge from these studies will help inform disease-targeted therapy development, for the prevention and treatment of cardiovascular complications in COVID-19.

Appendix 1: Summary definitions of clinical outcomes

A pre-specified, signed, *Clinical Outcomes Charter* will be provided to each recruitment centre. This will contain detailed endpoint definitions to facilitate consistent local adjudication and unbiased reporting. Endpoint definitions will align with the 2014 American College of Cardiology/American Heart Association Key Data Elements

and Definitions for Cardiovascular Endpoint Events in Clinical Trials [48]. In brief, these endpoints will include:

- 1) *Cardiovascular death* is defined as death occurring secondary to an acute myocardial infarction, sudden cardiac death, heart failure, stroke, death resulting from cardiovascular procedures or death due to cardiovascular haemorrhage.
- 2) *Non-cardiovascular death* is defined as any death with a specific cause that is not thought to be due to a cardiovascular cause. There should be unequivocal and documented evidence of a non-cardiovascular cause of death.
- 3) *Myocardial infarction* is defined as elevation of cardiac biomarkers above the 99th percentile of the upper reference limit in the setting of an appropriate clinical presentation in combination with diagnostic ischaemic electrocardiographic changes. Specific clinical classification of different types of myocardial infarction will be assigned from the 4th Universal Definition of Myocardial Infarction [12].
- 4) *Coronary artery revascularisation*, either by percutaneous coronary intervention (PCI) or coronary artery bypass graft surgery (CABG).
- 5) *Transient ischaemic attack* is defined as an episode of focal neurological dysfunction resulting from brain, retinal and spinal cord ischaemia, that is transient in nature and resolves within 24 h.
- 6) *Stroke* is defined as a focal or global neurological dysfunction secondary to brain, retinal or spinal cord injury resulting from haemorrhage or infarction.
- 7) *Pulmonary embolism* is defined based upon clinical evaluation and a diagnostic imaging test, ideally, computed tomography (CT) pulmonary angiography. If ventilation/perfusion scintigraphy is used, then the diagnosis may be accepted based on clinical evaluation and a high probability scan. The clinical evaluation and diagnosis of pulmonary embolism should align with the 2019 ESC Guidelines for the diagnosis and management of acute pulmonary embolism [49].
- 8) *Deep venous thrombosis (DVT)* diagnosis should be established based on a clinical evaluation, D-dimer elevation and imaging findings (duplex ultrasound or CT angiography).
- 9) *Myopericarditis* diagnosis will be adjudicated based upon the 2013 Position Statement of the European Society of Cardiology Working Group on Myocardial and Pericardial Diseases.(50)
- 10) *Hospitalisation for other cardiovascular cause:*
 - a) *Heart failure* events are defined as hospitalisation for heart failure or an urgent outpatient visit. A heart failure hospitalisation event must fulfil the

following criteria: primary admission diagnosis is heart failure, the patient experiences either worsening of heart failure symptoms or a new symptom, and requires an increase in therapy.

- b) *Arrhythmia* defined as hospitalisation with an arrhythmia (atrial, supraventricular and/or ventricular or brady-arrhythmia) documented by electrocardiography (single- or multi-lead) with a change in treatment (withhold, change in dose of existing medication, prescription of new medication for arrhythmia) and/or pacemaker therapy.
- c) *Chest pain/unstable angina* defined as an emergency/unplanned admission to a hospital setting that results in at least one overnight stay (i.e. a date change) with cardiac ischaemic-type symptoms at rest or minimal exertion.

Abbreviations

6MWT: Six minute walk test; BNP: Brain natriuretic peptide; BSCMR: British Society of Cardiovascular Magnetic Resonance; bSSFP: Balanced steady state free precession; C-MORE: Capturing Multi-ORgan Effects of COVID-19; CAD: Coronary artery disease; CMR: Cardiovascular magnetic resonance; COVID-19: Coronavirus disease 2019; CVD: Cardiovascular disease; ECG: Electrocardiogram; eCRF: Electronic case report form; ECV: Extracellular volume fraction; EDTA: Ethylenediaminetetraacetic acid; eGFR: Estimated glomerular filtration rate; EPI: Echo planar imaging; FBC: Full blood count; FOV: Field-of-view; GBGA: Gadolinium-based contrast agent; GCP: Good clinical practice; GRAPPA: Generalised auto-calibrating partially parallel acquisition; GRE: Gradient recalled echo; HASTE: Half-Fourier acquisition single-shot turbo spin echo; LGE: Late gadolinium enhancement; LV: Left ventricle/left ventricular; LVOT: Left ventricular outflow tract; NHS: National Health Service; NICOR: The National Institute for Cardiovascular Outcomes Research; P-HOSP-COVID: Post-hospitalisation COVID-19 study; QoL: Quality of life; RNA: Ribonucleic acid; RV: Right ventricle/right ventricular; SAEs: Serious adverse events; SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2; SCMR: Society for Cardiovascular Magnetic Resonance; SF-36: 36-Item Short Form Health Survey; ShMOLLI: Shortened Modified Look-Locker Inversion recovery; TE: Echo time; TI: Inversion time; TR: Repetition time; NIHR-UKRI: National Institute for Health Research—UK Research Institute; VLA: Vertical long axis; WHO: World Health Organization.

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Authors' contributions

All authors have participated in the design of the study and helped to draft the manuscript. All authors read and approved the final manuscript.

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Availability of data and materials

The datasets used and/or analysed during the current study will be available from the corresponding author on reasonable request. Anonymised data may be shared with other COVID-19 global initiatives.

Declarations

Ethics approval and consent for participation

Granted by the North West-Greater Manchester South Research Ethics Committee (20/NW/0292). All patients provided written informed consent.

Consent for publication

All patients have provided informed written consent. The funder and sponsor had no involvement in either the decision to publish, or, the published content.

Competing interests

CB is employed by the University of Glasgow which holds research and/or consultancy agreements with AstraZeneca, Abbott Vascular, Boehringer Ingelheim, GSK, HeartFlow, Opsens, and Novartis. CBD is the chief executive officer (part-time) of the Society for Cardiovascular Magnetic Resonance (SCMR). All other authors have no conflicts to declare.

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