Persistent Poor Health Post-COVID-19 Is Not Associated with Respiratory Complications or Initial Disease Severity

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Abstract

Rationale: Much is known about the acute infective process of SARS-CoV-2, the causative virus of the COVID-19 pandemic. The marked inflammatory response and coagulopathic state in acute SARS-CoV-2 may promote pulmonary fibrosis. However, little is known of the incidence and seriousness of post-COVID pulmonary pathology.

Objectives: We describe respiratory recovery and self-reported health following infection at time of outpatient attendance.

Methods: Infection severity was graded into three groups: (i) not requiring admission, (ii) requiring hospital admission, and (iii) requiring ICU care. Participants underwent chest radiography and six-minute-walk test (6MWT). Fatigue and subjective return to health were assessed and levels of C-reactive protein (CRP), interleukin-6, soluble CD25 and D-dimer were measured. The association between initial illness and abnormal chest x-ray, 6MWT distance and perception of maximal exertion was investigated.

Results: 487 patients were offered an outpatient appointment, of which 153 (31%) attended for assessment at a median of 75 days after diagnosis. 74 (48%) had required hospital admission during acute infection. Persistently abnormal chest x-rays were seen in 4%. The median 6MWT distance covered was 460m. Reduced distance covered was associated with frailty and length of inpatient stay. 95 (62%) felt that they had not returned to full health, while 47% met the case definition for fatigue. Ongoing ill-health and fatigue were associated with increased perception of exertion. None of the measures of persistent respiratory disease were associated with initial disease severity.

Conclusions: This study highlights the rates of objective respiratory disease and subjective respiratory symptoms following COVID-19 and the complex multifactorial nature of post-COVID ill-health.

COVID-19 infection, caused by SARS-CoV-2, has led to a global pandemic (1). The clinical and pathological features of acute infection have been extensively published, with a wide spectrum of disease seen, from asymptomatic infection to mild self-limiting symptoms to acute respiratory failure and the need for invasive mechanical ventilation (2, 3). A clinical picture similar to acute respiratory distress syndrome (ARDS) with refractory hypoxaemia is the primary cause of death in COVID-19 (4). There is a paucity of data surrounding the potential consequences and sequelae of infection. ARDS is a fibroproliferative disease, with lung biopsies taken at the time of ARDS showing fibrosis in more than half of affected patients (5, 6). The marked inflammatory response and coagulopathic state in response to SARS-CoV-2 may promote pulmonary fibrosis and lung damage (7-9). Looking at the follow-up of SARS patients from 2003, there are a small number who developed post-infectious fibrosis, with less than 5% of admitted patients affected (10, 11). There is an array of differing radiological appearances during acute COVID-19 infection (12). These changes are not limited to those seen in ARDS, and this has impacted on ventilatory management strategies for severe COVID-19 (13-15). Thus COVID pneumonitis may have lasting effects, even in the absence of ARDS (16).

Furthermore, acute SARS-CoV-2 infection is not limited to the respiratory system, and has multisystem effects, with evidence of cardiovascular, coagulation and gastrointestinal system disturbance in addition to the primary pulmonary disease (17-19). There has been recent interest in the possibility of so-called *long COVID,* whereby patients have persistence of a multitude of symptoms following initial infection resolution (20). The most common complaints reported following COVID-19 are breathlessness and persistent fatigue, although

the mechanisms underlying this are unclear (21). However, breathlessness is subjective and multifactorial and may not be due to respiratory compromise (22).

We set out to evaluate medium-term respiratory complications following SARS-CoV-2 infection, as defined by chest radiography, distance covered and maximal perceived exertion by six-minute-walk testing (6MWT). This is in line with recently published algorithms for the respiratory follow-up of COVID-19 patients (23). These algorithms recommend that all patients undergo chest radiography, with further testing suggested for those with abnormal imaging. We evaluated these assessments in the context of severity of initial infection, as well as ongoing inflammation at follow-up. We investigated persistent ill-health by also including subjective measures of fatigue and return to health.

Methods

Study Setting and Participants

This cross-sectional study was carried out in the post-COVID-19 review clinic at St James's Hospital (SJH), Dublin, Ireland. Informed written consent was obtained from all participants in the current study in accordance with the Declaration of Helsinki (24). Ethical approval for the current study was obtained from the Tallaght University Hospital (TUH)/SJH Joint Research Ethics Committee (reference REC 2020-04 (01)). Participants who had a positive SARS-CoV-2 PCR at our institution in the three-month period from March – May 2020 were recruited from the post-COVID-19 outpatient clinic. This included those managed as inpatients and staff members diagnosed at our centre but self-managed at home. Patients were not offered an

outpatient appointment if they were residents in long term care facilities. Patients attending the outpatient clinic were invited to participate in the current study by a research physician. In order to be considered for inclusion in the current study, participation had to occur at least 6 weeks after either: (i) date of last acute COVID-19 symptoms (for outpatients) and (ii) date of discharge for those who were admitted during their acute COVID-19 illness.

Clinical Covariate Assessment

All data was obtained at the time of outpatient assessment. Routine demographic information was collected from participants. Further information was obtained from patient records and included: dates of COVID-19 symptoms, inpatient admission and admission to the Intensive Care Unit (ICU). Peak oxygen requirements, peak C-reactive protein (CRP) levels and abnormal chest-ray findings during acute infection were also recorded for those admitted. The chest x-rays were scored using the *Brixia* system by a radiologist blinded to patient outcome. The *Brixia* score was proposed as an objective severity measure for chest x-ray abnormalities in acute COVID-19 (25). This score attributes a score of 0 – 3 for each lung zone based on the severity of changes seen, with a maximum score of 18 indicating the most severe disease. It has been shown to be associated with disease severity and mortality (26, 27). Patients were divided into non-admitted and admitted groups to allow for COVID illness severity assessment. The admitted group were further subdivided into those who required ICU care and those that did not. Participants were assessed for frailty by a member of the COVID clinical team which was operationalised using Rockwood's Clinical Frailty Scale (CFS) (range 1 – 9) (28). Patients underwent chest x-ray at the time of outpatient appointment to assess for the presence of

parenchymal disease and resolution of any previously-seen radiological abnormalities(29), as well as having CRP, IL-6, sCD25 and D-dimer measured in serum by ELISA (R&D systems).

A six-minute-walk test (6MWT) was used to assess cardiopulmonary and musculoskeletal function (30, 31). It has been previously validated in the assessment of ARDS survivors (32). The results of the 6MWT were compared to normative reference ranges for both a healthy population and a previously-published ARDS population (32). Total distance walked and significant desaturation (defined as oxygen saturation below 90%) were recorded. The Modified Borg Dyspnoea Scale (MBS) was used to assess perceived exertion during submaximal exercise (range 0 -10). The MBS has been widely used in both healthy and diseased states (33, 34).

To assess subjective recovery from COVID-19 illness, participants were asked a binary question regarding their perception of having returned to full health. Fatigue was assessed using the validated Chalder Fatigue Scale (CFQ-11) (35, 36). Participants are asked to answer these questions with reference to the past month in comparison to their pre-COVID-19 baseline, with responses measured on a Likert scale (0-3). From this a global score can be constructed out of a total of 33. This method is validated and closely resembles other fatigue questionnaires (37-40).

Statistical Analysis

All analysis was carried out using Stata, version 15.0 (StataCorp, College Station, Tx). Statistical significance was considered as $p < 0.05$.

We examined characteristics and outcome according to acute COVID-19 severity: (i) non-admitted (ii) admitted but not requiring ICU (iii) admitted to ICU. ANOVA, Kruskal-Wallis tests and chi-square tests were used as appropriate for univariate between-group differences. Tukey or Dunn's testing were used post-hoc. Pearson's and Spearman's tests were used to assess correlation between variables.

To analyse the impact of disease severity on respiratory outcomes we used linear regression, with each outcome (namely 6MWT distance covered and maximal MBS) as the dependent variable. We additionally analysed factors associated with abnormal chest x-ray at time of study participation. This was done using binary logistic regression. Models were adjusted for the confounding variables of age, sex and clinical frailty score. Results are reported as β coefficients or odds ratios (ORs) with 95% confidence intervals (CIs) and corresponding *p*-values. Linear models were examined for multi-collinearity by computing variance inflation factors and visually examining residual-versus-fit plots.

Results

Cohort Descriptors

There were 712 patients diagnosed with SARS-CoV-2 at our institution in the three-month period from March – May 2020. 400 (56%) were managed in the outpatient setting, with 312 (44%) admitted, 44 of whom (44/312, 14%) required ICU care. Of the 712 patients, 86 (12%) died. Following exclusion of those admitted patients who were long term care residents or had no contact details, 118 were contacted and offered an appointment, of whom 74 (63%)

attended. Of the 400 patients who self-managed in the community, 31 had no contact details. 369 were contacted, with 79 (21%) accepting an outpatient appointment. Thus 153 patients of a contactable 487 (31%) attended for follow up. Of these, just under half (74/153, 48%) had been admitted during their acute infection and 19/153 (12%) were admitted to ICU. The enrolment strategy and breakdown are shown in Figure 1. The median age of the outpatient cohort was 48 (35 – 59). The median time of follow up was 75 days after diagnosis (IQR 66 – 108). Those managed as inpatients had a shorter time to follow up (median 71 days, IQR 61 – 82) than those managed in the community (median 92 days, IQR 62 – 117) ($p<0.001$).

Characteristics of the cohort are given by disease severity category in Table 1. There were significant differences between the groups with respect to sex, age and clinical frailty score. The admitted group (both non-ICU and ICU) had an increased proportion of males, were older and had greater levels of frailty than the non-admitted group (all $p < 0.001$).
There were no differences in demographics between those admitted but not requiring ICU care and those that were admitted to ICU, but those admitted to ICU had a longer inpatient stay.

Respiratory Sequalae

A total of 115 (75%) participants underwent chest radiography at follow up. All patients admitted during acute infection had a follow up chest x-ray. Abnormal chest x-rays were found in 51/74 (69%) of admitted patients at time of initial infection. Persistent abnormal x-rays of either persistent infiltrate or atelectasis were found in 14 (19%) of the admitted cohort with no abnormal findings in those managed as outpatients. Abnormal chest x-ray findings were not associated with initial disease severity. These results are summarised in Table 2.

Length of hospital stay was associated with an increased likelihood of an abnormal x-ray, although other markers of disease severity showed no association (Supplemental Table 1). All 14 patients who had an abnormal follow up x-ray underwent repeat imaging 6 weeks later, with 5 having persistent abnormalities. Subsequent CT scans on these 5 patients demonstrated scarring in one (3 patients) and two (2 patients) lung zones. Thus, persistent x-ray abnormalities attributable to COVID-19 were seen in 4% (5/115) of our cohort.

Six-Minute-Walk Test and MBS

A total of 109 (71%) patients completed a 6MWT. The median distance covered was 460m (IQR 225 – 640). Distance covered was not associated with initial disease severity. These results are shown in Table 2. Length of inpatient stay was associated with reduced distance covered, but no other features of initial infection were associated with distance covered (Supplemental Table 1). Three patients (3/109, 3%) had an arterial oxygen saturation below 90% during the 6MWT. The median MBS reported was 3 (IQR 2 – 5). Maximal scores of perceived exertion were independent of initial disease severity (Table 2). The only predictor of increased MBS in the inpatient cohort was female sex (Supplemental Table 1).

Fatigue and Ill-Health

95 (62%) patients did not feel back to full health at the time of their outpatient assessment. The median fatigue score across the cohort was 15 (IQR 11 – 20). A total of 73 (48%) participants met the case definition for fatigue, and this was not associated with severity of initial infection (r^2 -0.09, p 0.25). Not feeling back to full health was associated with increased MBS (OR 1.3, CI

1.1 – 1.6, *p* 0.005). Similarly, fatigue was not associated with abnormal chest x-ray or inflammatory markers at follow up but was associated with reduced distance covered (β coefficient -0.02, CI -0.03 – -0.01, *p* 0.002) and increased MBS (β coefficient 0.85, CI 0.36 – 1.334, *p* 0.001). Fatigue and failure to feel back to full health were also closely correlated (β coefficient 5.34, CI 3.64 – 7.05, $p < 0.001$).

Discussion

Of the patients that attended for outpatient follow-up, we report reassuring findings regarding objective post-COVID respiratory complications at a median follow-up timepoint of 75 days, but clear evidence that patients have not returned to full fitness. Our pragmatic approach of repeat radiography followed by CT for persistent abnormalities produced an abnormal imaging rate of 4%. There was also no association with abnormal imaging and severe disease. The 6MWT distance covered by our cohort is below that reported in the healthy population (41). This is similar to data seen following the original SARS pandemic in 2003 (42). However, the distance covered in our cohort is higher than those previously reported at 3- and 6-month follow up of ARDS patients (32). The median distance covered is also higher than 350m, which has previously been shown to be associated with hospital admission and all-cause mortality in patients with pre-existing pulmonary disease (43). Under multivariate analysis, no disease-specific characteristics affected the distance covered. The presence of normal chest radiography in the majority of our cohort, coupled with very low rates of significant desaturation during 6MWT (3%) and a relatively large cohort size, suggest that clinically-

relevant fibrosis is an uncommon consequence of SARS-CoV-2 infection. This combination of readily-available tests helps overcome the relative lack of sensitivity of chest x-ray in the diagnosis of pulmonary fibrosis (44).

There is scant data available from other sites to compare our radiological findings. A single study in China performed high-resolution CT on 55 patients at three months, finding abnormalities in 39 of these, but symptomatic dyspnoea reported in fewer than 15% and three-quarters having normal pulmonary function tests (45). Fibrosis has been shown at biopsy in approximately half of all-cause ARDS patients at time of acute illness (6). However, ARDS-associated fibrosis is also closely linked with mortality, so it is plausible that those with significant fibrosis did not survive to follow up (46).

Significant morbidity persists, with 62% of patients reporting that they have not returned to full health. Fatigue is a common complaint in our cohort, confirming early reports from other centres (47). This failure to return to full health and deconditioning is supported by the associations between fatigue, subjective perception of not returning to full health and increased perception of maximal exertion. In addition to deconditioning, persistent low-grade inflammation post-infection may also contribute to systemic ill-health (48). These results support the need for more in-depth cardiovascular health and fitness assessment of those most severely affected, including cardiac imaging and maximal oxygen uptake assessment (49, 50).

Our findings are reflective of the 2003 SARS outbreak, with survivors reporting impairments in health-related quality of life at six months (n=110) (42). Similarly, a subset of patients in Toronto experienced persistent fatigue, diffuse myalgia, weakness and depression one year

after their acute illness and could not return to work (51). Over 40% of 233 SARS survivors in Hong Kong reported a chronic fatigue problem 40 months after infection (52).

Our study concerns findings around COVID-19-related sequalae in the medium-term. Median follow up was more than ten weeks after diagnosis, and participants were deemed recovered from initial infection, in line with what is currently understood of viral dynamics and infectivity (53-55). We feel that the findings are noteworthy on two main fronts. Firstly, they are reassuring regarding the long-term respiratory impact of COVID-19. Secondly, we have demonstrated the significant morbidity that persists following infection, affecting perception of health, ability to return to work, and the presence of enduring fatigue. This morbidity appears to be unrelated to initial infection severity. This has implications for both the delivery of adequate healthcare to all patients diagnosed with COVID-19 irrespective of need for hospitalisation, as well as the economic impact on the workforce. There appears to be a need for ongoing support and rehabilitation of patients experiencing long-term side-effects of COVID-19, including programmes to optimise patient's self-management of fatigue and perception of exertion post-COVID-19 (56). This is a topic that has been garnering much attention, but there is very limited published evidence thus far (57). We hope that this study can help inform ongoing decisions regarding the management of post-COVID symptoms.

Our single-centre study has several limitations worth noting. We were unable to assess the proportion of patients that declined an outpatient appointment. Telephone follow up was not feasible due to resource constraints. It is possible that those who have persistent ill-health are over-represented in our cohort. Similarly, we cannot generalise our objective respiratory results to the total COVID cohort. We report on a predominantly Caucasian population, which

may not be generalisable. It is a cross-sectional study at a single timepoint. Therefore, we suggest ongoing assessment of those displaying persistent ill-health. Furthermore, participants did not have 6MWT performed prior to infection, so changes from baseline are difficult to assess.

Conclusion

We present the medium-term respiratory and self-perceived health of patients at a median of 75 days after diagnosis. We found little evidence for post-infectious pulmonary fibrosis on chest x-ray or hypoxia on 6MWT. However, 62% of patients did not feel back to full health, and this was associated with increased perception of exertion. 47% of our cohort met the diagnostic criteria for fatigue, independent of initial severity of infection. This study highlights the persistence of ill health following SARS-CoV-2 infection that presents a serious burden to quality of life. The lack of association with infection severity highlights that this may be an issue for a large number of patients, and this should be used to inform management strategies for convalescent patients.

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Figure Legends

Figure 1. Patient Enrolment Diagram

Table 1: Cohort Demographics, Outpatient Results, and Inpatient Severity Markers

Results at time of initial infection	**Non-admitted N = 79**	**Admitted, non-ICU N = 55**	**Admitted, ICU N = 19**
Peak CRP, mg/ml, mean (SD)		64.4 (70.3)	178.6 (102.6)
Peak FiO2, %, mean (SD)		30 (15)	77 (20)
Abnormal CXR, n (%)		32 (58)	19 (100)
Brixia Score, mean (SD)		4.38 (3.37)	7.84 (4.69)
Length of Stay, days, median (IQR)		7 (5 – 13)	22 (14 – 29)
Demographics and results at time of outpatient assessment			
Age, years (SD)	40.2 (11.4)	56.4 (15.5)	54.5 (11.6)
Sex, female (%)	57 (72.2)	26 (47.3)	5 (26.3)
Ethnicity White (%) Asian (%) Hispanic (%) African (%)	 56 (70.9) 17 (21.5) 2 (2.5) 4 (5.1)	 45 (81.8) 6 (10.9) 0 (0) 4 (7.3)	 14 (73.7) 3 (15.8) 0 (0) 2 (10.5)
Clinical Frailty Score, median (IQR)	1 (1 – 1)	2 (2 – 3)	2 (1 – 3)
Back to full health, n (%)	27 (34)	27 (59)	9 (47)
Fatigue score, median (IQR)	17 (12 – 21)	15 (11 – 21)	14 (11 – 15)

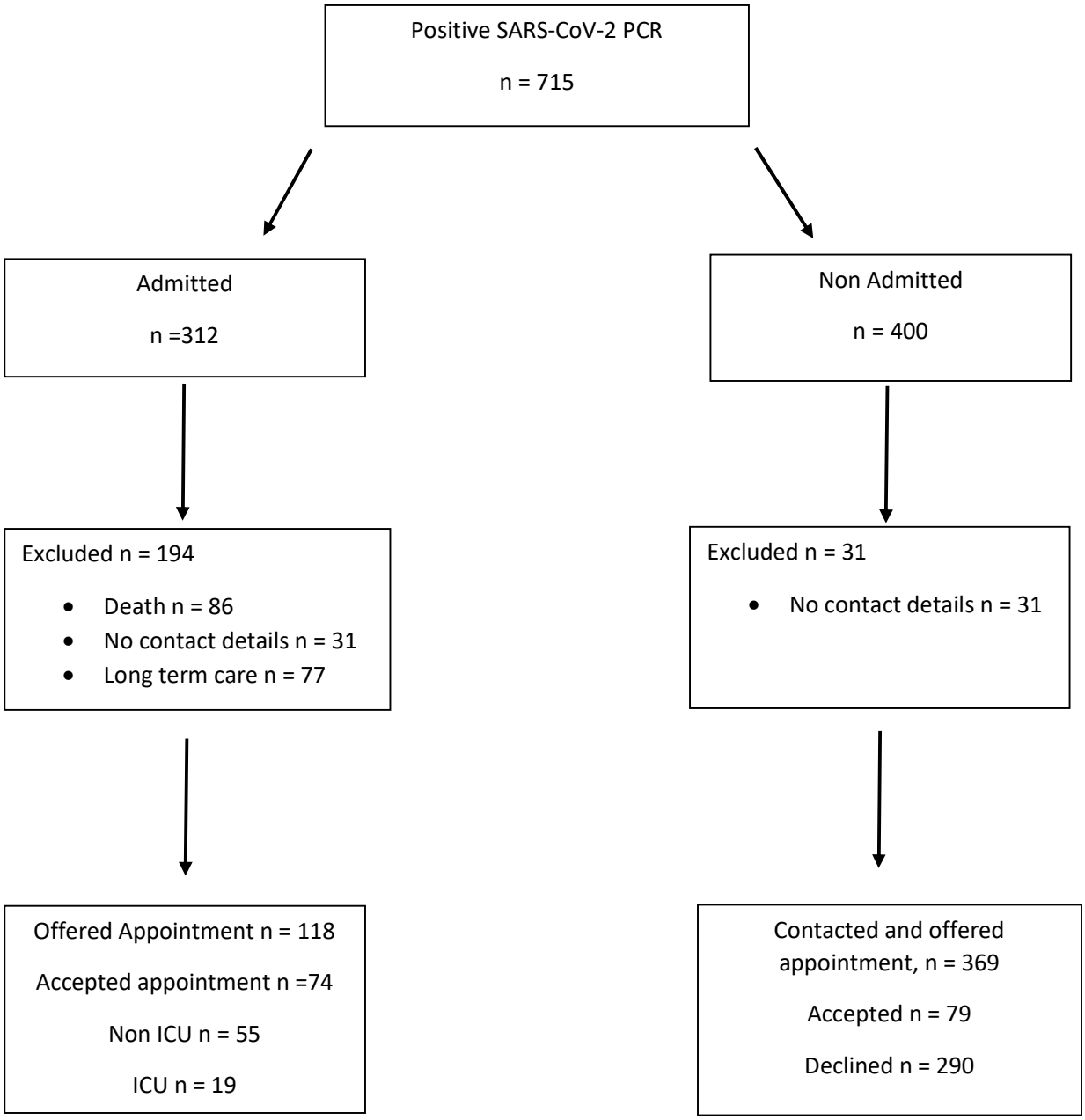
CRP, mg/ml, mean (SD)	2.12 (2.01)	3.61 (4.85)	1.60 (0.98)
IL-6, pg/ml, mean (SD)	3.55 (1.51)	4.58 (2.95)	3.54 (0.76)
sCD25, pg/ml, mean (SD)	825.47 (398.40)	1503.31 (777.76)	1534.18 (588.60)
D-dimer, ng/ml, mean (SD)	415.3 (775.5)	669.1 (799.9)	454.1 (209.9)

CRP = C reactive protein, FiO2 = fraction of inspired oxygen, CXR = chest x-ray, IL-6 = Interleukin-6, sCD25 = soluble CD25

Table 2: Relationship between respiratory outcomes and disease severity

	Abnormal chest x-ray		Distance at 6MWT		Maximal Borg at 6MWT	
	OR (95% CI)	P value	β coefficient (95% CI)	P value	β coefficient (95% CI)	P value
Disease Severity						
Non-admitted	1.0 (reference)	n/a	0 (reference)	n/a	0 (reference)	n/a
Admitted, non-ICU	2.6 (0.5 – 14.0)	0.26	-23.6 (-69.4 – 22.2)	0.31	-0.15 (-1.3 – 1.0)	0.79
Admitted, ICU	4.9 (0.8 – 30.1)	0.09	-27/1 (-85.2 – 31.0)	0.36	-0.56 (-2.0 – 0.9)	0.45
Age	1.0 (1.0 – 1.1)	0.39	-1.8 (-3.4 – -0.3)	0.02	0.01 (-0.03 – 0.04)	0.78
Sex, Female	1.1 (0.3 – 3.9)	0.85	-47.1 (-83.4 – -10.7)	0.01	0.95 (0.04 – 1.9)	0.04
CFS	0.9 (0.4 – 2.1)	0.81	-47.4 (-73.0 – -21.8)	< 0.001	0.65 (0.01 – 1.3)	0.048

6MWT = six-minute-walk test, OR = odds ratio, ICU = intensive care unit, CFS = Clinical Frailty Score


Positive SARS-CoV-2 PCR
n = 715
Admitted
n =312
Non Admitted
n = 400
Excluded n = 194
Death n = 86
No contact details n = 31
Long term care n = 77
Excluded n = 31
No contact details n = 31
Offered Appointment n = 118
Accepted appointment n =74
Non ICU n = 55
ICU n = 19
Contacted and offered appointment, n = 369
Accepted n = 79
Declined n = 290

Online Data Supplement

Persistent Poor Health Post-COVID-19 Is Not Associated with Respiratory Complications or Initial Disease Severity

Liam Townsend, Joanne Dowds, Kate O'Brien, Grainne Sheill, Adam H. Dyer, Brendan O'Kelly, John P. Hynes, Aoife Mooney, Jean Dunne, Cliona Ni Cheallaigh, Cliona O'Farrelly, Nollaig M Bourke, Niall Conlon, Ignacio Martin-Loeches, Colm Bergin, Parthiban Nadarajan, Ciaran Bannan

Supplemental Table 1: Abnormal chest x-ray at follow-up, inpatient factors

Predictor	Abnormal chest x-ray		Distance at 6MWT		Maximal Borg at 6MWT	
	OR (95% CI)	P value	β coefficient (95% CI)	P value	β coefficient (95% CI)	P value
Disease Severity						
Admitted, non-ICU	1.0 (reference)	n/a	0 (reference)	n/a	0 (reference)	n/a
Admitted, ICU	0.06 (0.001 – 2.1)	0.12	37.6 (-84.6 – 159.7)	0.53	-0.7 (-3.4 – 2.0)	0.59
Age	0.03 90.83 – 1.05)	0.25	0.3 (-4.1 – 4.7)	0.89	-0.03 (-0.1 – 0.07)	0.55
Sex, Female	0.67 (0.09 – 4.87)	0.70	-38.2 (-117.7 – 41.3)	0.33	1.9 (0.1 – 3.6)	0.04
CFS	1.12 (0.37 – 0.36)	0.84	-38.0 (-86.9 – 10.9)	0.12	0.8 (-0.3 – 1.8)	0.16
Peak CRP	0.99 (0.98 – 1.0)	0.17	0.5 (-0.02 – 1.1)	0.06	-0.0001 (-0.01 – 0.01)	0.99
Max FiO2	30.8 (0.24 – 3985.8)	0.17	-16.8 (-259.2 – 225.6)	0.89	-1.5 (-6.8 – 3.8)	0.57
Brixia score	1.03 (0.8 – 1.32)	0.83	-3.6 (-13.1 – 5.9)	0.44	0.07 (-0.1 – 0.3)	0.50
Length of stay	1.18 (1.02 – 1.36)	0.03	-6.1 (-11.9 – -0.19)	0.04	0.08 (-0.06 – 0.2)	0.25

6MWT = six-minute-walk test, ICU = intensive care unit, CFS = Clinical Frailty Score, CRP = C reactive protein, FiO2 = fraction of inspired oxygen, OR = odds ratio