

1 Multi-organ impairment in low-risk individuals with long COVID

2 Andrea Dennis PhD¹, Head of Biomarker Science, Perspectum

3 andrea.dennis@perspectum.com

4 Malgorzata Wamil PhD^{2,3}, Consultant Cardiologist gosia.wamil@googlemail.com

5 Sandeep Kapur MBBS⁴, Associate Medical Director kapur.sandeep@mayo.co.uk

6 Johann Alberts MBBCh⁵, Medical Director jalberts@alliance.co.uk

7 Andrew D. Badley MD⁶, Professor of Medicine & Chair, Mayo Clinic COVID Research

8 Taskforce badley.andrew@mayo.edu

9 Gustav Anton Decker MBBCh⁶, President, Mayo Clinic International

10 decker.anton@mayo.edu

11 Stacey A Rizza⁶, Professor of Medicine Rizza.stacey@mayo.edu

12 Rajarshi Banerjee DPhil*^{1,3}, Chief Executive and Honorary Consultant Physician

13 rajarshi.banerjee@perspectum.com

14 Amitava Banerjee DPhil*^{7,8,9}, Associate Professor of Clinical Data Science and Honorary

15 Consultant Cardiologist ami.banerjee@ucl.ac.uk

16 On behalf of the COVERSCAN study investigators (listed at the end of manuscript)

17

18 ¹Perspectum, 5520 John Smith Drive, Oxford, OX4 2LL, UK

19 ²Great Western Hospitals NHS Foundation Trust

20 ³Oxford University Hospitals NHS Foundation Trust

21 ⁴Mayo Clinic Healthcare, 15 Portland Pl, Marylebone, London W1B 1PT

22 ⁵Alliance Medical Limited, Icen Centre, Warwick Technology Park, Warwick, CV34 6DA

23 ⁶Mayo Clinic | 200 First Street SW, Rochester, MN 55905

24 ⁷Institute of Health Informatics, University College London, 222 Euston Road, London, UK

25 ⁸University College London Hospitals NHS Trust, 235 Euston Road, London, UK

26 ⁹Barts Health NHS Trust, The Royal London Hospital, Whitechapel Rd, London, UK

27 *joint senior author

28

29 - Corresponding authors: ami.banerjee@ucl.ac.uk; rajarshi.banerjee@perspectum.com

30

31

32

33

34

35

36

37

38

39

40

41 Multi-organ impairment in low-risk individuals with long COVID

42 Abstract

43 **Background:** Severe acute respiratory syndrome-coronavirus 2 (SARS-CoV-2) infection
44 has disproportionately affected older individuals and those with underlying medical
45 conditions. Research has focused on short-term outcomes in hospital, and single organ
46 involvement. Consequently, impact of long COVID (persistent symptoms three months post-
47 infection) across multiple organs in low-risk individuals is yet to be assessed.

48 **Methods:** An ongoing prospective, longitudinal, two-centre, observational study was
49 performed in individuals symptomatic after recovery from acute SARS-CoV-2 infection.
50 Symptoms and organ function (heart, lungs, kidneys, liver, pancreas, spleen) were assessed
51 by standardised questionnaires (EQ-5D-5L, Dyspnoea-12), blood investigations and
52 quantitative magnetic resonance imaging, defining single and multi-organ impairment by
53 consensus definitions.

54 **Findings:** Between April and September 2020, 201 individuals (mean age 44 (SD 11.0)
55 years, 70% female, 87% white, 31% healthcare workers) completed assessments following
56 SARS-CoV-2 infection (median 140, IQR 105-160 days after initial symptoms). The
57 prevalence of pre-existing conditions (obesity: 20%, hypertension: 6%; diabetes: 2%; heart
58 disease: 4%) was low, and only 18% of individuals had been hospitalised with COVID-19.
59 Fatigue (98%), muscle aches (88%), breathlessness (87%), and headaches (83%) were the
60 most frequently reported symptoms. Ongoing cardiorespiratory (92%) and gastrointestinal
61 (73%) symptoms were common, and 42% of individuals had ten or more symptoms.
62 There was evidence of mild organ impairment in heart (32%), lungs (33%), kidneys (12%),
63 liver (10%), pancreas (17%), and spleen (6%). Single (66%) and multi-organ (25%)
64 impairment was observed, and was significantly associated with risk of prior COVID-19
65 hospitalisation ($p < 0.05$).

66 **Interpretation:** In a young, low-risk population with ongoing symptoms, almost 70% of
67 individuals have impairment in one or more organs four months after initial symptoms of
68 SARS-CoV-2 infection. There are implications not only for burden of long COVID but also
69 public health approaches which have assumed low risk in young people with no
70 comorbidities.

71 **Funding:** This work was supported by the UK's National Consortium of Intelligent Medical
72 Imaging through the Industry Strategy Challenge Fund, Innovate UK Grant 104688, and also
73 through the European Union's Horizon 2020 research and innovation programme under
74 grant agreement No 719445.

75

76

77 **Introduction**

78 Early in the COVID-19 pandemic, research and clinical interest in SARS-CoV-2 (Severe
79 acute respiratory syndrome-coronavirus 2)-induced organ damage was predominantly
80 focused on the respiratory system(1). There have been indirect effects on other organ
81 systems and disease processes, such as cardiovascular diseases and cancers, through
82 changes in health systems or behaviours of patients and health professionals(2-4). In
83 addition, beyond an acute systemic inflammatory response, evidence for direct COVID-19-
84 related effects on multiple organs is accumulating, with potential long-term impacts for
85 individuals as well as health systems(5-8). However, no study to-date has included detailed
86 characterisation of all major organ systems following SARS-CoV-2 infection.

87

88 COVID-19 represents a convergence of an infectious disease, under-treated non-
89 communicable diseases and social determinants of health, as a “syndemic”(9). Pre-existing
90 non-communicable diseases and risk factors are important predictors of poor COVID-19
91 outcomes, whether intensive care admissions or mortality(2). Research has focused on the
92 acute phase of SARS-CoV-2 infection, in hospitalised patients, and on individuals that have
93 died from COVID-19(10-12). It is clear that COVID-19 can have longer multiple symptoms
94 and long-term effects(13), but “long-COVID” is yet to be fully defined(14-15), partly due to
95 lack of understanding of medium- and long-term pathophysiology across organ systems.

96

97 Long COVID in low-risk individuals, who represent up to 80% of the population(2), has public
98 health importance in terms of burden of disease and healthcare utilisation, and therefore has
99 urgent policy relevance across countries. However, in the UK, government policies have
100 emphasised excess risk of mortality in moderate- and high-risk conditions, including
101 “shielding”(2) and commissioning of a risk calculator to identify those at highest risk of
102 COVID-19 severity and mortality(16). As the pandemic progresses, there is growing concern
103 regarding prolonged isolation strategies for people with vulnerable conditions and at highest
104 risk of severe COVID-19 outcomes(17). These approaches have assumed low risk of SARS-
105 CoV-2 infection in younger individuals without underlying conditions, based on their low
106 excess mortality, but without knowledge of the chronic pulmonary and extrapulmonary
107 effects of COVID-19.

108

109 In order to better understand the long-term impact of COVID-19 and ultimately inform
110 preventive measures at health system level, we performed a pragmatic, prospective study in
111 low-risk individuals with symptom assessment, multi-organ magnetic resonance imaging

(MRI) and blood investigations for inflammatory markers at three months post-COVID-19 diagnosis.

Methods

Patient population and study design

In an ongoing, prospective study, 201 participants were enrolled at two UK sites (Perspectum, Oxford and Mayo Clinic Healthcare, London) between April 2020 and August 2020 and completed baseline assessment by 14 September 2020 (**Figure 1**). Participants were eligible for enrolment if they tested positive by the oro/nasopharyngeal throat swab for SARS-CoV-2 by reverse-transcriptase-polymerase-chain reaction (n=62), a positive antibody test (n=63), or had typical symptoms and were determined to have COVID-19 by two independent clinicians (n=73). Exclusion criteria were symptoms of active respiratory viral infection (temperature $>37.8^{\circ}\text{C}$ or three or more episodes of coughing in 24 hours); discharged from hospital in the last 7 days; and contraindications to MRI, including implanted pacemakers, defibrillators, other metallic implanted devices; claustrophobia. The study protocol was approved by a UK ethics committee (20/SC/0185), registered (<https://clinicaltrials.gov/ct2/show/NCT04369807>) and all patients gave written informed consent.

To assess the burden of multi-organ involvement after SARS-CoV2 infection

Organ function was assessed by patient-reported validated questionnaires, fasting blood investigations (as listed below) and multi-organ MRI. MRI was the chosen imaging modality (as in UK Biobank) because it is: (1) safe, with no radiation exposure, no need for intravenous contrast, minimal contact with the radiographer; (2) quantitative, repeatable and robust, with $>95\%$ acquisition and image processing success rate; (3) informative through a repository of digital data which can be shared in the research community for independent analysis and research; (4) rapid and scalable, i.e. a 35-minute scan can phenotype the lung, heart, kidney, liver, pancreas and spleen. At time of MRI, we completed (i) questionnaires for quality of life (EQ-5D-5L(18)), addressing mobility, self-care, usual activity, pain and anxiety, and breathlessness (Dyspnoea-12(19)) and (ii) full blood count, serum biochemistry (sodium, chloride, bicarbonate, urea, creatinine, bilirubin, alkaline phosphatase, aspartate transferase, alanine transferase, lactate dehydrogenase, creatinine kinase, gamma-glutamyl transpeptidase, total protein, albumin, globulin, calcium, magnesium, phosphate, uric acid, fasting triglycerides, cholesterol (total, HDL, LDL), iron, iron-binding capacity (unsaturated and total) and inflammatory markers (erythrocyte sedimentation rate, ESR; high sensitivity-C-Reactive Protein, CRP) (TDL laboratories, London).

Magnetic Resonance Image Analysis

Multi-organ MRI data were collected at both study sites (Oxford: MAGNETOM Aera 1.5T, Mayo Healthcare London; MAGNETOM Vida 3T; both from Siemens Healthcare Erlangen, Germany). The COVERSCAN Multiparametric MRI assessment typically required 35mins per patient, including lungs, heart, liver, pancreas, kidneys and spleen by standardised methodology (**Supplementary methods**).

Definition of organ impairment

MRI-derived measurements from the heart, lungs, kidney, liver, pancreas and spleen were compared with established reference ranges (**Table S1**) to determine impairment for each organ. An individual organ was classified as impaired if at least one of the metrics calculated for that organ was outside the reference range. Excessive organ fat was not considered as an indicator of impairment on the assumption that this was likely pre-existing and thus treated separately. Organ impairment was defined for each metric according to established cut-offs (Table S1) and was grouped by evidence of: borderline or low ejection fraction and evidence of myocarditis in the heart; reduced pulmonary dynamic measurements in the lungs; elevated cortical T1 in the kidneys; borderline or definite inflammation in the liver and pancreas; and splenomegaly from spleen length.

Statistical analysis

All statistical analyses were performed using R software (version 3.6.1) with a p-value less than 0.05 considered statistically significant. Descriptive statistics were used to summarise baseline participant characteristics. Mean and standard deviation (SD) were used to describe normally distributed-continuous variables, median with interquartile range (IQR) for non-normally distributed, and frequency and percentage for categorical variables.

Mean difference in quantitative organ metrics between hospitalised versus not hospitalised were compared using the Wilcoxon test, and difference in the counts of the binary outcomes of those with evidence of organ abnormalities compared using Fisher's test. Multi-organ impairment was defined as impairment to ≥ 2 organs. Associations between multi-organ impairment and symptoms, comorbidities and pre-existing risk factors were assessed using Spearman's correlation. Based on the observed differences between hospitalised and non-hospitalised groups, multivariate logistic regression models were used to assess risk factors for COVID-19 hospitalisation.

Results

The mean age was 44.0 (SD: 11.0) years. 70% of individuals were female, 87% were white, 31% were healthcare workers, 18% had been hospitalised with COVID-19. Assessment (symptoms, blood and MRI) was a median 140 (IQR 105-160) days after initial symptoms. Relevant past medical history included smoking (3%), asthma (18%), obesity (20%), hypertension (6%), diabetes (2%) and heart disease (4%). The hospitalised group were older ($p=0.001$), had a higher proportion of non-white participants ($p=0.038$), and were more likely to report 'inability to walk' ($p=0.01$) than non-hospitalised individuals. There were no other significant differences between risk factors or symptoms reported between the groups. The most commonly reported on-going symptoms (regardless of hospitalisation status) were fatigue (98%), muscle ache (88%), shortness of breath (87%) and headache (83%) (**Table 1, Figure 2(a)**). Ongoing cardiorespiratory (92%) and gastrointestinal (73%) symptoms were common. 99% of individuals had four or more and 42% had ten or more symptoms. 52% of patients reported persistent moderate problems undertaking usual activities (level 3 or greater in the relevant EQ-5D-5L question). 20% reported Dyspnoea-12 ≥ 15 (equivalent to ~ 3 on the MRC dyspnoea grade).

Blood investigations

Triglycerides ($p=0.002$), cholesterol ($p=0.021$), LDL-cholesterol ($p=0.005$) and transferrin saturation ($p=0.005$) were more likely to be abnormal in hospitalised versus non-hospitalised individuals. Mean corpuscular haemoglobin concentration (26%), alanine transferase (14%), lactate dehydrogenase (16%), triglycerides (12%) and cholesterol (42%) were all abnormally high in $\geq 10\%$ of all individuals (without separation by hospitalisation status). ESR (13%), bicarbonate (13%), uric acid (16%) and high-sensitivity CRP (13%) were abnormally high in $\geq 10\%$ of individuals in the hospitalisation group. Bicarbonate (10%), phosphate (13%), uric acid (11%), and transferrin saturation (19%) were abnormally low in $\geq 10\%$ of individuals (without separation by hospitalisation status) (**Table S2**).

Single and multi- organ impairment

Impairment was present in the heart in 32% (myocarditis in 11%; systolic dysfunction in 23%), lungs in 33%, kidneys in 12%, liver in 10%, pancreas in 17%, and 6% had evidence of splenomegaly (**Table 2, Figure 2(b)**). 66% of individuals had impairment in one or more organ systems. There was evidence of multi-organ impairment in 25% of individuals, with varying degrees of overlap across multiple organs (**Figure 1 and 3**). Organ impairment was

more common in hospitalised versus non-hospitalised individuals. Measures of inflammation in the kidneys and pancreas, and ectopic fat in the pancreas and liver, were also higher in hospitalised individuals (all $p < 0.05$)(**Figure 2(b)**).

Association between symptoms, blood investigations and organ impairment

Figure 4 shows the percentage of reported symptoms in those with organ impairment (per organ). Multi-organ involvement was associated with more serious symptoms (fatigue, breathlessness etc), but no clear pattern was observed linking symptoms to organ impairment. Regression analysis did not show any association between specific organ impairment and specific symptoms or blood investigations. Increasing age (OR: 1.06 [CI: 1.02-1.10], $p < 0.01$), increased liver volume (OR: 1.18 [CI: 1.06-1.30], $p < 0.001$) and having multi-organ impairment (OR: 2.75 [CI: 1.22-6.22], $p < 0.05$), all significantly increased the likelihood of being hospitalized, adjusting for gender and BMI.

Discussion

In the first study to-date evaluating medium-term impairment across multiple organs following SARS-CoV2 infection, we had three major findings. First, in young individuals, largely without risk factors, pre-existing disease or hospitalisation, there was significant symptom burden and evidence of heart, lung, liver and pancreas impairment four months post-COVID-19. Second, symptoms and blood investigations predicted neither organ impairment nor hospitalisation. Third, cardiac (myocarditis and systolic dysfunction) and lung impairment have similar prevalence in low-risk individuals with long COVID.

The short-term symptoms likely to predict COVID-19(20) persist four months post-infection, particularly fatigue, shortness of breath, myalgia, headache and arthralgia. In this young cohort with low prevalence of comorbidities, the extent of symptom burden and organ impairment is concerning. Models of population COVID-19 impact have been based on age, underlying conditions and mortality, excluding morbidity or potential for multi-organ impairment and chronic diseases(21, 22). Moreover, studies highlighting extrapulmonary COVID-19 manifestations emphasised acute phase of illness(20). Although we describe mild rather than severe organ impairment, the pandemic's scale and high infection rates in lower risk individuals (by age and underlying conditions), suggest a medium- and longer- term impact of SARS-CoV-2 infection which cannot be ignored in healthcare or policy spheres.

Although there may be an immunologic basis for variations in progression and severity of SARS-CoV-2 infection in different individuals(24), prediction models to-date have high rates of bias and poor performance(25). We found clustering of cardiorespiratory and gastrointestinal symptoms with evidence of impairment in heart, liver and pancreas respectively, but blood investigations were not associated with particular patterns of organ impairment as determined by COVERSCAN multi-organ assessment. Neither symptoms nor blood investigations were predictive of organ impairment. In acutely unwell patients, the focus has been on recognition of respiratory dysfunction and early provision of ventilatory support, but chronic multi-organ function has not been described systematically. Ongoing studies are considering chronic impact of COVID-19(26) but excluding non-hospitalised, low-risk individuals with and without organ impairment, which we will be investigating further in the longer term. As well as interest in specialist long COVID clinical services(27), there is a role for multi-organ assessment and ongoing evaluation, including low-risk, non-hospitalised individuals, perhaps even in the absence of symptoms.

Acute myocarditis and cardiogenic shock have been described(28), as well as high prevalence of myocarditis in hospitalised COVID-19 patients(29). In American athletes, although recent COVID-19 was associated with myocarditic changes, many non-infected patients also showed these changes(30). We now add that one third of low-risk individuals with long COVID syndrome have cardiac impairment in the form of mild systolic dysfunction or myocarditis three months following SARS-CoV-2 infection. Whilst causality cannot be attributed, cardiac function can be viewed as a risk factor for severe infection and an explanation of persistent symptoms in long COVID. As longitudinal data across organs become available, potential significance of our findings in the liver, kidney and pancreas needs to be explored.

Implications for research

Our findings at four months post-infection and future findings have three research implications. First, as countries face second pandemic waves, models of the pandemic's impact must include long COVID, whether quality of life, healthcare utilisation, productivity and economic effects. Second, there is urgent need for further multi-organ assessment, including blood and imaging analysis in the COVID-19 context, as well as linkage with primary and secondary care data, so that long COVID can be properly defined. Third, further longitudinal investigation of clustering of symptoms and organ impairment will inform health services research to plan multidisciplinary care pathways.

Implications for clinical practice and public health

There are three implications for COVID-19 management. First, as well as highlighting the potential for MRI across organ systems following SARS-CoV-2 infection, our findings signal the need for monitoring and follow-up in at least the medium- and longer-term, especially for extrapulmonary sequelae. Second, as the search for effective COVID-19 vaccines and treatments continues, potential and real long-term multi-organ consequences of SARS-CoV-2 infection in low-risk individuals reinforce the central importance of minimising infection through social distancing, wearing of masks, physical isolation and other population-level measures. Third, both in terms of managing baseline risk, and monitoring and treating complications across organ systems, long COVID requires management across specialities (e.g. cardiology, gastroenterology) and disciplines (e.g. communicable and non-communicable diseases).

Strengths and limitations

Our study is an ongoing, prospective, longitudinal cohort study with detailed blood and imaging characterisation of organ function, despite limited clinical examination with video consultations in the era of COVID-19. By recruiting ambulatory patients after infection with

broad inclusion criteria (e.g. SARS-CoV-2 testing by virus RNA, antibody or antigen), we focus on individuals at lower risk of severity and mortality from acute SARS-CoV-2 infection. Our cardiac MRI protocol excluded gadolinium contrast as concerns regarding COVID-19-related renal complications remain. We relied on native T1 mapping to detect and characterise myocardial inflammation, allowing non-invasive tissue characterisation which was previously evaluated as superior to gadolinium MRI for acute myocarditis(31).

We report baseline findings following SARS-CoV-2 infection. In our pragmatic study design, the diagnosis of COVID-19 was by multiple methods, partly limited by access to laboratory testing during the pandemic. Causality of the relationship between organ impairment and infection cannot be deduced, but may be addressed by longitudinal follow-up of individuals with organ impairment. Our study population was limited by ethnicity despite disproportionate impact of COVID-19 in non-white individuals. Pulse oximetry and spirometry were added later to the protocol and follow up; they were not included from the outset to limit interaction and exposure between trial team and patients. We did not include healthy controls or MRI assessment of brain or muscle function.

Conclusions

Long COVID has a physiological basis, with measurable patient-reported outcomes and organ impairment. Medium- and long-term evaluation and monitoring of multi-organ function beyond symptoms and blood investigations is likely to be required, even in lower risk individuals. Health system responses should emphasise suppression of population infection rates, as well as management of pre- and post-COVID-19 risk factors and chronic diseases.

369

370

371

372

373 *COVERSCAN study investigators*

374 Perspectum: Mary Xu, Faezah Sanaei-Nezhad, Andrew Parks, Andrea Borghetto, Matthew
375 D Robson, Petrus Jacobs, John Michael Brady, Carla Cascone, Soubera Rymell, Jacky Law,
376 Virginia Woolgar, Velko Tonev, Claire Herlihy, Rob Suriano, Tom Waddell, Henrike Puchte,
377 Alessandra Borlotti, Arun Jandor, Freddie Greatrex, Robin Jones, Georgina Pitts, Ashleigh
378 West, Marion Maguire, Anu Chandra, Naomi Jayaratne, Dali Wu, Stella Kin, Mike Linsley,
379 Valentina Carapella, Isobel Gordon, George Ralli, John McGonigle, Darryl McClymont,
380 Boyan Ivanov, James Owler, Diogo Cunha, Tatiana Lim, Carlos Duncker, Madison Wagner,
381 Marc Goldfinger, Adriana Roca, Charlotte Erpicum, Matthew David Kelly, Rexford D
382 Newbould, Catherine J Kelly, Andrea Dennis, Sofia Mouchti, Arina Kazimianec, Helena
383 Thomaides-Briers, Rajarshi Banerjee

384 Mayo Clinic: Sandeep Kapur, Louise McLaughlin, Stacey A. Rizza

385 University College London: Amitava Banerjee

386 Great Western Hospitals NHS Foundation Trust: Malgorzata Wamil

387 University of Oxford: Yi-Chun Wang, Tom Waddell

Contributorship statement:

389 Study design: AD, SK, RB, JA, SR

390 Patient recruitment: SK, RB, COVERSCAN team

391 Data collection: MW, LM, COVERSCAN team

392 Data analysis: AD, COVERSCAN team, AB

393 Data interpretation: AB, AD, MW, RB

394 Initial manuscript drafting: AB, AD, RB

395 Critical review of early and final versions of manuscript: all authors

396 Specialist input: cardiology (MW, AB); general medicine (RB, ADB, GAD); infectious disease
397 (SAR, ADB); imaging (MR, RB); statistics (AD); epidemiology/public health (AB); primary
398 care (SK); healthcare management (JA).

Funding acknowledgements

400 AB is supported by research funding from NIHR, British Medical Association, Astra-Zeneca,
401 UK Research and Innovation, and the Innovative Medicines Initiative-2 (BigData@Heart
402 Consortium, under grant agreement No. 116074, supported by the European Union's
403 Horizon 2020 research and innovation programme and EFPIA; chaired by DE Grobbee and
404 SD Anker, partnering with 20 academic and industry partners and ESC). This work was

supported by the UK's National Consortium of Intelligent Medical Imaging through the Industry Strategy Challenge Fund, Innovate UK Grant 104688, and also through the European Union's Horizon 2020 research and innovation programme under grant agreement No 719445.

Research in Context

Evidence before this study

We searched PubMed, medRxiv, bioRxiv, arXiv, and Wellcome Open Research for peer-reviewed articles, preprints, and research reports on long COVID syndrome and medium- and long-term impact of coronavirus disease 2019 (COVID-19), using the search terms "coronavirus", "COVID-19", and similar terms, "organ impairment", "organ function" and "morbidity", up to September 30, 2020. We found no prior studies of medium- or long-term multi-organ impairment due to COVID-19. Prior studies have considered acute phase of illness and hospitalised patients, focusing on "high-risk" individuals based on age and underlying conditions. Without longer term data including lower risk individuals, full population impact of the pandemic cannot be assessed and health system responses cannot be planned.

Added value of this study

In 201 individuals with low risk for COVID-19 severity and mortality (mean age 44 years, 20% obesity, 6% hypertension, 2% diabetes and 4% heart disease, 18% hospitalised), we assessed symptoms, blood investigations and multi-organ magnetic resonance imaging across organ systems, four months following SARS-CoV-2 infection. 99% and 42% had ≥ 4 and ≥ 10 symptoms respectively. Mild organ impairment was present in at least one organ in 66% and in 2 or more organs in 25% of individuals. Multi-organ impairment was associated with hospitalisation.

Implications of all the available evidence

These analyses support strategies to suppress and minimise the infection rate in the population; medium- and long-term follow-up after SARS-CoV-2 infection with detailed evaluation across organ systems; and management of underlying conditions and risk factors before and after infection. For the first time, we provide multi-organ assessment in young, low-risk individuals with long COVID to inform healthcare and policy responses.

References

1. World Health Organization. Clinical management of severe acute respiratory infection (SARI) when COVID-19 disease is suspected. Interim guidance 13 March 2020. <https://www.who.int/docs/default-source/coronaviruse/clinical-management-of-novel-cov.pdf>
2. Banerjee A, Pasea L, Harris S, Gonzalez-Izquierdo A, Torralbo A, Shallcross L, Noursadeghi M, Pillay D, Sebire N, Holmes C, Pagel C, Wong WK, Langenberg C, Williams B, Denaxas S, Hemingway H. Estimating excess 1-year mortality from COVID-19 according to underlying conditions and age in England: a rapid analysis using NHS health records in 3.8 million adults. *Lancet* May 30;395(10238):1715-1725
3. Banerjee A, Chen S, Pasea L, Lai A, Katsoulis M, Denaxas S, Nafilyan V, Williams B, Wong WK, Bakhai A, Khunti K, Pillay D, Noursadeghi M, Wu H, Pareek N, Bromage D, McDonagh T, Byrne J, Teo JT, Shah A, Humberstone B, Tang LV, Shah ASV, Rubboli A, Guo Y, Hu Y, Sudlow CLM, Lip GYH, Hemingway H. Excess deaths in people with cardiovascular diseases during the COVID-19 pandemic. *Medrxiv*. Preprint. 2020. Online 11/6/2020. <https://www.medrxiv.org/content/10.1101/2020.06.10.20127175v1>
4. Lai AG, Pasea L, Banerjee A, Denaxas S, Katsoulis M, Chang WH, Williams B, Pillay D, Noursadeghi M, Swanton C, Linch D, Hughes D, Forster MD, Johnson P, Turnbull C, DATA-CAN, Cooper M, Jones M, Pritchard-Jones K, Sullivan R, Lawler M, Hall G, Davie C, Hemingway H. Estimating excess mortality in people with cancer and multimorbidity in the COVID-19 emergency. *BMJ Open*. 2020. In press.
5. Pavon AG, Meier D, Samim D, Rotzinger DC, Fournier S, Marquis P, Monney P, Muller O, Schwitter J. First Documentation of Persistent SARS-Cov-2 Infection Presenting With Late Acute Severe Myocarditis. *Can J Cardiol*. 2020 Aug;36(8):1326.e5-1326.e7.
6. Alqahtani SA, Schattenberg JM. Liver injury in COVID-19: The current evidence. *United European Gastroenterol J*. 2020 Jun;8(5):509-519.
7. Farouk SS, Fiaccadori E, Cravedi P, Campbell KN. COVID-19 and the kidney: what we think we know so far and what we don't. *J Nephrol*. 2020 Jul 20:1-6.

8. Somasundaram NP, Ranathunga I, Ratnasamy V, Wijewickrama PSA, Dissanayake HA, Yogendranathan N, Gamage KKK, de Silva NL, Sumanatilleke M, Katulanda P, Grossman AB. The Impact of SARS-Cov-2 Virus Infection on the Endocrine System. *J Endocr Soc.* 2020 Jul 2;4(8):bvaa082.
9. Horton R. Offline: COVID-19 is not a pandemic. *Lancet* 2020. 396; 874.
10. Shovlin CL, Vizcaychipi MP. Implications for COVID-19 triage from the ICNARC report of 2204 COVID-19 cases managed in UK adult intensive care units. *Emerg Med J.* 2020 Jun;37(6):332-333.
11. Docherty AB, Harrison EM, Green CA, Hardwick HE, Pius R, Norman L, Holden KA, Read JM, Dondelinger F, Carson G, Merson L, Lee J, Plotkin D, Sigfrid L, Halpin S, Jackson C, Gamble C, Horby PW, Nguyen-Van-Tam JS, Ho A, Russell CD, Dunning J, Openshaw PJ, Baillie JK, Semple MG; ISARIC4C investigators. Features of 20 133 UK patients in hospital with covid-19 using the ISARIC WHO Clinical Characterisation Protocol: prospective observational cohort study. *BMJ.* 2020 May 22;369:m1985. doi: 10.1136/bmj.m1985.
12. Williamson EJ, Walker AJ, Bhaskaran K, Bacon S, Bates C, Morton CE, Curtis HJ, Mehrkar A, Evans D, Inglesby P, Cockburn J, McDonald HI, MacKenna B, Tomlinson L, Douglas IJ, Rentsch CT, Mathur R, Wong AYS, Grieve R, Harrison D, Forbes H, Schultze A, Croker R, Parry J, Hester F, Harper S, Perera R, Evans SJW, Smeeth L, Goldacre B. Factors associated with COVID-19-related death using OpenSAFELY. *Nature.* 2020 Jul 8. doi: 10.1038/s41586-020-2521-4.
13. World Health Organization. What we know about Long-term effects of COVID-19.9 September 2020. https://www.who.int/docs/default-source/coronaviruse/risk-comms-updates/update-36-long-term-symptoms.pdf?sfvrsn=5d3789a6_2
14. Nabavi N. Long covid: How to define it and how to manage it. *BMJ.* 2020 Sep 7;370:m3489.
15. Greenhalgh T, Knight M, A'Court C, Buxton M, Husain L. Management of post-acute covid-19 in primary care. *BMJ.* 2020 Aug 11;370:m3026.
16. National Institute for Health Research. New risk prediction model could help improve guidance for people shielding from COVID-19. 23 June 2020. <https://www.nihr.ac.uk/news/new-risk-prediction-model-could-help-improve-guidance-for-people-shielding-from-covid-19/25096>
17. Wise J. Covid-19: Experts divide into two camps of action—shielding versus blanket policies. *BMJ* 2020;370:m3702. <https://www.bmj.com/content/370/bmj.m3702>
18. Janssen MF, Pickard AS, Golicki D, Gudex C, Niewada M, Scalone L, Swinburn P, Busschbach J. Measurement properties of the EQ-5D-5L compared to the EQ-5D-3L

514 across eight patient groups: a multi-country study. *Qual Life Res* 2013
515 Sep;22(7):1717-1727

516 19. Yorke J, Moosavi SH, Shuldham C, Jones PW. Quantification of dyspnoea using
517 descriptors: development and initial testing of the Dyspnoea-12. *Thorax*. 2010
518 Jan;65(1):21-6. doi: 10.1136/thx.2009.118521. Epub 2009 Dec 8.

519 20. Menni C, Valdes AM, Freidin MB, Sudre CH, Nguyen LH, Drew DA, Ganesh S,
520 Varsavsky T, Cardoso MJ, El-Sayed Moustafa JS, Visconti A, Hysi P, Bowyer RCE,
521 Mangino M, Falchi M, Wolf J, Ourselin S, Chan AT, Steves CJ, Spector TD. Real-
522 time tracking of self-reported symptoms to predict potential COVID-19. *Nat Med*.
523 2020 Jul;26(7):1037-1040.

524 21. Gupta A, Madhavan MV, Sehgal K, Nair N, Mahajan S, Sehrawat TS, Bikdeli B,
525 Ahluwalia N, Ausiello JC, Wan EY, Freedberg DE, Kirtane AJ, Parikh SA, Maurer
526 MS, Nordvig AS, Accili D, Bathon JM, Mohan S, Bauer KA, Leon MB, Krumholz HM,
527 Uriel N, Mehra MR, Elkind MSV, Stone GW, Schwartz A, Ho DD, Bilezikian JP,
528 Landry DW. Extrapulmonary manifestations of COVID-19. *Nat Med*. 2020
529 Jul;26(7):1017-1032. doi: 10.1038/s41591-020-0968-3.

530 22. Palmer K, Monaco A, Kivipelto M, Onder G, Maggi S, Michel JP, Prieto R, Sykara G,
531 Donde S. The potential long-term impact of the COVID-19 outbreak on patients with
532 non-communicable diseases in Europe: consequences for healthy ageing. *Aging Clin*
533 *Exp Res*. 2020 Jul;32(7):1189-1194.

534 23. Wyper GMA, Assunção R, Cuschieri S, Devleeschauwer B, Fletcher E, Haagsma JA,
535 Hilderink HBM, Idavain J, Lesnik T, Von der Lippe E, Majdan M, Milicevic MS, Pallari
536 E, Peñalvo JL, Pires SM, Plaß D, Santos JV, Stockton DL, Thomsen ST, Grant I.
537 Population vulnerability to COVID-19 in Europe: a burden of disease analysis. *Arch*
538 *Public Health*. 2020 May 29;78:47.

539 24. Mathew D, Giles JR, Baxter AE, Oldridge DA, Greenplate AR, Wu JE, Alanio C, Kuri-
540 Cervantes L, Pampena MB, D'Andrea K, Manne S, Chen Z, Huang YJ, Reilly JP,
541 Weisman AR, Ittner CAG, Kuthuru O, Dougherty J, Nzingha K, Han N, Kim J,
542 Pattekar A, Goodwin EC, Anderson EM, Weirick ME, Gouma S, Arevalo CP, Bolton
543 MJ, Chen F, Lacey SF, Ramage H, Cherry S, Hensley SE, Apostolidis SA, Huang
544 AC, Vella LA; UPenn COVID Processing Unit, Betts MR, Meyer NJ, Wherry EJ. Deep
545 immune profiling of COVID-19 patients reveals distinct immunotypes with therapeutic
546 implications. *Science*. 2020 Sep 4;369(6508):eabc8511.

547 25. Wynants L, Van Calster B, Collins GS, Riley RD, Heinze G, Schuit E, Bonten MMJ,
548 Damen JAA, Debray TPA, De Vos M, Dhiman P, Haller MC, Harhay MO, Henckaerts
549 L, Kreuzberger N, Lohman A, Luijken K, Ma J, Andaur CL, Reitsma JB, Sergeant JC,
550 Shi C, Skoetz N, Smits LJM, Snell KIE, Sperrin M, Spijker R, Steyerberg EW, Takada

- T, van Kuijk SMJ, van Royen FS, Wallisch C, Hooft L, Moons KGM, van Smeden M. Prediction models for diagnosis and prognosis of covid-19 infection: systematic review and critical appraisal. *BMJ*. 2020 Apr 7;369:m1328. doi: 10.1136/bmj.m1328.
26. PHOSP-COVID: Post-HOSPitalisation COVID-19 study. <https://www.phosp.org/>
27. NHS to offer 'long covid' sufferers help at specialist centres. 7 October 2020 <https://www.england.nhs.uk/2020/10/nhs-to-offer-long-covid-help/>
28. Chau VQ, Giustino G, Mahmood K, Oliveros E, Neibart E, Oloomi M, Moss N, Mitter SS, Contreras JP, Croft L, Serrao G, Parikh AG, Lala A, Trivieri MG, LaRocca G, Anyanwu A, Pinney SP, Mancini DM. Cardiogenic Shock and Hyperinflammatory Syndrome in Young Males with COVID-19. *Circ Heart Fail*. 2020 Aug 26. doi: 10.1161/CIRCHEARTFAILURE.120.007485. Online ahead of print.
29. Puntmann VO, Carerj ML, Wieters I, et al. Outcomes of Cardiovascular Magnetic Resonance Imaging in Patients Recently Recovered From Coronavirus Disease 2019 (COVID-19). *JAMA Cardiol*. Published online July 27, 2020. doi:10.1001/jamacardio.2020.3557.
30. Rajpal S, Tong MS, Borchers J, et al. Cardiovascular Magnetic Resonance Findings in Competitive Athletes Recovering From COVID-19 Infection. *JAMA Cardiol*. Published online September 11, 2020. doi:10.1001/jamacardio.2020.4916.
31. Ferreira VM, Piechnik SK, Dall'Armellina E, Karamitsos TD, Francis JM, Ntusi N, et al. T1 mapping for the diagnosis of acute myocarditis using CMR: comparison to T2-weighted and late gadolinium enhanced imaging. *JACC Cardiovasc Imaging*. 2013;6(10):1048-58)

Figures and Tables

Table 1: Baseline demographics and symptoms in 201 low-risk individuals with long-COVID.

Table 2: Evidence of organ impairment in 201 low-risk individuals with long-COVID.

Figure 1: Natural history of long COVID, the COVERSCAN study in low-risk individuals (n=201) and policy recommendations.

Figure 2: Proportion of low-risk individuals with long-COVID by hospitalisation (n=201) for (a) symptoms; and (b) evidence of organ impairment.

Figure 3: Multi-organ impairment in low-risk individuals with long COVID by gender and hospitalisation (n=201).

Figure 4: Clustering of reported symptoms and organ impairment for individuals with long-COVID (n=201).

Table 1: Baseline demographics and symptoms in 201 low-risk individuals with long-COVID.*

	All (n=201) N (%)	Not hospitalised (n=164) N(%)	Hospitalised (n=37) N(%)	p
Patient characteristics				
Age (yrs, mean; sd)	44(11.0)	43(10.9)	50(10.0)	
Female (No, %)	140(69.7)	117(71.3)	23(62.2)	
BMI (kg.m ⁻² , median; IQR)	25.7(22.7,28.1)	25.3(22.6,27.7)	27.2(23.1,31.0)	
Ethnicity				
White	174(86.6)	146(89.0)	28 (75.7)	
Mixed	3(1.5)	3(1.8)	0 (0)	
South Asian	8(4.0)	5(3.0)	3 (8.1)	
Black	5(2.5)	3(1.8)	2 (5.4)	
Comorbidities and risks				
Smoking				
Never	132 (65.7)	108 (65.9)	24 (64.9)	
Current	6 (3.0)	6 (3.7)	0 (0.0)	
Ex	63 (31.3)	50 (30.5)	13 (35.1)	
Health care worker	62 (30.8)	49 (29.9)	13 (35.1)	
Asthma	36 (17.9)	33(20.1)	3 (8.1)	
BMI				
≥25 kg/m ²	112 (56.3)	87 (53.7)	25 (67.6)	
≥30 kg/m ²	40 (20.1)	28 (17.3)	12 (32.4)	
Hypertension	12 (6.0)	10 (6.1)	2 (5.4)	
Diabetes	4 (2.0)	4 (2.4)	0 (0.0)	
Previous heart disease	8 (4.0)	7 (4.3)	1 (2.7)	
Symptoms				
Fatigue	197 (98.0)	160 (97.6)	37 (100.0)	
Muscle ache	176 (87.6)	145 (88.4)	31 (83.8)	
Shortness of breath	175 (87.1)	140 (85.4)	35 (94.6)	
Headache	166 (82.6)	139 (84.8)	27 (73.0)	
Joint pain	157 (78.1)	128 (78.0)	29 (78.4)	
Fever	151 (75.1)	127 (77.4)	24 (64.9)	
Chest pain	147 (73.1)	116 (70.7)	31 (83.8)	
Cough	148 (73.6)	119 (72.6)	29 (78.4)	
Sore throat	143 (71.1)	120 (73.2)	23 (62.2)	
Diarrhoea	119 (59.2)	92 (56.1)	27 (73.0)	
Abnormal pain	108 (53.7)	91 (55.5)	17 (45.9)	
Wheezing	97 (48.3)	74 (45.1)	23 (62.2)	
Inability to walk	81 (40.3)	59 (36.0)	22 (59.5)	
Runny nose	68 (33.8)	55 (33.5)	13 (35.1)	
Time interval				
Initial symptoms-to-assessment (days: median, [IQR])	(n=1 missing) 140 (105, 160)	(n=1 missing) 140 (106, 162)	138 (97, 150)	
COVID-19 positive-to-assessment (days: median, [IQR])	(n=3 missing) 70 (42, 112)	(n=3 missing) 67 (39, 109)	105 (59, 126)	

* Continuous data presented as means (SD) for normally distributed data and median (IQR) for non-normally distributed data and categorical data as count (%). Comparisons between patients and man

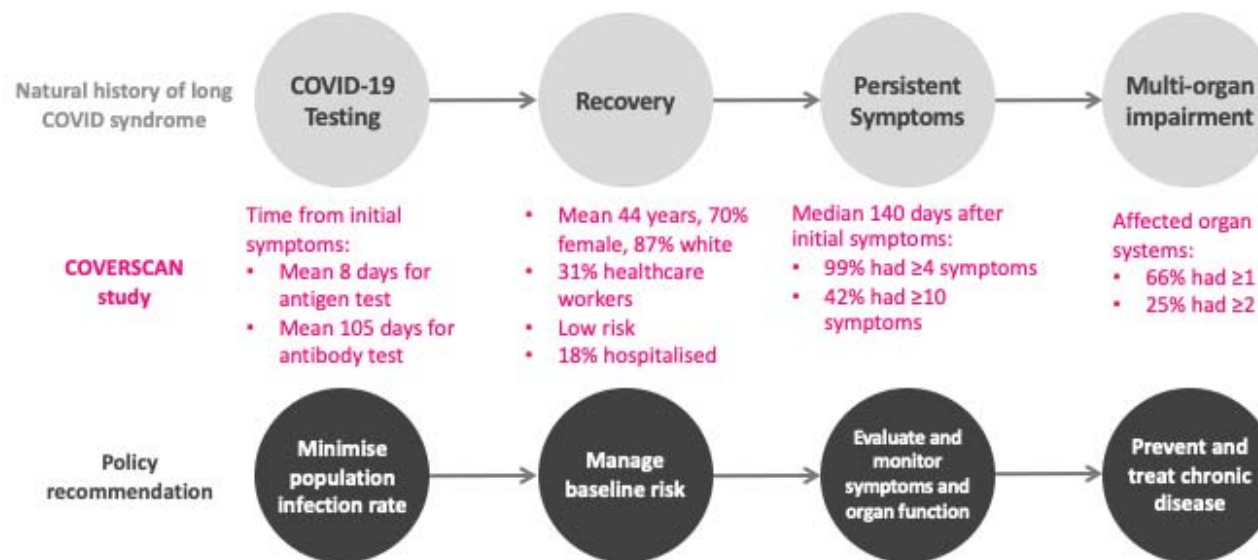
aged at home vs hospitalised were conducted using Wilcoxon Rank sum test for continuous data and Fisher exact test for categorical data.

Table 2: Evidence of organ impairment in 201 low-risk individuals with long-COVID.

Measurement	All (n=201) N(%)	Not hospitalised (n=164) N(%)	Hospitalised (n=37) N(%)	p
HEART				
Left ventricular ejection fraction (%)				
• Normal (>55%)	155 (77.1)	129 (78.7)	26 (70.3)	0.079
• Borderline impairment (50-55%)	38 (18.9)	31 (18.9)	7 (18.9)	
• Definite impairment (<50%)	8 (4.0)	4 (2.4)	4 (10.8)	
Left ventricular end diastolic volume (ml)				
• >214ml in M; >178ml in W	27 (13.4)	18 (11.0)	9 (24.3)	0.057
Evidence of myocarditis				
• ≥ 3 segments with high T1 (≥1264ms at 3T; ≥1015ms at 1.5T)	22 (10.9)	18 (11.0)	4 (10.8)	1
LUNGS				
Deep Breathing Fractional area change	(n= 11 missing)	(n= 8 missing)	(n= 3 missing)	
• < 39%	63 (33.2)	47 (30.1)	16 (47.1)	0.071
KIDNEYS				
Kidney cortex T1	(n= 12 missing)	(n= 8 missing)	(n= 4 missing)	
• Normal (<1610 ms at 3T; <1191ms at 1.5T)	175 (88.4)	146 (90.7)	29 (78.4)	0.046
• Definite impairment (≥1610ms at 3T; ≥1191ms at 1.5T)	23 (11.6)	15 (9.3)	8 (21.6)	
PANCREAS				
Pancreatic inflammation (T1 in ms)				
• Normal (<800ms)	157 (83.1)	136 (87.2)	21 (63.6)	0.003
• Borderline (800-865ms)	20 (10.6)	11 (7.1)	9 (27.3)	
• Significant (>865ms)	12 (6.3)	9 (5.8)	3 (9.1)	
Pancreatic fat	(n= 6 missing)	(n= 4 missing)	(n= 2 missing)	
• Normal (<5%)	126 (64.6)	111 (69.4)	15 (42.9)	0.005
• Borderline (5-10%)	44 (22.6)	33 (20.6)	11 (31.4)	
• Significant(>10%)	25 (12.8)	16 (10.0)	9 (25.7)	
LIVER				
Liver Inflammation (cT1 in ms)	(n= 1 missing)	(n= 1 missing)		
• Normal (<800ms)	181 (90.5)	150 (92.0)	31 (83.8)	0.040
• Borderline (800-825ms)	5 (2.5)	5 (3.1)	0 (0.0)	
• Significant (>825ms)	14 (7.0)	8 (4.9)	6 (16.2)	
Liver fat				
• Normal (<5%)	162 (80.6)	138 (84.1)	24 (64.9)	0.025
• Borderline (5-10%)	18 (9.0)	12 (7.3)	6 (16.2)	
• Definite (>10%)	21 (10.4)	14 (8.5)	7 (18.9)	
SPLEEN				
Splenic length (mm)	(n= 10 missing)	(n= 10 missing)		
• Normal (Table S1)	179(9.4)	144(9.5)	35 (9.5)	1
• Borderline (Table S1)	12 (6.3)	10 (6.5)	2 (5.4)	

*Data are presented as count (%). Comparisons between patients managed at home vs hospitalised were conducted using Fisher exact test.

690 Figure 1: Natural history of long COVID, the COVERSCAN study in low-risk individuals (n=201) and policy recommendations.

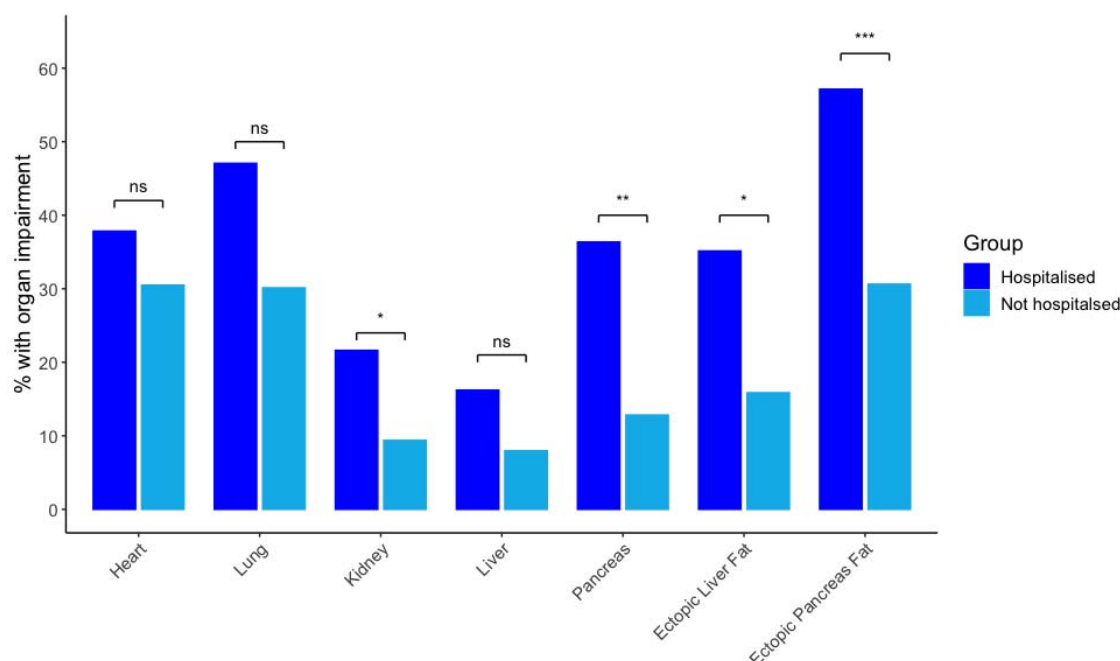


691
692

693

Figure 2: Proportion of low-risk individuals with long-COVID by hospitalisation (n=201) for (a) symptoms; and (b) evidence of organ impairment.

(a)



(b)

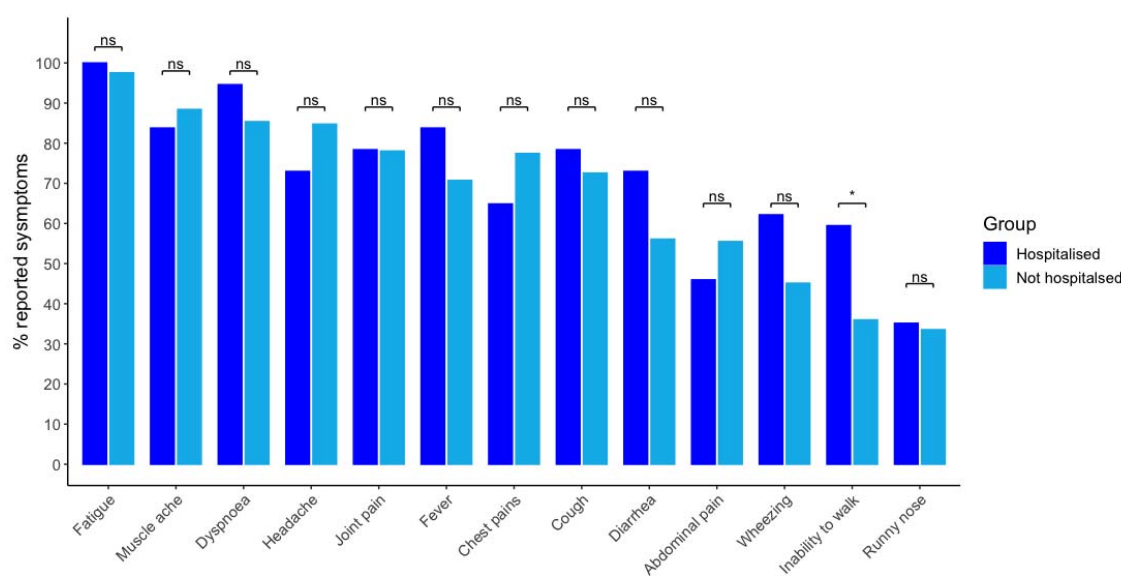
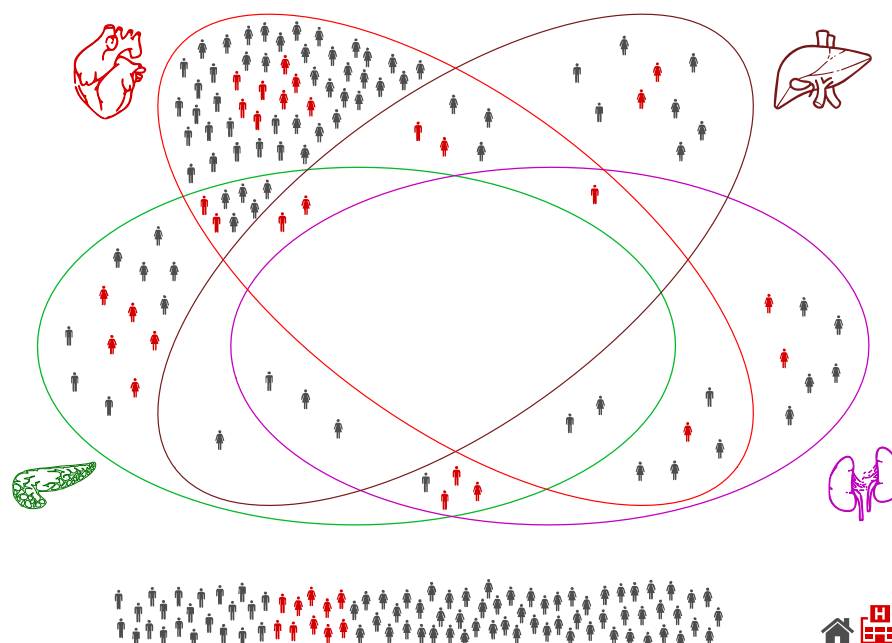
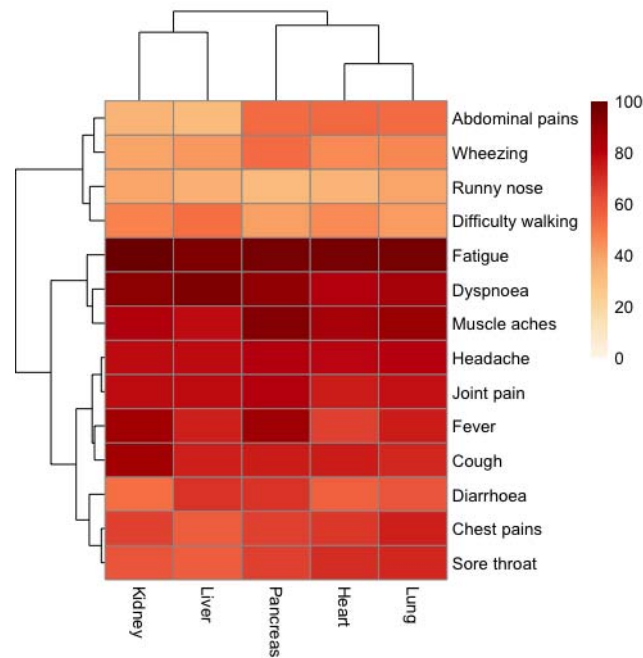


Figure 3 Multi-organ impairment in low-risk individuals with long COVID by gender and hospitalisation (n=201).



727 Figure 4: Clustering of reported symptoms and organ impairment for individuals with long-
728 COVID (n=201).



729
730
731
732
733
734
735
736
737
738
739
740
741
742
743
744
745
746
747