**Title: A prospective multicentre multiorgan magnetic resonance imaging study of patients post-hospitalisation for COVID-19**

**C-MORE/PHOSP-COVID Collaborative Group**

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Research in context

Evidence before the study

A systematic search of PubMed and Embase databases for studies with multiorgan imaging including lungs, heart, brain, liver and kidneys published between Jan 1, 2021, and December, 2022, without language restrictions was conducted. Search terms related to COVID-19 (“COVID-19”, “COVID-2019”, “SARS-CoV-2”, “2019-nCoV”, “2019-SARSCoV-2”), hospitalisation (“hospital”), long-term follow-up (“follow-up”, “long term”, “sequelae”, “long Covid”), multiorgan (“multiorgan, multi-organ) and MRI (“magnetic resonance imaging”, “MRI”) were used. There was only one comprehensive multiorgan MRI study covering five major organs which was conducted by us (n=58); two studies (UK n=159; Hamburg n=443) evaluated three or four organs on MRI and investigated predominantly non-hospitalised patients. Single-organ MRI studies were frequent, but did not examine the cumulative burden of multimorbidity or multiorgan dysfunction on patient recovery following severe acute infection. At the time of the search, there were no multiorgan MRI follow-up studies in post-hospitalised COVID-19 patients at the 5-6 month follow-up time point. One follow-up MRI study of non-hospitalised COVID-19 patients (UK n=534) employed a limited non-contrast (non-clinical) protocol and evaluated longitudinal organ health in patients with mild infection. This study reported a prevalence of 56% single organ abnormalities. None of these studies evaluated the association of multiorgan health (lungs, heart, brain, liver, kidneys) with recently identified post-COVID symptom clusters relevant to post-hospitalised patients (PHOSP-COVID symptom clusters based on physical, mental and cognitive impairment). We also found no study investigating the association of systemic inflammation and multiorgan (five organs) health among post-hospitalised patients·

Added value of this study

In one of the largest prospective, multicentre multiorgan MRI follow-up study of post-hospitalised COVID-19 patients and contemporary non-COVID-19 controls, we report several novel findings: 1) We describe a high burden of multiorgan abnormalities on MRI among patients (one in three) 5 months post-COVID-19 hospitalisation; 2) An excess burden of lungs, brain and renal abnormalities were observed among patients; 3) Both cardiac and liver MRI abnormalities were comparable between patients and our non-COVID control population; 4) Novel associations between specific symptoms and organ dysfunction were observed, including the association of multiorgan abnormalities with more impaired patterns of recovery; 5) Post-hospitalised patients with persistently abnormal markers of inflammation at follow-up were more likely to have multiorgan MRI abnormalities than those without.

Implications of all evidence available

These findings highlight the need to prioritise multidisciplinary services in the follow-up of patients recovering from moderate to severe SARS-CoV-2 infection. Specifically, management of pulmonary and extrapulmonary health (neuro-cognitive and renal) may be important in the long term for patients. Our study highlights the sensitivity of advanced imaging to guide surveillance frequency and therapeutic interventions, and the vulnerability of individuals to future insults. It also stresses the importance of risk factor and comorbidity management, which should remain a priority for clinicians, given their close association with severity of acute disease and impaired recovery.

Abstract

**Introduction**

The multiorgan impact of moderate to severe coronavirus infections in the post-acute phase is still poorly understood. We sought to evaluate the excess burden of multiorgan abnormalities post-COVID-19 hospitalisation, evaluate their determinants and explore associations with patient-related outcome measures.

**Methods**

In a prospective UK-wide multicentre magnetic resonance imaging (MRI) follow-up study, 259 adults (aged ≥18 years) discharged from hospital following COVID-19 and 52 contemporary controls (no prior COVID-19, SARS-CoV-2 nucleocapsid antibody negative) underwent multiorgan MRI (lungs, heart, brain, liver and kidneys) which were both qualitatively (with clinical adjudication where relevant) and quantitatively assessed. Participants also underwent detailed recording of symptoms, physiological and biochemical tests. The primary outcome was the excess burden of multiorgan abnormalities (two or more organs) relative to controls and this was further adjusted for potential confounders.

**Findings**

Patients discharged from hospital (March 2020 to November 2021) were assessed at a median of 5·0 months (IQR 4·3–6·4). Patients were older, living with more obesity, and had more comorbidities than non-COVID-19 controls. Multiorgan abnormalities were more frequent among patients versus controls (60·6% versus 26·9%, p<0·001) and independently associated with COVID-19 status (Odds Ratio 2·9 [95% CI 1·5, 5·8], p=0·002) after adjusting for relevant confounders. Patients were more likely to have lung abnormalities (p<0·001, parenchymal abnormalities), brain abnormalities (p<0·001, more white matter hyperintensities and regional brain volume reduction) and kidney abnormalities (p=0·014, lower medullary T1 and loss of corticomedullary differentiation), whereas cardiac and liver MRI abnormalities were comparable between patients and controls. Abnormal MRI findings were more common in older patients with comorbidities and more severe acute infection, but also present in those with fewer comorbidities and less severe infection. Presence of lung MRI abnormalities was associated with a two-fold risk of chest tightness, whereas multiorgan abnormalities were associated with impaired patterns of patient-reported recovery.

**Interpretation**

Post-hospitalisation COVID-19 patients are at risk of multiorgan abnormalities in the medium term. Our findings emphasize the need for proactive multidisciplinary care pathways, with the potential for imaging to guide surveillance frequency and therapeutic stratification.

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Introduction

Background

Long-standing multiorgan impairment following severe acute coronavirus infections-2 (SARS-CoV-2) has been a major concern for individuals recovering from severe infections (such as following hospitalisation(1, 2)) and is thought to be due to multitude of factors including direct viral cytotoxicity(3) chronic inflammation(4),, ischaemic injury(5), acute reactivation of other viruses(6), metabolic derangements, and acute treatment effects (especially invasive ventilation). Numerous reports of delayed organ complications like myocarditis, stroke and pulmonary emboli have led to speculations the multiorgan dysfunction caused by COVID-19 may be responsible for impaired recovery and ongoing symptoms in individuals, also termed as Long COVID. However, what is currently unknown is the precise burden of persistent multiorgan impairment after hospitalization with COVID-19 and the impact this may have on patient recovery and symptoms in individuals.

Magnetic resonance imaging (MRI) has several strengths as a safe and reproducible tool for the assessment of post-COVID manifestations.(7) In a previous pilot study, we applied multiorgan MRI(8) to delineate the extent of organ injury in post-COVID-19 survivors (i.e., after hospital admission) and noted moderate associations between inflammatory markers and abnormal tissue characteristics, implying a dominant role of inflammation. Others have also observed persistent deviations in haemostatic pathways after infection.(9) To further evaluate the burden of multiorgan dysfunction and its impact on patient recovery following moderate to severe SARS-CoV-2 infection, we embarked on this prospective UK-wide multiorgan multicentre MRI follow-up study of post-hospitalised COVID-19 patients called the C-MORE study (Capturing MultiORgan Effects of COVID-19).

Study objectives:

C-MORE was developed to 1) characterise the excess prevalence of multiorgan abnormalities among COVID-19 patients relative to SARS-CoV-2 uninfected controls, 2) provide mechanistic insights into the source of multiorgan dysfunction, and 3) evaluate their impact on patient-reported outcome measures post-COVID-19.

Methods

Study design: Prospective observational multicentre cohort study.

Setting and participants: Nested within a nationally prioritised COVID-19 follow-up programme called PHOSP-COVID (Post-hospitalisation COVID-19 study) (10), the C-MORE study enrolled patients admitted to hospital with either polymerase chain reaction (PCR) confirmed or clinically diagnosed COVID-19 between 1st March 2020 – 1st November 2021, and who consented to participate in the PHOSP-COVID study (Leeds West Research Ethics Committee (20/YH/0225)).(10, 11) As part of the PHOSP-COVID study (Tier 2 arm), prospective clinical evaluation (e.g., blood sampling, questionnaires, lung function test) took place within 4 weeks of the MRI in 500 consenting patients.

Individuals who were 1) asymptomatic for previous COVID-19, 2) not hospitalised and 3) had a negative SARS-CoV-2 PCR and nucleocapsid antibody were invited prospectively from the community in Oxford to serve as controls. Controls underwent routine blood tests, selected questionnaires and lung function testing.

C-MORE was set up in 13 out of 40 Tier 2 PHOSP-COVID sites, which also hosted a 3 tesla MRI scanner (minimum requirement). The sites were located in Oxford, London (3 centres), Manchester, Sheffield, Leeds, Leicester, Cambridge, Nottingham and Birmingham. We excluded individuals with end-stage renal failure (eGFR<30ml per 1·74ml/min/kg) or contraindications to MRI (e.g. claustrophobia, relevant metal implant, implanted device like defibrillator or pacemaker).

C-MORE was registered on ClinicalTrials.gov (<https://clinicaltrials.gov/ct2/show/NCT04510025>) and approved by North West - Preston Research Ethics Committee (20/NW/0235, <https://phosp.org/resource/>). The prespecified primary endpoint was the excess burden of multiorgan abnormalities on MRI among patients post-hospitalisation for COVID-19 relative to non-COVID-19 controls.

On the day of the MRI, heart rate, temperature, oxygen saturation and blood pressure were recorded. All other blood tests were undertaken within four weeks of the study visit.

*MRI Acquisition:* Lungs, heart, brain, liver and kidney scans were acquired using a 3-tesla MRI scanner (see **supplementary material**).

Lung MRI included a T2-weighted scan and perfusion imaging to assess the extent of lung parenchymal involvement and perfusion.

Cardiac MRI included cine imaging to assess biventricular volumes and function, T1 and T2 mapping, and post-contrast T1 mapping and late gadolinium enhancement (LGE) imaging for assessment of inflammation, diffuse and focal fibrosis, respectively.

Brain MRI included T1- and T2-weighted imaging to evaluate global and regional brain volumes, and assess for inflammatory changes. Diffusion-weighted imaging and susceptibility-weighted imaging were qualitatively assessed for ischaemic and haemorrhagic injury.

Liver MRI included T2\* imaging to assess liver iron and liver T1 mapping to assess liver fibrosis and inflammation. A multiecho gradient echo sequence was also acquired to assess liver fat via proton density fat fraction (PDFF).

Renal MRI included T2-weighted anatomical imaging to assess renal volumes and T1 mapping to assess renal fibro-inflammation and corticomedullary differentiation.

*MRI analyses:* Quantitative and qualitative (specifically for lungs, heart, brain scans) analyses were undertaken by organ-specific core labs, where blinded image analyses were performed.

Lungs scans were qualitatively assessed by two accredited MRI experts, with a third experienced radiologist adjudicating cases of disagreement. Both presence/absence (score 0 = ≤5% of lung involvement, 1 – 5% of lung involvement) and extent of parenchymal abnormalities (up to 25%, 26-50%, 51-75%, 76-100%) were evaluated. Lung perfusion was quantitatively assessed as previously described(8), and global pulmonary blood flow, blood volume and mean transit time were computed.

Cardiac analyses were undertaken using cvi42 software (Circle Cardiovascular Imaging Inc, Version 5·12, Calgary, Canada).(12) Qualitative readouts of LGE imaging were undertaken by three experienced cardiac MRI readers.

Brain image processing was undertaken using an adapted version of the processing pipeline created for the UK Biobank brain imaging analysis (<https://www.fmrib.ox.ac.uk/ukbiobank/>). Qualitative assessments of brain images were undertaken by an experienced neuroradiologist.

Quantitative analyses of liver metrics, including PDFF, liver iron and iron-corrected T1 (Liver cT1) were also undertaken using well-established methods.(13)

Renal volumes, cortical and medullary T1, markers of microstructural health, were computed for both kidneys. Further details on image analyses are provided in the **supplementary section**.

*Organ abnormalities on MRI:*Patients were assessed for single or multiple organ abnormalities (involvement of ≥2 organs) based on deviations in qualitative and quantitively MRI characteristics as described in the **supplementary section**.

*Pulmonary function:*Pulmonary function tests included assessment of forced expiratory volume at one second (FEV1), forced vital capacity (FVC) and, in some centres, assessment of carbon monoxide diffusion gas transfer.

*Patient-related outcome measures:*Participants underwent a series of questionnaires to assess self-reported symptoms of anxiety, depression, cognition, health-related quality of life, symptoms of breathlessness, fatigue, short physical performance battery, post-traumatic stress disorder (GAD-7, PHQ-9, MOCA, EQ-5D-5L utility index, Dyspnoea-12, FACIT-F, Short Physical Performance Battery, PCL-5). Based on the data from these questionnaires, post-COVID-19 patients were assigned to one of four previously described PHOSP-COVID symptom clusters(11) (see **supplementary material** for further details).(11)

Role of funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Statistical analyses

The primary outcome was the difference in the proportion of individuals with multiorgan abnormalities (>2 organ abnormalities), a binary variable, between cases and controls. All other comparisons were exploratory, and correction for multiple testing was therefore not applied. Statistical analysis was conducted with R version 4.1.0 and R Studio version 1.4.1717.

Categorical summary statistics are presented as counts and percentages of non-missing data. Where continuous measures were skewed, we report median and interquartile range; otherwise, mean and standard deviation were reported.

We assessed group-wise differences across multiorgan imaging metrics between controls and patients at follow-up, as well as across cohort characteristics between patients with and without organ abnormalities.

In univariate analyses, chi-square tests and Fisher’s exact test were used to compare proportions where appropriate. Where continuous measures were skewed, a Mann-Whitney U test was used; otherwise, a two-group Welch test was used to compare group means.

To assess multivariate group-wide differences between patients and controls, linear and logistic regression analyses were applied with inverse probability weighting to adjust for age, sex, body mass index, smoking, hypertension, hypercholesterolemia, diabetes, pre-existing comorbidities (cardiac, brain, liver, lung and renal) and scanner manufacturer. These covariates were selected given their association with imaging abnormalities in previous work (14). Continuous imaging outcomes were scaled for normality where necessary, and differences in brain imaging outcomes were additionally adjusted by head size, date of imaging and scanner table position. Differences associated with follow-up abnormality status were assessed with linear (β coefficient) and logistic regression models (odds ratio) adjusted by age, sex, smoking, obesity, hypertension, Charlson comorbidity index and scanner manufacturer. We additionally undertook sensitivity analysis by excluding individuals who had a WHO progression scale 7-9 during admission to examine if our associations remained robust to this exclusion.

Results

Data from the first consecutive 259 patients and 52 non-COVID-19 controls are presented in **Table 1 and Table 2**. The median time of scan from hospital discharge was 5·0 months (IQR 4·2 to 6·3 months). Of the patients, 28% were non-white in ethnic origin versus 27% of controls. Patients were older (57±12 years vs controls 49±14 years, p<0·001), with similar BMI (31±6 kg/m2 vs controls 29±8 kg/m2, p=0·114) and more likely to be ex-smokers (36% vs 12%, p=0·001). Nearly one in three patients (27%) had severe SARS-CoV-2 infection (WHO class ≥ 6). Steroids, anticoagulation and antiviral therapy (Remdesivir) were administered in 75%, 52% and 25% of patients respectively. Further details on cohort characteristics are listed in the **supplementary material.**

*Pulmonary health:* Nearly one in three COVID-19 patients (32%, 81/257) reported a pre-existing respiratory condition, compared with 15% (8/52) of controls (**Table 1**)

During hospital admission, 55% of patients (141/255) needed supplemental oxygen by mask or nasal prongs, 20% (51/255) required high flow or non-invasive ventilation, and 7% (18/255) required invasive ventilation. The remaining 18% of patients (45/255) did not need oxygen therapy during hospital admission**.**

At five months post-hospital discharge, more patients had lung MRI abnormalities affecting >5% of parenchyma (35% (90/259) compared to controls 6% (3/49), (padj <0·001; where padj refer to the pvalue from multivariate models where the effect of the variable of interest is adjusted for the covariates) (**Table 2**). Of the patients with an abnormal lung MRI, 72% had no prior respiratory disease. Semi-quantitative analyses detected higher average T2 signal and heterogeneity in T2 signal among patients relative to controls (padj <0·001 for both), a finding also evident when patients with critical COVID-19 (WHO 7-9) were excluded. Average global pulmonary blood volume, blood flow and mean transit time were not significantly different between patients and controls (padj >0·20 for all, **Supplementary Table 1A**).

Follow-up lung function assessment revealed more pulmonary function defects among patients. On average, FEV1 and FVC were lower in patients versus controls (padj<0·001), whereas the ratio of FEV1 to FVC was higher in keeping with a restrictive lung function pattern (padj=0·005). Nearly one in four patients (23%) had an abnormal FEV1 (<80% of predicted normal FEV1) and abnormal FVC (22%) compared to 4% and 0% of controls (**Supplementary Table 1A**).

Among all patients, lung MRI abnormalities independently associated with acute factors including longer hospital admission duration, abnormal chest x-ray, acute cardiac injury and proning (marker of severe hypoxaemia). At follow-up, patients with lung MRI abnormalities had lower FEV1 and higher FEV1/FVC ratio (**Supplementary Table 1B, Figure 2**). Heterogeneity in lung parenchymal signal on MRI (**Supplementary Table 2**) is also associated with persistently raised CRP (>5mg/L). After excluding those with pre-existing lung disease, all associations remained, except that patients with lung MRI abnormalities were more likely to have FVC <80% predicted and lower TLCO. (**Supplementary Table 1C**). Lung MRI abnormalities were associated with chest tightness, joint pain and impaired quality of life. After excluding pre-existing lung disease, an abnormal lung MRI was associated with cough and chest tightness (**Supplementary Table 1 C**).

*Cardiac health:* Patients had higher burden of cardiac comorbidities (16%) relative to controls (4% respectively, p=0·043) (**Table 1)**

Acute myocardial injury (as defined as a troponin, NT-pro B-type natriuretic peptide/BNP above 1x upper normal limits) was reported in 15% (38/255) of patients. At follow-up, abnormal troponin was seen in 4% (5/139), and abnormal NT-pro BNP seen in 18% (32/174) of patients.

Abnormal cardiac MRI findings were noted in 21% (54/259) of patients and 25% (12/49) of controls (padj=0·297) (**Table 2**). Biventricular indexed stroke volumes were smaller in patients vs controls, while right ventricular function, average myocardial T1, T2 and extracellular volume fraction were similar between patients and controls. Although within the normal range, patients had lower average left ventricular ejection fraction (EF) (60·5±6·0 % vs 62·9±5·5 % in controls, padj=0·048). Seven percent of patients had left ventricular dysfunction (EF<52%) and 4% had right ventricular dysfunction (EF<48%). (**Supplementary Table 3A**)

One in eight (14%) patients had a pathological pattern of LGE, similar to controls (12%, padj=0·418). Among patients, 9% had possible/probable myocarditis LGE pattern (vs 12 % of controls, padj=0·05). 6% had possible/probable ischaemic LGE pattern (vs 2% of controls, padj=0·795), and 1% had mixed LGE pattern (vs 0% of controls, p=1·0). Pericardial effusion was seen in 1% of patients (vs 2% of controls, p=0·512). Active myocarditis, as per the updated Lake Louise criteria(15) (increase in both myocardial T1 and T2), was rare, affecting only 1% of patients (4/231) at a median follow-up of 5 months versus 3/52 controls.

Of the patients with cardiac MRI abnormalities, 34% (18/53) had pre-existing cardiac disease, and 21% (11/53) had evidence of acute cardiac injury during hospital admission. Factors that associated with cardiac MRI abnormalities in all patients included older age, cardiac comorbidity, abnormal chest x-ray and elevated acute D-dimer levels. At follow-up, patients with cardiac MRI abnormalities were more likely to have increased NT-pro B-type natriuretic peptide, reduced renal function or eGFR, and reduced lung function (FEV1/FVC ratio, and KCO) compared to those without (**Figure 2,** **Supplementary Table 3B**). After excluding patients with cardiac comorbidities, older age, abnormal chest x-ray, acute and follow-up elevated d-dimer and follow-up renal impairment remained associated with cardiac MRI abnormalities (**Supplementary Table 3C**).

Cardiac MRI abnormalities were not associated with patient-reported outcome measures, including symptoms of chest pain or breathlessness.

*Brain health:* Pre-existing neurological diagnoses were comparable across patients (4%) and controls (2%, padj=0·433) (**Table 1** )

At follow-up, qualitative brain MRI abnormalities were noted in 50% of patients (109/218) versus 18% of controls (9/50, p < 0·001, padj=0·003) (**Table 2**). White matter lesions and small vessel disease were more common among patients, who also had smaller grey matter volumes relative to controls, specifically in areas important for higher cognitive function including memory and emotional processing and autonomic nervous function (hippocampus, amygdala, cerebellum, thalamic nuclei), motor control (bilateral putamen), audio-visual processing (bilateral middle temporal gyrus), visual processing (bilateral cuneus and intra-calcarine cortex) and wakefulness/consciousness and thermoregulation (thalamic nuclei). Patients also had lower regional brain volumes involving areas important for spatial memory formation (left posterior cingulate cortex), language processing and perception (supramarginal cortex), and pain perception (insula) (**Supplementary Table 4A**). Brain MRI abnormalities were more common among patients even after excluding patients with critical COVID-19.

Of those with brain MRI abnormalities, only 5% (5/109) had pre-existing known neurological disease. Older age, diabetes, higher acutely elevated CRP, higher bilirubin and lower use of therapeutic anticoagulation were associated with clinically-evident brain MRI abnormalities among patients (**Supplementary Table 4B, Figure 2**). At follow up higher white cell count, higher urinary albumin:creatinine ratio (ACR) and higher platelet count associated with brain MRI abnormalities. These associations remained even after excluding cases with pre-existing neurological disease (**Supplementary Table 4C**).

Of note, persistently raised CRP (≥5mg) was associated with regional brain atrophy involving areas important for memory, emotional processing (amygdala nuclei), audio-visual processing (superior, mid, inferior temporal gyrus), control of autonomic functions (brain stem), and visuospatial memory (cuneus) (**Supplementary table 2**) among patients.

Qualitative and quantitative brain MRI abnormalities were not linked to any patient-reported outcome measure after confounder adjustment.

*Liver health:* Five percent of patients (14/257) reported pre-existing liver diagnoses, while no known liver comorbidities were reported in controls (**Table 1**).

Acuteliver biochemistry (combining alanine transaminase (ALT), alkaline phosphatase (ALP), bilirubin or gamma-glutamyl transferase, GGT) was abnormal in 58% (141/244) of patients during the acute phase. At follow up, liver biochemistry was abnormal (>1xULN) in 14% (30/221) of patients. Abnormal liver MRI findings (i.e., elevated liver inflammation, liver iron or fat) were frequent among patients but similarly prevalent among controls (60% vs 58%, padj=0·306) (**Table 2**). Patients had comparable mean liver cT1 (padj=0·471) and liver fat (padj=0·191) with controls but lower liver iron (padj<0·001) (**Supplementary Table 5A)**.

Among all patients, liver MRI abnormalities were associated with obesity, diabetes, and higher Charlson comorbidity index, acute CRP >5mg/L and acute steroid treatment. At follow-up, patients with liver MRI abnormalities had higher serum ALT, poorer lung function (lower FEV1, FVC and FEV1/FVC ratio), lower B-type natriuretic peptide, higher HbA1c, higher haemoglobin and white cell count compared to those without MRI abnormalities (**Supplementary Table 5B, Figure 2**). After excluding patients with pre-existing liver disease, all associations remained except those with acute CRP and steroid treatment (**Supplementary Table 5C**).

There was no statistically significant association between liver MRI abnormalities and abdominal or gastrointestinal symptoms. However, patients with liver MRI abnormalities were more likely to report symptoms of depression and less likely to report impaired quality of life.

*Renal health:* Five percent (14/259) of patients had pre-existing kidney disease (versus 2% of controls, padj=0·441) (**Table 1**).

During the acute phase, 17% (42/255) of patients had acute kidney injury. At follow-up,renal impairment (eGFR<60ml/min per 1·73m2) persisted in 6% (13/220) patients versus none of the controls. Renal abnormalities on MRI were more frequent among patients (23% (57/246) vs 6% (3/48) in controls, p=0·014) (**Table 2**). Total renal volumes indexed to body surface were similar between patients and controls. On average, renal medullary T1 was lower in patients (1895±88ms vs 1935 ±72ms, p=0·002), while cortical T1 did not differ between patients and controls (p=0·136). Renal corticomedullary differentiation, a marker of renal microstructural health, was lower in patients (371±58 vs controls 402 ±50 ms, p=0·001). After adjusting for confounders, renal MRI abnormalities tended to be more frequent among patients (OR 2.36 95% CI 0.89 - 8.02) relative to controls (**Supplementary** **Table 6A**).

Of the patients with abnormal renal MRI, 14% (8/57) had pre-existing known renal disease, and 29% (16/56) had acute kidney injury during admission. In all patients, renal MRI abnormalities were associated with older age, lower BMI, comorbid conditions including renal and cardiac disease, higher acute cardiac troponin and use of non-steroidal anti-inflammatories. At follow-up, patients with renal MRI abnormalities were more likely to have higher serum creatinine, urinary albumin : creatinine ratio >10 mg/g (ACR), higher serum NT pro-BNP, lower FEV1:FVC ratio, higher platelet counts, lower white cell count and a tendency to lower haemoglobin when compared to those without MRI abnormalities (**Supplementary** **Table 6B, Figure 2**). In patients without pre-existing renal disease, all associations remained except those with platelet count, serum creatinine and urinary ACR (**Supplementary** **Table 6C**).

There were no statistically significant associations between renal MRI abnormalities and patient-reported outcome measures.

*Multiorgan MRI abnormalities:* Patients had a higher burden of multiorgan MRI abnormalities relative to controls (61% versus 27%, padj<0·001, **Table 2**). The combination of lung, liver and brain abnormalities was the most common combination of organ abnormalities (**Figure 3**), likely reflecting both premorbid and post-COVID-19 injury.

Post-hospitalised COVID-19 patients were at a nearly three-fold risk (Odds Ratio 2·9 [95% CI 1·5, 5·8], padj=0·002) of two or more organ involvement after adjusting for pre-existing comorbidities (**Figure 4, Table 2**) or for Charlson comorbidity index (**Supplementary Figure 4**) when compared with controls.

Patients with more severe acute disease (WHO clinical progression score≥6) had the highest risk of multiorgan MRI abnormalities compared to controls. However, even after excluding individuals with critical COVID-19 (WHO 7-9), multiorgan abnormalities were more frequent among patients versus controls (**Table 2, Figure 4**). Acute treatment with steroids was not associated with a lower burden of multiorgan abnormalities. Patients with a follow-up CRP of <5 mg/L and ≥ 5 mg/L were at a two and three-fold risk of multiorgan MRI abnormalities, respectively, when compared to controls with normal or abnormal CRP. Patients from the severe and most severe PHOSP-COVID symptom cluster (indicating severe mental and physical impairment) were four times more likely to have multiorgan MRI abnormalities than controls.

Discussion

Key results

Our study demonstrates the significant burden of multiorgan abnormalities in post-hospitalised COVID-19 patients, with nearly one in three patients having an excess burden of multiorgan injury. When compared to controls, we noted a higher proportion of lung, brain and renal MRI abnormalities among patients. Organ abnormalities on imaging were associated with older age and severity of acute infection, with evidence of both vascular and inflammatory patterns of injury observed. We found that lung MRI abnormalities were associated with symptoms of chest tightness and impaired lung function, and multiorgan abnormalities were linked to patterns of impaired recovery at 5-months post-hospital discharge.

Follow-up studies of post-hospitalised COVID-19 patients have previously observed a high prevalence of pulmonary diffusion abnormalities,(16) with a recent meta-analysis of pooled data from 15 studies suggesting that 32·6% of patients exhibit ground glass pulmonary interstitial changes up to 12 months from infection.(17) In the present study, an excess of 28% of patients had lung MRI abnormalities, which were also associated with impaired gas transfer (TLCO). Although longitudinal studies(18, 19) suggest that such abnormalities may recover over time, 10% of individuals may develop pulmonary fibrosis by 2 years.(20) Tropism of SARS-CoV-2 for endothelial cells(21) and pericytes(22) has led to speculations that pulmonary vascular dysfunction may prevail in the long term. Numerous retrospective investigations(1, 23, 24) have observed an increased risk of arterial and venous thrombosis, with COVID-19 hospitalisation conferring the highest risk. To our knowledge, this is the first multicentre study to evaluate pulmonary perfusion in a large post-hospitalised COVID-19 patient cohort, and contrary to expectations, pulmonary perfusion measures (global pulmonary blood flow, blood volume or mean transit time) did not differ between patients and controls. Our findings suggest that complex mechanisms likely underpin pulmonary perfusion changes seen after COVID-19.

The medium to long-term effects of COVID-19 on the heart have been a subject of intense debate.(25) Early imaging studies of convalescent patients raised concerns about a high burden of myocarditis.(26) However, subsequent post-mortem studies and cardiac biopsies failed to confirm these findings.(27) Here, blinded image analyses by an experienced core lab team found comparable abnormalities in patients and controls. Specifically, a diagnosis of myocarditis was no more common in patients and did not predict ongoing symptoms. By contrast, patients did exhibit reduced left ventricular systolic function relative to controls. Investigators of the Hamburg health study(28) also noted a significant reduction in cardiac function on follow-up transthoracic echocardiography in non-hospitalised patients. Whilst these findings are intriguing, unmeasured residual confounders may still mediate differences, and the routine use of transthoracic echocardiography may be sufficient as a screening tool, whereas cardiac MRI may be more appropriate if the pretest probability of ongoing ischaemic or inflammatory injury is high.(29)

Cognitive impairment and brain fog are common manifestations post-COVID-19. In a study of UK Biobank participants with brain MRI pre- and post-infection, detailed quantitative analyses revealed grey matter volume reduction and abnormal diffusion parameters in regions of the brain involved in olfactory signal processing and memory.(30) Here, we noted a high burden of white matter hyperintensities and small vessel disease in patients not specifically referred for neurological symptoms, a finding that persisted after excluding severe cases and adjusting for pre-existing neurological diagnoses. Our findings suggest that vascular patterns of injury are common, and that patients with more severe infections have lower grey matter volumes(30) involving multiple regions of the brain relevant to working memory, emotion, visuo-auditory processing and autonomic nervous function. By contrast, total brain volume and CSF volume did not differ, and clinically evident MRI abnormalities did not associate with cognitive function. These findings highlight the diminished neurological reserve and vulnerability of post-hospitalised COVID-19 patients for future insults.

Histologically validated, quantitative liver MRI metrics are gaining importance as prognostically-relevant surrogates of liver fat and inflammation in infectious and metabolic diseases.(13) Liver cT1, a marker of fibrosis and inflammation, was shown in one previous study of non-hospitalised Long COVID patients to associate with cognitive impairment.(31) In the present study, there were similar rates of liver abnormalities among patients and controls, and liver cT1 did not associate with cognitive function, implying that the liver may not be a major organ for persistent post-COVID damage.

Follow-up studies of patients hospitalised with COVID-19 report a decline in renal function in up to 30% of patients.(16) A retrospective study of electronic health records from the veterans’ health care database observed a 13% increase in relative risk of renal impairment among non-hospitalised patients.(32) Others(8, 33) have also noted abnormalities in the renal cortex and medulla on renal MRI. As the largest multicentre study examining renal health on MRI, we noted that 23% of our patients have renal abnormalities. Specifically, corticomedullary differentiation, a reliable marker of renal health, was reduced in patients, and MRI abnormalities associated with follow-up renal function. Our study also newly reports the determinants of renal MRI abnormalities, aligning well with factors that predict long-term renal outcomes in other studies.(34)

Although lung MRI abnormalities did associate with chest tightness and impaired lung function, there was a surprising disconnect between other organ injury and persistent symptoms, underscoring the complex biology that underlies long COVID. However, when evaluating the impact of multiorgan injury on composite measures of patient recovery (e.g., persistent severe and very severe physical and mental impairment and impaired recovery), a novel association was noted relative to controls. Therefore, whilst the yield of multiorgan MRI for elucidating specific symptoms is uncertain, a normal MRI may provide reassurance to patients. Indeed, this hypothesis is currently being investigated in a randomised UK study of non-hospitalised post-COVID patients called STIMULATE-ICP.(35)

**Implications for policy, practice and research**

Severe SARS-CoV-2 infections are declining following widespread vaccination. However, older vulnerable patients globally still require hospital care and millions continue to suffer from the long-term complications of COVID-19. International consensus on multidisciplinary follow-up care pathways remains opaque.(36, 37) As the most comprehensive follow-up MRI study, we provide important insights into the significant burden of persistent multiorgan pathology, with implications for ongoing management. Specifically, impaired patient recovery is linked to multiorgan dysfunction post-COVID-19 and follow-up multidisciplinary services should focus on pulmonary, renal, vascular and neurological health in the long term.(35)

Although biochemical and MRI abnormalities were associated in some organs, neither biochemistry nor a lack of symptoms could exclude underlying imaging abnormalities, highlighting the value of more sensitive imaging-based assessments. Whilst the long-term functional implications of some MRI abnormalities require clarification, many of these markers have been shown to associate with poor clinical outcomes in other diseases reminding us to be vigilant of the future risk of moderate to severe COVID-19.

Study limitations

Our study is ongoing, and this early report is intended to help guide clinical follow-up for patients. The study is limited by its small sample size, inadequate power to examine multiple associations, susceptibility to acquisition and survival bias. Our controls were not previously hospitalized, but this study aimed to describe the excess burden of severe infections relative to general non-COVID-19 population. Lung MRI is less precise for quantification of lung parenchymal abnormalities relative to computed tomography and may have underestimated prevalence of lung abnormalities.

*Generalisability:* Our patients are younger, less obese, and were less likely to need intensive care or mechanical ventilation than individuals currently needing hospital admission following COVID-19; hence the burden of multiorgan dysfunction is likely to be underestimated. Missing data was variable across parameters, but the study was adequately powered for its primary endpoint. The study’s cross sectional design does not allow for distinction of pre-morbid disease from infection-specific emergent manifestations and only patients with non-omicron SARS-CoV-2 variants were enrolled, limiting the generalisability of our findings.

In summary, in our prospective MRI study of post-hospitalised COVID-19 patients, multiorgan MRI abnormalities were three-fold more common among patients post-hospital discharge for COVID-19 and linked with poor patient-reported recovery. Both inflammatory and/or vascular/haemostatic patterns of injury were observed across some organs. These findings underscore the need for multi-targeted therapies and integrated multidisciplinary follow-up services for post-hospitalised COVID-19 patients.

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**Contribution of writing group authors.**

The manuscript was initially drafted by BR and SN, with support from CM, and further developed by the writing committee. BR, SN, CM, SM, KM, EMT, PZ, SF, MK, JW, SKP, CEB, MC, RAE, LVW, OE, HJCM, ASi, MJD, ABD, NIL, JDC, L-PH, AH, MM and KP, made substantial contributions to the conception and design of the work. All authors contributed to data interpretation, critical review and revision of the manuscript, and final approval of the version to be published. BR, CM and RAE have accessed and verified the data. All authors are responsible for the decision to submit the manuscript, and are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

**Declaration of interest**

BR received funding support from the BHF Oxford CRE and NIHR Oxford BRC. In the past 3 years, BR received payment or honoraria for lectures/presentations or educational events from Axcella Therapeutics. In the past 3 years, SN received grants funding from NIHR Oxford BRC, BHF, UKRI. SN received consulting fees from Perspectum. SN has/had shares in Perspectum Ltd. In the past 3 years, PF, DW received grants funding from NIHR. DW received payment or honoraria for lectures/presentations or educational events from Biomerieux. AD received grants funding from Bayer, Gilead, Pfizer, Astrazeneca, Novartis. AD received consulting fees from Boehringer, Bayer, Gilead, Pfizer, GSK, Astrazeneca, Novartis. AD received support from attending meetings and or travel forAstra Zeneca, Chiesi, GSK. AD has participated on the data safety monitoring board or advisory board for Bayer. LH received grants funding from GSK, Schering Plough, Synairgen, Novartis and Roche/Genentech, MedImmune. 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**Data sharing**

Data sharing The protocol, consent form, definition and derivation of clinical characteristics and outcomes, training materials, regulatory documents, requests for data access and other relevant study materials are available online at <https://www.phosp.org>.

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Figure Legends:

**Figure 1.** **CONSORT diagram of recruitment.** SARS-CoV-2 Severe acute coronavirus-2, COVID coronavirus disease.

**Figure 2. Factors associated with single organ injury at follow-up with corresponding effect size.** Figure summarising the key clinical characteristics of patients that associate with single organ injury, including follow-up clinical measures.

**Figure 3. Venn diagram depicting overlap of organ abnormalities post-hospitalisation for COVID-19 and depicting the most common triad of organ abnormalities.** Numbers in brackets represent the absolute number of people with relevant organ abnormalities on MRI**.**

**Figure 4. Determinants of multiorgan injury on MRI among post-hospitalised patients recovering from COVID-19.** Forest plot depicting the medium-term effect of hospitalisation for COVID-19 on multiorgan health stratified by inflammatory burden, WHO severity, comorbidity status, severity of acute infection, and recovery status relative to control. (p values from multivariate analyses adjusted for age, sex, body mass index, smoking, hypertension, hypercholesterolemia, diabetes, pre-existing comorbidities and scanner manufacturer are displayed).

**Tables:**

**Table 1: Baseline characteristics of post-hospitalised COVID-19 patients and non-COVID-19 controls.**

**Table 2: Comparison of clinical and selected MRI findings of post-hospitalised COVID-19 patients and non-COVID-19 controls.**