Original Article

Mental Health Symptoms and Illness Trajectory Following COVID-19 Hospitalization: A Cohort Study

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Abstract

Background: The multisystem associations between baseline mental health status and coronavirus disease-19 (COVID)-19 illness trajectory are uncertain. **Objectives:** This article will investigate the associations between baseline mental health status and disease trajectory following COVID-19 hospitalization, which may have implications for practice and future research. **Methods:** The Chief Scientist Office Cardiovascular and Pulmonary Imaging in severe acute respiratory syndrome (SARS) COVID-19 study is a prospective, observational, multicenter, longitudinal, secondary care cohort study that assessed the time-course of multi-organ injury in posthospital survivors of COVID-19. Patients were assessed in-hospital, at 28–60 days after discharge and in the longer term using electronic health record linkage. **Results:** One hundred and fifty-two patients (mean ± standard deviation [SD] age 54.3 ± 11.8 years, 43% female, 40% most socio-economically deprived quintile, 33% history of mental health history) were enrolled and had mental health serially assessed using the Patient Health Questionnaire-4 (PHQ-4) questionnaire. Fifty-three (35%) had PHQ-4 score of 6–12 consistent with moderate-severe symptoms of anxiety or depression and this was associated with diagnostic criteria for myocarditis ($P = 0.0498$). Moderate-severe symptoms of anxiety or depression were positively associated with higher perception of illness, lower health-related quality of life (HRQoL), and poorer physical function. The mean (SD) duration of follow-up after hospital discharge was 428 (86) days (range, 290–627 days). PHQ-4 score was not associated with clinical outcomes at follow-up. **Conclusions:** In patients who have been hospitalized with COVID-19, moderate-severe symptoms of anxiety or depression were associated with myocarditis, worse HRQoL, higher perception of illness, and lower levels of physical function. **Public Registration:** ClinicalTrials.gov identifier is NCT04403607.

Keywords: Long coronavirus disease-19, mental health, post-coronavirus disease-19 condition, severe acute respiratory syndrome-coronavirus-2

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Introduction

Coronavirus disease-19 (COVID-19) and the measures taken to prevent its spread have impaired the physical and mental well-being of people worldwide. Population studies have shown mental health disorders to be associated with a more severe course of COVID-19, higher COVID-19 mortality, and increased risk of developing post-COVID-19 conditions.[1] This has been partly attributed to a higher burden of comorbidities and more unhealthy lifestyle factors.[2] However, there appear to be direct effects of COVID-19 on both mental health and cognitive function, with some patients reporting symptoms of depression, anxiety, memory loss, and concentration difficulties up to 1 year following COVID-19 infection.[3,4] The cognitive impairment is commonly referred to as "brain fog" and appears to be associated with illness severity, but the exact mechanism is not yet fully understood.[5] There have been suggestions that innate immune responses and CNS inflammation could be contributory to the neuropsychiatric sequelae of COVID-19.[6]

The Chief Scientist Office Cardiovascular and Pulmonary Imaging in severe acute respiratory syndrome (SARS) Coronavirus disease-19 (CISCO-19) study is a prospective, observational, multicentre, longitudinal, secondary care cohort study that assessed the time-course of multi-organ injury in posthospital survivors of COVID-19 during convalescence and controls. Adjudicated myocarditis persisting 28–60 days post-COVID-19 affected 1 in 8 (13%) patients, and the likelihood of myocarditis was associated with lower health-related quality of life (HRQoL), enhanced illness perception, enhanced depression score, lower physical activity, and lower predicted maximal oxygen utilization (mL/kg/min). One in seven patients died or were hospitalized, and two in three patients had additional outpatient episodes of secondary care, considerably higher than controls.[7]

This longitudinal cohort study provides serial, multisystem insights including during hospitalisation for COVID-19, at 28–60 days postdischarge and in the longer term using electronic health record linkage. This prespecified analysis explores mental and physical health and HRQoL, and their changes over time, using validated patient reported outcome measures linked to objective laboratory measures of illness severity and clinical outcomes. This article will allow a greater understanding of the associations between baseline mental health status and disease trajectory following COVID-19 hospitalisation, which may have implications for practice and future research.

Methods

Study design

The design, baseline characteristics, and primary outcome results of CISCO-19 (ClinicalTrials.gov identifier is NCT04403607) have been described.[7,8] Clinical information, a 12-lead digital electrocardiogram (ECG), blood and urine biomarkers, and patient-reported outcome measures (PROMS) were acquired at enrolment (visit 1) and again during convalescence, 28–60 days postdischarge (visit 2). Chest computed tomography (CT), including pulmonary and coronary angiography and cardio-renal magnetic resonance imaging (MRI), were acquired at the second visit.

The EQ-5D-5L, brief illness perception questionnaire (BIPQ), the International Physical Activity Questionnaires (IPAQ), and the duke activity status index (DASI) were used at enrolment and 28–60 days to assess health status. These tools were chosen as validated assessments of HRQoL, illness perception, and physical activity with consideration for patient time across two clinical visits.

The Patient Health Questionnaire-4 (PHQ-4) is a self-reported questionnaire first used to screen for depression and anxiety symptoms in the primary care settings.[9] It is a validated instrument containing four questions, with the first two addressing depression and the latter two focusing on anxiety. Participants rate the frequency of each symptom experienced over the past 2 weeks on a 0–3 scale (0 = "Not at all," 1 = "Several days," 2 = "More than half the days," and 3 = "Nearly every day"). The overall score ranges from 0 to 12, with higher scores indicating more severe symptoms. Symptoms are categorizing into minimal or no symptoms (0–2), mild symptoms (3–5), moderate symptoms (6–8), and severe symptoms (9–12).

This prespecified analysis compares the characteristics, disease severity, and clinical outcomes of patients with scores of 0–5 (minimal and mild symptoms) to those with scores of 6–12 (moderate and severe symptoms).

Study setting

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

Population

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

The inclusion criteria were: (1) age ≥18 years old; (2) history of an unplanned hospital visit, e.g. emergency department or hospitalization >24 h for COVID-19 confirmed by a laboratory test (e.g., polymerase chain reaction; (3) ability to comply with study procedures; and (4) ability to provide written informed consent.

The exclusion criteria were as follows: (1) contraindication to MRI (e.g. severe claustrophobia and metallic foreign body) and (2) lack of informed consent.

Statistics

The statistical analyses were predefined in a Statistical Analysis Plan.

Results

In total, 1,306 patients were screened between May 22, 2020 and March 16, 2021, and 267 provided written informed consent. One hundred and fifty-nine patients were evaluated at 28–60 days after the last episode of hospital care. This analysis only considers these patients who attended both visit 1 and visit 2. Complete PHQ-4 score data were available for 152 such patients [Table 1]. The CONSORT flow diagram is provided in Figure 1.

Ninety-nine (65%) patients had a baseline PHQ-4 score between 0 and 5, indicative of minimal or mild symptoms and 53 (35%) patients had a score between 6 and 12, indicative of moderate or severe symptoms of anxiety or depression.

Clinical characteristics

The average age of the participants was 54 years, with 132 (87%) being white, 66 (43%) female, and 35 (23%) health-care workers. These characteristics did not show a significant association with mental health status [Table 1]. No significant differences were observed in the baseline demographics, past medical history, comorbidity risk scores, or admission blood tests between the groups. Moderate-severe symptoms of anxiety or depression at enrolment were associated with diagnostic criteria for myocarditis [Table 2].

Mental health

There was no statistically significant difference between the two groups in terms of their mental health histories. For instance, 43 participants (28%) had a history of depression with 25 (25%) in the PHQ-4 0–5 group and 18 (34%) in the PHQ-4 6–12 group (P = 0.2637). Similarly, a history of anxiety was reported by 21 participants (14%), with 10 (10%) in the lower-scoring group and 11 (21%) in the higher-scoring group (P = 0.0858).

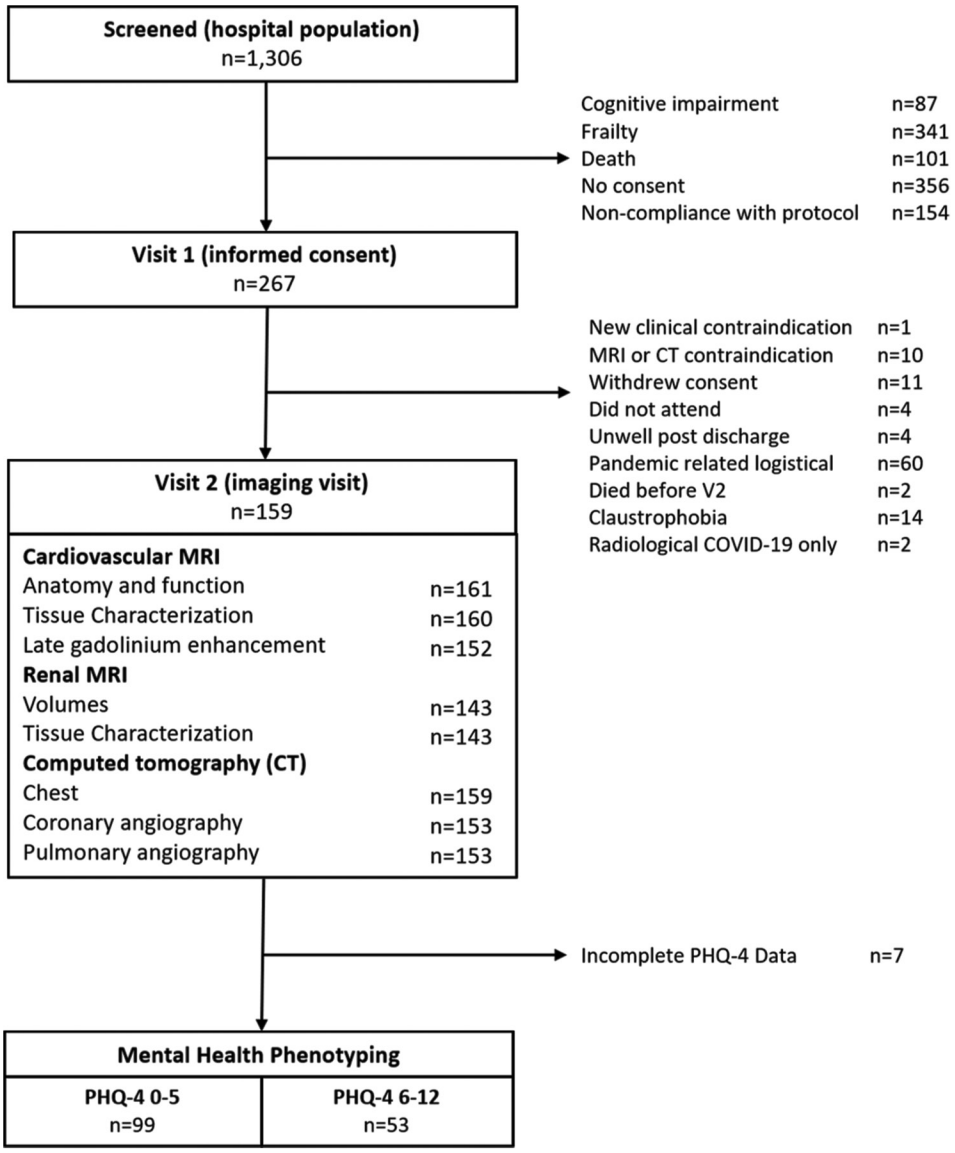


Figure 1: Flow diagram of the clinical study. MRI=Magnetic resonance imaging, CT=Computed tomography, PHQ=Patient health questionnaire

Coronavirus disease-19 illness

There were no significant differences in COVID-19 severity (as measured by the World Health Organization Clinical Severity Score), treatments for COVID-19, or durations of hospital stays [Table 2]. Similarly, no significant discrepancies were observed between the two groups concerning functional cardiac imaging, renal imaging, and biomarkers at enrolment and at 28–60 days postdischarge.

However, some differences were present. The nonischemic distribution of late gadolinium enhancement, indicative of myocardial scarring, was significantly higher in the PHQ-4 0–5 group (22% vs. 8%, $P = 0.0355$). Similarly, myocardial inflammation, as determined by the Lake Louise criteria, was higher in the PHQ-4 6–12 group ($P = 0.0498$).

Health-related quality of life

There were significant differences in HRQoL measures based on mental health status [Table 3]. Patients with PHQ-4 scores of 0–5 generally reported higher HRQoL scores compared to those with scores of 6–12. At enrolment, patients with PHQ-4 scores of 0–5 had a significantly higher health utility score (0.80 ± 0.17) compared to those with scores of 6–12 (0.63 ± 0.25, $P < 0.0001$). The trend continued at 28–60 days postdischarge, with patients in the PHQ-4 0–5 group reporting higher health utility scores (0.82 ± 0.20) compared to the PHQ-4 6–12 group (0.69 ± 0.25, $P = 0.0007$).

Illness perception

At enrolment, patients with PHQ-4 scores of 0–5 exhibited a lower BIPQ score (38.2 ± 11.8) compared to those with scores of 6–12 (50.0 ± 9.2, $P < 0.0001$). Similarly, at 28–60 days postdischarge, individuals in the PHQ-4 0–5 group had a lower BIPQ score (33.4 ± 14.2) compared to the PHQ-4 6–12 group (42.3 ± 14.2, $P = 0.0004$).

Physical function

Patients with PHQ-4 scores of 0–5 demonstrated significantly higher levels of physical activity based on IPAQ scores, with 80% falling into the "High" physical activity category, compared to only 46% in the PHQ-4 6–12 group ($P = 0.0153$). Moreover, assessments using the DASI score and DASI maximal oxygen uptake (VO_{2max})

Key question

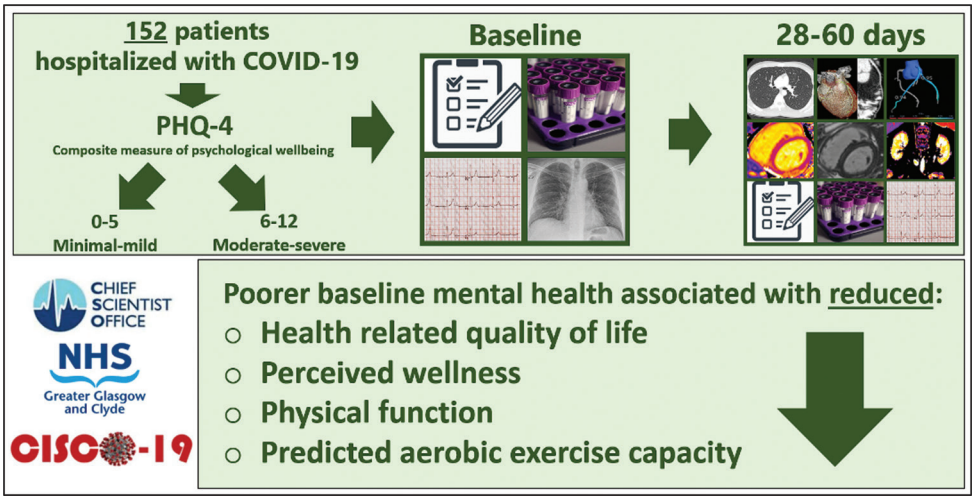
What are the associations between COVID-19 hospitalisation and mental health symptoms?

Key finding

In patients who have been hospitalised with COVID-19, moderate-severe anxiety or depression is associated with worse health-related quality of life, higher perception of illness, and lower levels of physical function. There were no significant differences between the two groups for clinical outcomes. There was a trend towards a higher proportion of deaths (any cause) in the group with moderate-severe anxiety or depression at enrolment. There was no significant difference in referrals to secondary care with symptoms consistent with NICE188 guideline criteria for post-COVID-19 conditions (Long COVID).

Message for readers

Identifying this group as having increased risk of worse health-related quality of life and physical function following COVID-19 hospitalisation would allow for targeted early assessment and intervention.



Central Illustration: Associations with moderate to severe anxiety or depression scores at enrolment.

NICE=National Institute for Health and Care Excellence; PHQ-4=Patient Health Questionnaire-4; NHS=National Health Service; CISCO-19=Chief Scientist Office Cardiovascular and Pulmonary Imaging in SARS Coronavirus disease-19

Table 1: Clinical characteristics of the study population, by mental health status at enrolment

	All (n = 152)	Mental health status		P
		PHQ-4: 0–5 (n = 99)	PHQ-4: 6–12 (n = 53)	
Demographics				
Age (years)	54.3±11.8	55.4±12.5	52.3±10.3	0.1166
Sex, *n* (%)				
Male	86 (57)	62 (63)	24 (45)	0.0584
Female	66 (43)	37 (37)	29 (55)	
Most deprived SIMD quintile, *n* (%)	58 (40)	39 (41)	19 (39)	0.8586
Healthcare worker, *n* (%)	35 (23)	26 (26)	9 (17)	0.2290
Ethnicity, *n* (%)				
White	132 (87)	89 (90)	43 (81)	0.3208
Asian	14 (9)	7 (7)	7 (13)	
Other	6 (4)	3 (3)	3 (6)	
Presenting characteristics				
Weight (kg)	87±18	86±18	89±18	0.3134
Height (cm)	170±10	171±10	168±10	0.1160
BMI (kg/m^2)	30.2±6.3	29.5±6.0	31.6±6.6	0.0519
Body surface area (m^2)	2.0±0.2	2.0±0.2	2.0±0.2	0.6210
Heart rate (bpm)	95±19	96±20	93±19	0.4079
Systolic blood pressure (mmHg)	128±19	130±21	126±17	0.2298
Diastolic blood pressure (mmHg)	77±13	78±13	77±13	0.5793
Peripheral oxygen saturation (%)	93±6	93±6	94±7	0.8918
Respiratory rate (/min)	24±13	24±15	23±7	0.7482
WHO clinical severity score, *n* (%)				
Hospitalized, no oxygen therapy	49 (32)	28 (28)	21 (40)	0.4704
Oxygen by mask or nasal prongs	69 (45)	49 (49)	20 (38)	
Noninvasive ventilation	19 (12)	12 (12)	7 (13)	
Mechanical ventilation	15 (10)	10 (10)	5 (9)	
COVID-19 diagnosis, *n* (%)				
PCR test	152 (100)	99 (100)	53 (100)	1.0000
Nosocomial	7 (5)	6 (6)	1 (2)	0.4224
Radiology, chest radiograph or CT scan				
Typical of COVID-19	106 (76)	72 (77)	34 (76)	0.9780
Atypical of COVID-19	9 (6)	6 (6)	3 (7)	
Unlikely	4 (3)	3 (3)	1 (2)	
Normal	20 (14)	13 (14)	7 (16)	
Acute COVID-19 therapy, *n* (%)				
Oxygen	103 (68)	71 (72)	32 (60)	0.2022
Steroid	85 (56)	58 (59)	27 (51)	0.3949
Antiviral	40 (26)	30 (30)	10 (19)	0.1757
Noninvasive respiratory support	30 (20)	18 (18)	12 (23)	0.5270
Intensive care	24 (16)	17 (17)	7 (13)	0.6431
Invasive ventilation	14 (9)	10 (10)	4 (8)	0.7715
Intravenous inotrope	7 (5)	3 (3)	4 (8)	0.2387
Mental health history, *n* (%)				
Any history	50 (33)	28 (28)	22 (42)	0.1066
History of depression	43 (28)	25 (25)	18 (34)	0.2637
History of anxiety	21 (14)	10 (10)	11 (21)	0.0858
History of personality disorder	1 (1)	1 (1)	0	1.0000
History of schizophrenia	0	0	0	1.0000
History of bipolar affective disorder	0	0	0	1.0000
History of substance abuse	2 (1)	1 (1)	1 (2)	1.0000
Cardiovascular history, *n* (%)				
Smoking				

Contd...

Table 1: Contd...

	All (n = 152)	Mental health status		P
		PHQ-4: 0–5 (n = 99)	PHQ-4: 6–12 (n = 53)	
Never	103 (68)	66 (67)	37 (70)	0.2381
Former	40 (26)	29 (29)	11 (21)	
Current	9 (6)	4 (4)	5 (9)	
Hypercholesterolaemia	70 (46)	47 (47)	23 (43)	0.7331
Hypertension	54 (36)	37 (37)	17 (32)	0.5950
Diabetes mellitus	31 (20)	18 (18)	13 (25)	0.4007
Chronic kidney disease	7 (5)	4 (4)	3 (6)	0.6951
CCS angina class				
No angina	148 (97)	96 (97)	52 (98)	1.0000
Angina class I–IV	4 (3)	3 (3)	1 (2)	
Heart failure	6 (4)	2 (2)	4 (8)	0.1837
Myocardial infarction	16 (11)	10 (10)	6 (11)	0.7888
Stroke or TIA	4 (3)	1 (1)	3 (6)	0.1222
Peripheral vascular disease	1 (1)	1 (1)	0	1.0000
Previous PCI	10 (7)	6 (6)	4 (8)	0.7399
Previous CABG	2 (1)	2 (2)	0	0.5428
Cardiovascular disease and/or treatment	69 (45)	47 (47)	22 (42)	0.4995
Risk scores				
ISARIC-4c in-hospital mortality risk (%)	11.6±10.0	11.9±9.7	11.1±10.7	0.6408
Q-risk 3, 10-year cardiovascular risk (%)	13.5±11.2	13.6±10.6	13.5±12.4	0.9827
Charlson comorbidity index	1.8±1.8	1.9±1.7	1.8±1.9	0.7817
Preexisting maintenance medication, *n* (%)				
Aspirin	11 (7)	6 (6)	5 (9)	0.5164
Statin	41 (27)	25 (25)	16 (30)	0.5670
Beta-blocker	19 (12)	12 (12)	7 (13)	1.0000
Angiotensin converting enzyme inhibitor	33 (22)	23 (23)	10 (19)	0.6802
Angiotensin receptor blocker	9 (6)	6 (6)	3 (6)	1.0000
Oral anticoagulation	7 (5)	4 (4)	3 (6)	0.6951
Laboratory results, index admission				
Initial hemoglobin (g/L)	141±16	141±15	140±17	0.6438
Initial platelet count (10^9/L)	239±95	233±93	251±98	0.2536
Initial white cell count (10^9/L)	7.36±5.63	7.57±6.58	6.98±3.19	0.5410
Initial lymphocyte count (10^9/L)	1.56±4.77	1.75±5.89	1.21±0.63	0.5137
Peak D-dimer (ng/mL)	1794±5605	2357±6689	613±1364	0.1618
Minimum eGFR (mL/min/1.73 m^2)	82.1±27.7	82.4±25.6	81.7±31.4	0.8865
Acute kidney injury, *n* (%)	18 (13)	9 (10)	9 (18)	0.2010
Peak HS-troponin I (ng/L)	4.0 (3.0–12.5)	4.0 (3.0–11.0)	4.0 (3.0–12.8)	0.3925
Peak ferritin (µg/L)	367 (178–864)	391 (180–861)	318 (171–912)	0.7097
Peak C-reactive protein (mg/L)	103 (37–181)	102 (51–181)	110 (27–183)	0.5464
Peak HbA1c (mmol/mol)	47.4±18.2	47.8±19.3	46.8±16.1	0.7651
Initial albumin (g/L)	34.1±5.3	34.2±5.3	33.9±5.4	0.7587
Timelines				
Hospitalized, *n* (%)	136 (89)	89 (90)	47 (89)	0.7888
Duration of admission (days)	5 (3–11)	5 (3–12)	5 (2–10)	0.7667
Symptom onset to primary outcome (days)	64 (53–72)	63 (53–72)	64 (54–72)	0.6832
Diagnosis to primary outcome (days)	60 (49–68)	59 (48–68)	61 (51–68)	0.6440

BMI=Body mass index, SIMD=Scottish index of multiple deprivation, PHQ=Patient Health Questionnaire, WHO=World Health Organization, PCR=Polymerase chain reaction, CT=Computed tomography, CCS=Canadian Cardiovascular Society, TIA=Transient ischemic attack, PCI=Percutaneous coronary intervention, CABG=Coronary artery bypass grafting, eGFR=Estimated glomerular filtration rate, HS=High-sensitivity, HbA1c=Glycated hemoglobin, ISARIC=International severe acute respiratory and emerging infection consortium

estimate revealed that individuals in the PHQ-4 0–5 group had better physical function compared to those with PHQ-4 scores of 6–12 (DASI score at enrolment: 23.3 ± 19.0 vs. 12.7 ± 13.8, P = 0.0005; DASI VO_{2max} estimate at enrolment:

Table 2: Multi-system phenotypying by mental health status at enrolment: Serial electrocardiography, biomarkers of inflammation, metabolism, renal function, and haemostasis, and heart, lung, and kidney imaging at 28–60 days postdischarge

	All	Mental health status		*P*
		PHQ-4: 0–5	PHQ-4: 6–12	
Electrocardiogram				
Myopericarditis criteria, *n* (%)				
Admission	*n* = 143, 30 (21)	*n* = 91, 21 (23)	*n* = 52, 9 (17)	0.5232
Enrolment	*n* = 140, 43 (31)	*n* = 89, 25 (28)	*n* = 51, 18 (35)	0.4471
28–60 days postdischarge	*n* = 136, 31 (23)	*n* = 90, 21 (23)	*n* = 46, 10 (22)	1.0000
CT chest 28–60 days postdischarge	*n* = 150	*n* = 98	*n* = 52	
Ground glass opacity and/or consolidation, *n* (%)	67 (45)	46 (47)	21 (40)	0.4924
Reticulation and/or architectural distortion, *n* (%)	45 (30)	30 (31)	15 (29)	0.8538
Atelectasis, *n* (%)	12 (8)	10 (10)	2 (4)	0.2184
Pulmonary arterial thrombus, *n* (%)	4 (3)	2 (2)	2 (4)	0.6082
Visual estimate of % of total lung area abnormal	14.6±19.3	14.6±19.1	14.6±19.8	0.9941
CT coronary angiogram 28–60 days postdischarge	*n* = 149	*n* = 98	*n* = 51	
Coronary calcium - Agatston score	142±509	146±435	135±631	0.9072
MESA percentile	59.8±34.8	61.7±34.2	55.4±36.4	0.4560
Obstructive coronary artery disease, *n* (%)	20 (14)	14 (15)	6 (12)	0.8016
FFRCT patient-level (all coronary arteries) 28–60 days postdischarge	*n* = 127	*n* = 82	*n* = 45	
Median FFR_{CT}	0.93±0.03	0.93±0.03	0.93±0.03	0.7471
Minimum FFR_{CT}	0.80±0.10	0.80±0.10	0.81±0.09	0.5802
Minimum FFR_{CT} ≤0.8, *n* (%)	46 (36)	30 (37)	16 (36)	1.0000
Cardiac MRI 28–60 days postdischarge	*n* = 152	*n* = 99	*n* = 53	
LV end diastolic volume index (mL/m^2)	76.2±16.6	75.9±16.9	76.7±16.2	0.7784
LV end systolic volume index (mL/m^2)	35.4±12.8	35.1±12.3	36.1±13.8	0.6361
LV ejection fraction (%)	54.1±9.7	54.3±9.9	53.7±9.5	0.7189
LV mass (g)	92.1±25.7	93.2±24.8	90.0±27.5	0.4723
RV end diastolic volume index (mL/m^2)	73.3±17.0	73.7±18.2	72.6±14.7	0.7183
RV end systolic volume index (mL/m^2)	35.9±11.1	36.1±12.1	35.7±8.8	0.8528
RV ejection fraction (%)	50.9±10.6	51.1±11.6	50.5±8.4	0.7623
Myocardial tissue characterisation	*n* = 151	*n* = 98	*n* = 53	
Increased global T1 (>1,233 ms), *n* (%)	53 (35)	32 (33)	21 (40)	0.4752
Increased global T2 (>44 ms), *n* (%)	10 (7)	5 (5)	5 (9)	0.3220
T2 ratio (myocardium/serratus anterior muscle)	1.69±0.23	1.67±0.23	1.73±0.23	0.0914
Increased global extracellular volume (>27.4%), *n* (%)	69 (51)	41 (47)	28 (57)	0.2878
Late gadolinium enhancement, *n* (%)	*n* = 151	*n* = 98	*n* = 53	
Myocardial late gadolinium enhancement	29 (19)	22 (22)	7 (13)	0.1987
Ischaemic distribution	8 (6)	5 (6)	3 (6)	1.0000
Nonischaemic distribution	24 (17)	20 (22)	4 (8)	0.0355
Myocardial inflammation (Lake Louise criteria), *n* (%)				
No evidence (0/2)	17 (11)	13 (13)	4 (8)	0.0498
Probable (1/2)	69 (46)	50 (51)	19 (36)	
Definite (2/2)	65 (43)	35 (36)	30 (57)	
Renal MRI	*n* = 135	*n* = 86	*n* = 49	
Average volume of right and left kidneys (mL)	153±31	153±31	152±31	0.8357
Average cortex T1 of right and left kidneys (ms)	1,545±62	1,546±62	1,543±63	0.7882
Average medulla T1 of right and left kidneys (ms)	1,933±69	1,935±73	1,931±62	0.7569
Average T1 corticomedullary differentiation of kidneys	0.80±0.03	0.80±0.03	0.80±0.03	0.9549
Biomarkers at enrolment, central laboratory	*n* = 151	*n* = 99	*n* = 52	
eGFR (mL/min/1.73 m^2)	96 (87–106)	95 (83–105)	98 (90–107)	0.1604
C-reactive protein (mg/L)	5.5 (1.6–21.7)	5.5 (1.1–21.4)	5.8 (2.0–21.5)	0.6510
HS-troponin I (ng/L)	3.3 (2.2–5.8)	3.2 (2.3–6.0)	3.9 (2.0–5.5)	0.9889
NT-pro BNP (ng/L)	114 (57–258)	115 (52–258)	108 (62–249)	0.8797
Total bilirubin (µmol/L)	5.6 (4.3–7.9)	5.9 (4.4–8.1)	5.2 (3.9–7.4)	0.1770

Contd...

Table 2: Contd...

	All	Mental health status		*P*
		PHQ-4: 0–5	PHQ-4: 6–12	
Total cholesterol (mmol/L)	4.85±1.34	4.81±1.28	4.92±1.47	0.6293
Triglycerides (mmol/L)	2.23±1.22	2.19±1.23	2.30±1.22	0.6063
HDL cholesterol (mmol/L)	1.07±0.33	1.09±0.31	1.04±0.37	0.3580
Biomarkers at 28–60 days postdischarge, central laboratory (control group samples from enrolment visit)				
eGFR (mL/min/1.73 m^2)	96 (84–105)	94 (81–105)	97 (87–107)	0.2717
C-reactive protein (mg/L)	1.8 (0.9–3.5)	1.6 (0.7–3.4)	2.1 (1.2–3.4)	0.1750
HS-troponin I (ng/L)	2.1 (1.3–4.0)	2.2 (1.5–4.4)	1.8 (0.6–3.5)	0.0534
NT-pro BNP (ng/L)	83 (54–198)	102 (57–209)	68 (53–126)	0.1250
D-dimer (ng/mL)	208±257	232±292	163±170	0.1265

CT=Computed tomography, MRI=Magnetic resonance imaging, LV=Left ventricular, RV=Right ventricular, eGFR=Estimated glomerular filtration rate, HS=High-sensitivity, NT-pro BNP=N-terminal pro-brain natriuretic peptide, PHQ=Patient Health Questionnaire, HDL=High-density lipoprotein, FFR=Fractional flow reserve, MESA=Multi-ethnic study of atherosclerosis

Table 3: Health status, illness perception, anxiety and depression, and physical function, by mental health status at enrolment

	All	Mental health status		*P*
		PHQ-4: 0–5	PHQ-4: 6–12	
Health-related quality of life, EQ-5D-5L				
Heath utility score at enrolment	0.74±0.22	0.80±0.17	0.63±0.25	<0.0001
Heath utility score at 28–60 days postdischarge	0.77±0.23	0.82±0.20	0.69±0.25	0.0007
Your health today VAS at enrolment	61.54±21.95	65.77±20.48	53.64±22.59	0.0010
Your health today VAS at 28–60 days postdischarge	72.97±19.47	74.70±18.63	69.79±20.73	0.1406
Brief Illness Perception Questionnaire score				
At enrolment	42.3±12.3	38.2±11.8	50.0±9.2	<0.0001
At 28–60 days postdischarge	36.5±14.8	33.4±14.2	42.3±14.2	0.0004
Anxiety and depression, PHQ-4				
Anxiety score at enrolment	2.13±2.08	0.86±1.03	4.51±1.32	<0.0001
Anxiety score at 28–60 days postdischarge	1.76±1.96	1.11±1.42	3.00±2.26	<0.0001
Depression score at enrolment	2.19±1.95	1.07±1.06	4.28±1.43	<0.0001
Depression score at 28–60 days postdischarge	1.77±1.88	1.18±1.57	2.92±1.93	<0.0001
Total score at enrolment	4.32±3.78	1.93±1.70	8.79±2.18	<0.0001
Total score at 28–60 days postdischarge	3.52±3.68	2.29±2.81	5.92±4.00	<0.0001
Physical function, *n* (%)				
IPAQ score at enrolment				
Low	112 (80)	66 (73)	46 (92)	0.0153
Moderate	16 (11)	15 (17)	1 (2)	
High	12 (9)	9 (10)	3 (6)	
IPAQ score at 28–60 days postdischarge				
Low	65 (52)	35 (42)	30 (70)	0.0159
Moderate	43 (34)	34 (41)	9 (21)	
High	18 (14)	14 (17)	4 (9)	
DASI score at enrolment	19.6±18.0	23.3±19.0	12.7±13.8	0.0005
DASI score at 28–60 days postdischarge	24.3±17.6	26.5±17.4	20.2±17.3	0.0344
DASI $VO_{2\ max}$ estimate at enrolment	18.0±7.8	19.6±8.2	15.1±6.0	0.0005
DASI $VO_{2\ max}$ estimate at 28–60 days postdischarge	20.1±7.6	21.0±7.5	18.3±7.4	0.0344

DASI=Duke activity status index, IPAQ=International Physical Activity Questionnaire, PHQ=Patient Health Questionnaire, EQ-5D-5L=Europe quality of life-5 Dimension-5 Level, VAS=Visual analogue scale

19.6 ± 8.2 vs. 15.1 ± 6.0, P = 0.0005; DASI score at 28–60 days postdischarge: 26.5 ± 17.4 vs. 20.2 ± 17.3, P = 0.0344).

Clinical outcomes

Follow-up was continued to December 13, 2021 and complete follow-up was achieved in all of the participants. The

mean (standard deviation [SD]) duration of follow-up after hospital discharge for individuals included in this analysis was 428 (86) days (range, 290–627 days). There were no significant differences between the two groups for clinical outcomes [Table 4]. There was a trend toward a higher proportion of deaths (any cause) in the group with moderate-severe anxiety or depression at enrolment (PHQ-4 6–12 group vs. PHQ-4 0–5 group, $P = 0.0554$).

There was no significant difference in referrals to secondary care with symptoms consistent with National Institute for Health and Care Excellence 188 guideline[10] criteria for post-COVID-19 conditions (Long COVID) [Central Illustration].

Discussion

Approximately 1 in 4 people in Scotland are affected by mental health problems. In 2021, 14% of people reported two or more symptoms of anxiety, and 11% reported two or more symptoms of depression.[11] This backdrop of a high prevalence of high mental health problems provides a context to this study.

Our analysis assessed the associations between mental health at the time of discharge following hospitalization for COVID-19 in a reasonably large and carefully phenotyped cohort utilizing multi-organ, cross-sectional imaging, serum and urine biochemistry, patient-reported outcomes, and clinical follow-up up to a mean of 428 days after hospital discharge.

Our findings explore the nuanced relationships between mental health and its subsequent effects on HRQoL and illness perception. The pronounced decline in HRQoL emphasizes mental health's profound role in shaping one's perceived well-being. HRQoL is a multifaceted parameter, reflecting physical health and psychological, emotional, and social functioning.[12]

Variations in illness perception between the groups follow a similar pattern. Illness perception is inherently subjective and is influenced by many factors, including psychological wellbeing. Those affected by more severe psychological symptoms might perceive their illness as more debilitating, threatening, or chronic, even if their clinical presentations are comparable to others. This altered perception could subsequently shape their coping mechanisms, recovery trajectories, and overall health outcomes.[13]

The differences in physical function between patients with moderate-severe anxiety or depression compared to individuals with less severe symptoms, despite similar anthropometry, disease severity and past medical histories, provide insights into the overarching influence of mental health. Physical function is closely linked to an individual's mental state. Those experiencing heightened symptoms of anxiety or depression might find themselves less motivated to engage in physical activities, or they may perceive physical tasks as more challenging, leading to reduced functionality. Physical activity and exercise are associated with reduced risk of chronic disease through primary and secondary prevention and management.[14] Lower levels of physical activity in the group with moderate to severe symptoms could impact recovery from COVID-19, management of preexisting conditions, and increased risk of future chronic disease.[15] To date, there are no evidence-based therapies for patients with persisting physical symptoms after COVID-19. The effects of exercised-based intervention are being evaluated (NCT04900961).[16]

Counterintuitively, there was no statistically significant difference between the two groups in terms of prior mental health diagnoses and symptoms of moderate and severe anxiety or depression at baseline. One might anticipate that those with a history of mental health conditions would inherently be more susceptible to post-COVID psychological distress. However, our data suggest otherwise. Some possible causes for this could be the effective treatment of known mental health conditions, underdiagnosis in some populations, or recent onset of symptoms. The latter could be driven by the psychological toll of COVID-19 hospitalization itself or the often-isolating effects of contemporaneous national lockdown measures.

Overall, our study has pathological insights into systemic pathways linking mental health with physical function and

Table 4: Clinical outcomes by mental health status at enrolment

	All ($n = 152$)	Mental health status		P
		PHQ-4: 0–5 ($n = 99$)	PHQ-4: 6–12 ($n = 53$)	
Duration of follow-up				
Days to visit 3 or death	418 (369–451)	419 (370–452)	416 (360–447)	0.6496
Outcomes, *n* (%)				
Death or hospitalization (any cause)	22 (14)	14 (14)	8 (15)	0.8944
Secondary care (outpatients), *n* (%)				
Any outpatient referral	102 (67)	68 (69)	34 (64)	0.6481
Acute COVID-19 (<28 days)	14 (9)	12 (12)	2 (4)	0.0889
Ongoing COVID-19 (28–84 days)	18 (12)	9 (9)	9 (17)	0.1402
Long COVID-19 (>84 days)	55 (36)	38 (38)	17 (32)	0.4025
Cardiology	21 (14)	17 (17)	4 (8)	0.1124
Respiratory	51 (34)	37 (37)	14 (26)	0.2568
Physiotherapy	20 (13)	11 (11)	9 (17)	0.3046

PHQ=Patient Health Questionnaire

HRQoL. When anxiety and depression scores were compared with disease measures expressed as continuous data (laboratory variables) and PROMS, some clinically relevant findings were observed. A higher percentage of people with moderate-severe anxiety and depression at enrolment had diagnostic criteria for myocarditis [Table 2]. This observation points to the impact of myocarditis complicating COVID-19 on the mental health of affected individuals. On the other hand, there were no other associations observed between PHQ-4 score and objective measures of multisystem involvement. This finding suggests that hospitalization with COVID-19, rather than the severity of the illness, is a key factor in physical and mental health.

The clinical course of COVID-19 is characterized by persisting, multi-system inflammation associated with index disease severity.[7] One proposed explanation for "brain fog" following COVID-19 is neuroinflammation.[17] The observed higher rates of myocardial inflammation in those with poorer mental health following their COVID-19 infection generate the hypothesis that these patients may also experience enhanced inflammation in the brain. Further research using intracranial imaging is warranted to investigate this hypothesis.

We did not observe statistically significant associations between anxiety or depression at baseline and clinical outcomes in the longer term. One explanation may relate to statistical power since clinical outcomes are binary events and the sample size ($n = 152$) and number of events ($n = 22$ deaths or hospitalization) during follow-up were limited.

Implications for practice

Identifying this group as having increased risk of worse HRQoL and physical function following COVID-19 hospitalization would allow for targeted early assessment and intervention. This could involve a multidisciplinary approach, including psychological assessment, psychiatric input, and physiotherapy. It would also give insight to the etiology of such sequelae, which may guide or optimize the management.

Limitations

The sample size is limited, but consistent with a longitudinal study involving serial multi-organ assessments. One third of the patients enrolled at baseline did not reattend at 28–60 days postdischarge. The reasons included death and disability due to impairments in physical and cognitive function. In addition to this, the mean (SD) duration of follow-up was 428 (86) days (range, 290–627 days), which could provide a limited understanding long-term mental health outcomes.

The PHQ-4 questionnaire is a self-reported measure of depression and anxiety symptoms. This could be subject to perception bias and does not assess for a broader range of mental health presentations.

The CISCO-19 control group ($n = 29$) was not assessed with serial PHQ-4 questionnaires, so were not included in this paper. Future research with inclusion of a COVID-19 negative control group would allow for a greater understanding of the impact of COVID-19 on mental health.

This study focuses on patients hospitalized with COVID-19 in the UK, and findings may not be consistent with other regions, demographics, and health-care systems.

Conclusions

In patients who have been hospitalized with COVID-19, moderate-severe anxiety or depression is associated with worse HRQoL, higher perception of illness, and lower levels of physical function.

Author contributions

Colin Berry designed the study and wrote the first draft of the manuscript with Harriet Lomholt-Welch and Andrew J Morrow. Alasdair MacIntosh and Alex McConnachie developed the statistical analysis plan and performed the statistical analyses. Each co-author contributed to either the delivery of the study or helped to devise the protocol. All authors have given final approval for the current version to be published.

Ethical statement

The study was approved by the UK National Research Ethics Service (Reference 20/NS/0066) and performed in accordance with the Declaration of Helsinki. All patients gave written informed consent.

Data availability statement

Data requests will be considered by the Steering Group which includes representatives of the Sponsor, the University of Glasgow, senior investigators independent of the research team, and the chief investigator. The Steering Group will take account of the scientific rationale, ethics, coordination, and resource implications. Data access requests should be submitted by E-mail to the Chief Investigator (Colin Berry, corresponding author). The source data includes the deidentified numerical data used for the statistical analyses and deidentified imaging scans (MRI, CT) and ECGs. Data access will be provided through the secure analytical platform of the Robertson Centre for Biostatistics. This secure platform enables access to deidentified data for analytical purposes without the possibility of removing the data from the server. Requests for transfer of deidentified data (including source imaging scans) will be considered by the Steering Group, and if approved, a collaboration agreement would be expected. The Steering Group will consider any cost implications, and cost recovery would be expected on a not-for-profit basis.

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Conflicts of interest

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