The Medical Journal of Australia – **accepted article – 22 December 2020**

High rate of persistent symptoms up to 4 months after community and hospital-managed SARS-CoV-2 infection

David R Darley
Staff Specialist
St Vincent's Hospital Sydney
Department of Thoracic Medicine
Darlinghurst, New South Wales, Australia

PhD Candidate
University of New South Wales
Faculty of Medicine
St Vincent's Clinical School
St Vincent's Hospital
Sydney, New South Wales, Australia

Gregory J Dore
Head, Viral Hepatitis Clinical Research Program
University of New South Wales
The Kirby Institute
Sydney, New South Wales, Australia

Clinical Academic
St Vincent's Hospital Sydney
Department of Infectious Diseases
Darlinghurst, New South Wales, Australia

Lucette Cysique
Neuropsychologist
St Vincent's Hospital Sydney
Institute for Applied Medical Research
Darlinghurst, New South Wales, Australia

University of New South Wales
Department of Psychology
Sydney, New South Wales, Australia

Kay A Wilhelm
Consultant liaison Psychiatrist
St. Vincent's Hospital
CL Psychiatry
Darlinghurst, New South Wales, Australia

Professor
The University of Notre Dame Australia
School of Medicine
Sydney Campus
Department of Psychiatry
Darlinghurst, New South Wales, Australia

David Andresen
Staff Specialist
St Vincent's Hospital Sydney
Department of Infectious Diseases
Darlinghurst, New South Wales, Australia

Katrina Tonga
Staff Specialist
St Vincent's Hospital Sydney
Department of Thoracic Medicine
Darlinghurst, New South Wales, Australia

University of New South Wales
Faculty of Medicine
St Vincent's Clinical School
St Vincent's Hospital
Sydney, New South Wales, Australia

Emily Stone
Staff Specialist
St Vincent's Hospital Sydney
Department of Thoracic Medicine
Darlinghurst, New South Wales, Australia

University of New South Wales
Faculty of Medicine
St Vincent's Clinical School
St Vincent's Hospital
Sydney, New South Wales, Australia

Anthony Byrne
Staff Specialist
St Vincent's Hospital Sydney
Department of Thoracic Medicine
Darlinghurst, New South Wales, Australia

University of New South Wales
Faculty of Medicine
St Vincent's Clinical School
St Vincent's Hospital
Sydney, New South Wales, Australia

Marshall Plit
Staff Specialist
St Vincent's Hospital Sydney
Department of Thoracic Medicine
Darlinghurst, New South Wales, Australia

University of New South Wales
Faculty of Medicine
St Vincent's Clinical School
St Vincent's Hospital
Sydney, New South Wales, Australia

Jeffrey Masters
Advanced Trainee
St Vincent's Hospital Sydney
Department of Infectious Diseases
Darlinghurst, New South Wales, Australia

Helen Tang
Basic Physician Trainee
St Vincent's Hospital Sydney
Department of Infectious Diseases
Darlinghurst, New South Wales, Australia

Bruce Brew
Staff Specialist
St Vincent's Hospital Sydney
Department of Neurology
Darlinghurst, New South Wales, Australia

Philip Cunningham
Chief Operating Officer
St Vincent's Hospital Sydney
Institute for Applied Medical Research
Darlinghurst, New South Wales, Australia

Anthony Kelleher
Professor and Program Head
The Kirby Institute
University of New South Wales
Darlinghurst, New South Wales, Australia

Staff Specialist
St Vincent's Hospital Sydney
Department of Immunology
Darlinghurst, New South Wales, Australia

Gail Matthews
Associate Professor
University of New South Wales
The Kirby Institute for Infection and Immunity in Society
Kensington, New South Wales, Australia

Clinical Academic
St Vincent's Hospital Sydney
Department of Infectious Diseases
Darlinghurst, New South Wales, Australia

Competing interests: No relevant disclosures

Abstract

Recovery after severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection remains uncertain. A considerable proportion of patients experience persistent symptoms after SARS-CoV-2 infection which impacts health-related quality of life and physical function. Multi-disciplinary follow-up is recommended for patients with post-COVID illness and to assess health-related quality of life and physical function.

Research Letter

The spectrum of recovery following community-managed and hospitalised severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection remains uncertain (1-5). A prospective cohort (the ADAPT study) was established of all adult patients, with confirmed positive SARS-CoV-2 RNA PCR at St Vincent's Hospital Sydney, to characterise the long-term effects and explore their association with initial COVID-19 disease severity. Study participants are prospectively observed under a pre-defined schedule of assessments, with follow-up planned through 12 months post-COVID-19. The specific aims of this study are to determine the prevalence and nature of persistent symptoms after SARS-CoV-2 infection, to evaluate lung function, health-related quality of life, neurocognitive and olfactory abnormalities in the recovery period and to characterise the longitudinal immune response. In this letter, we report interim results from the initial study assessments which were performed up to 4 months after first detection of SARS-CoV-2. All individuals with confirmed SARS-CoV-2 RNA positive at St Vincent's Hospital testing clinics and able to be contacted were offered enrolment into the study (**Supplementary Figure 1**). The study was approved

by the St Vincent's Hospital Research Ethics Committee (2020/ETH00964) and the timing of the baseline visit was dependent on this. Between April and June 2020, 78 individuals were enrolled, of whom 69 were managed in the community (30 mild, 39 moderate, see **Supplementary Table 1** for definitions) and 9 hospitalised (2 admitted into intensive care for acute respiratory distress syndrome). The mean patient age is 47 (16), with 27 females, 65 Caucasian and 39 infections acquired overseas (see **Supplementary Table 2** for demographics). The most commonly self-reported medical co-morbidities were hypertension and asthma, while 37 patients had no co-morbidities. The most common reported initial COVID-19 symptoms were fatigue in 62, cough in 50, and headache in 44 individuals. At median 69 days after diagnosis (IQR 64-83), 31 patients had persistent symptoms including fatigue in 17, shortness of breath in 15 and chest tightness in 4 **(Figure 1)**, including 7 hospitalised and 24 community-managed individuals. Complex lung function testing at median 113 (IQR 105-131) days post-infection was performed in 65 individuals **(Table 1)**. Abnormal total lung capacity (TLC) < lower limit of normal (LLN) was seen in a small proportion of patients (12%), but median TLC %-predicted was significantly lower in the hospitalised 91 (IQR 78-99) compared with the community population 102 (IQR 92-107), p=0.02 (Mann-Whitney U Test). Abnormal diffusion capacity for carbon monoxide ($DLCO_{cor}$) %-predicted, less than LLN values, was observed in 11 individuals with a trend to higher proportions in the hospitalised population. When considering the largely maintained ventilatory capacity, this may indicate an association with pulmonary vascular disease. Neurocognitive impairment, performed under supervision by trained examiners using the CogState computerised battery, was low (8 individuals) but associated with abnormal olfaction (4 individuals) (6). Concerningly, a considerable proportion of patients experience persistent symptoms after SARS-CoV-2 infection including fatigue, chest pain and

breathlessness. Although more common following severe illness, 35% community-managed patients within ADAPT have persistent symptoms several months post infection. Ongoing follow-up of this cohort will generate data on the longer-term trajectory of recovery post COVID-19 illness and provide insights into the mechanisms of systemic inflammation after SARS-CoV-2 infection, and its immunologic correlates.

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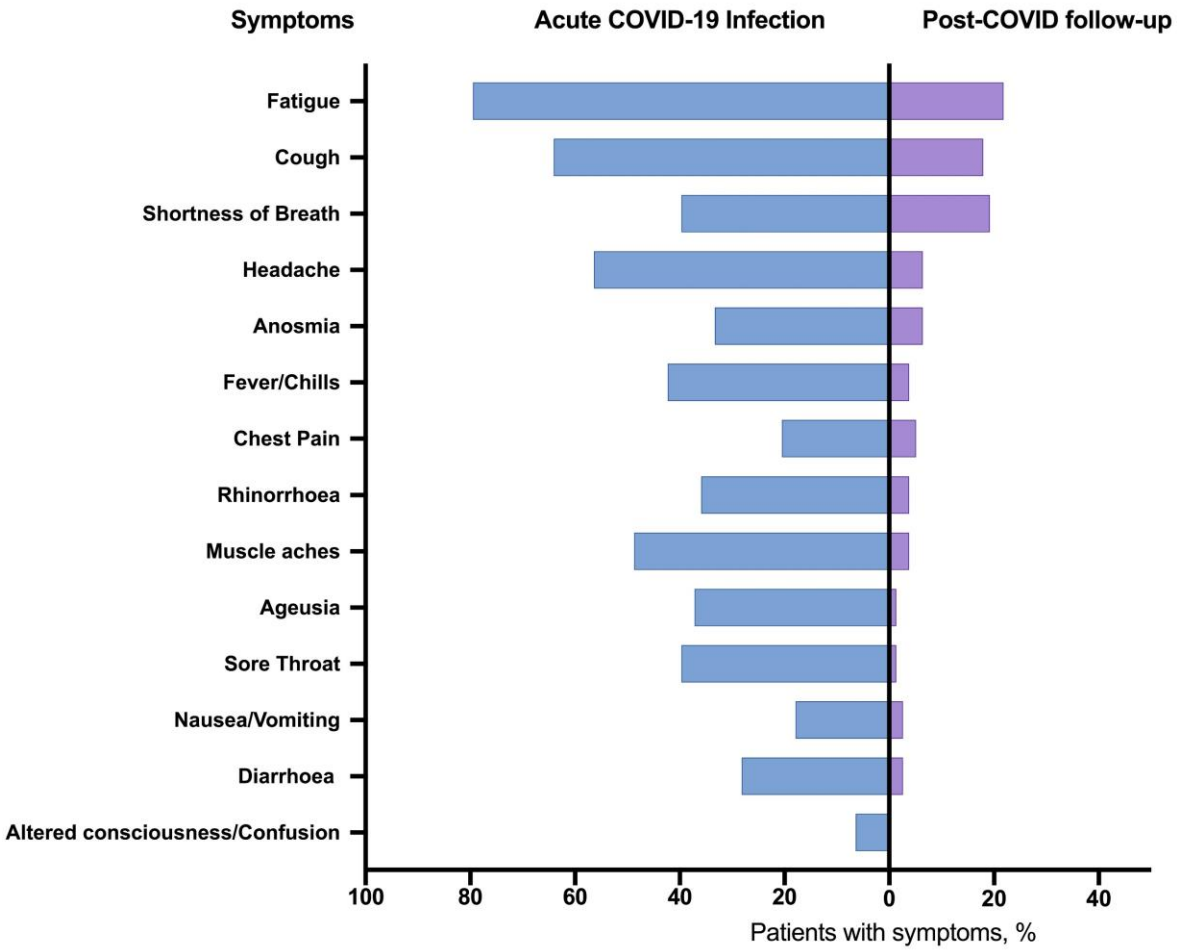
Figure 1 Symptoms at initial infection and first follow-up at median 69 (IQR 64-83) days in n=78 patients.



Analytic Flow Diagram

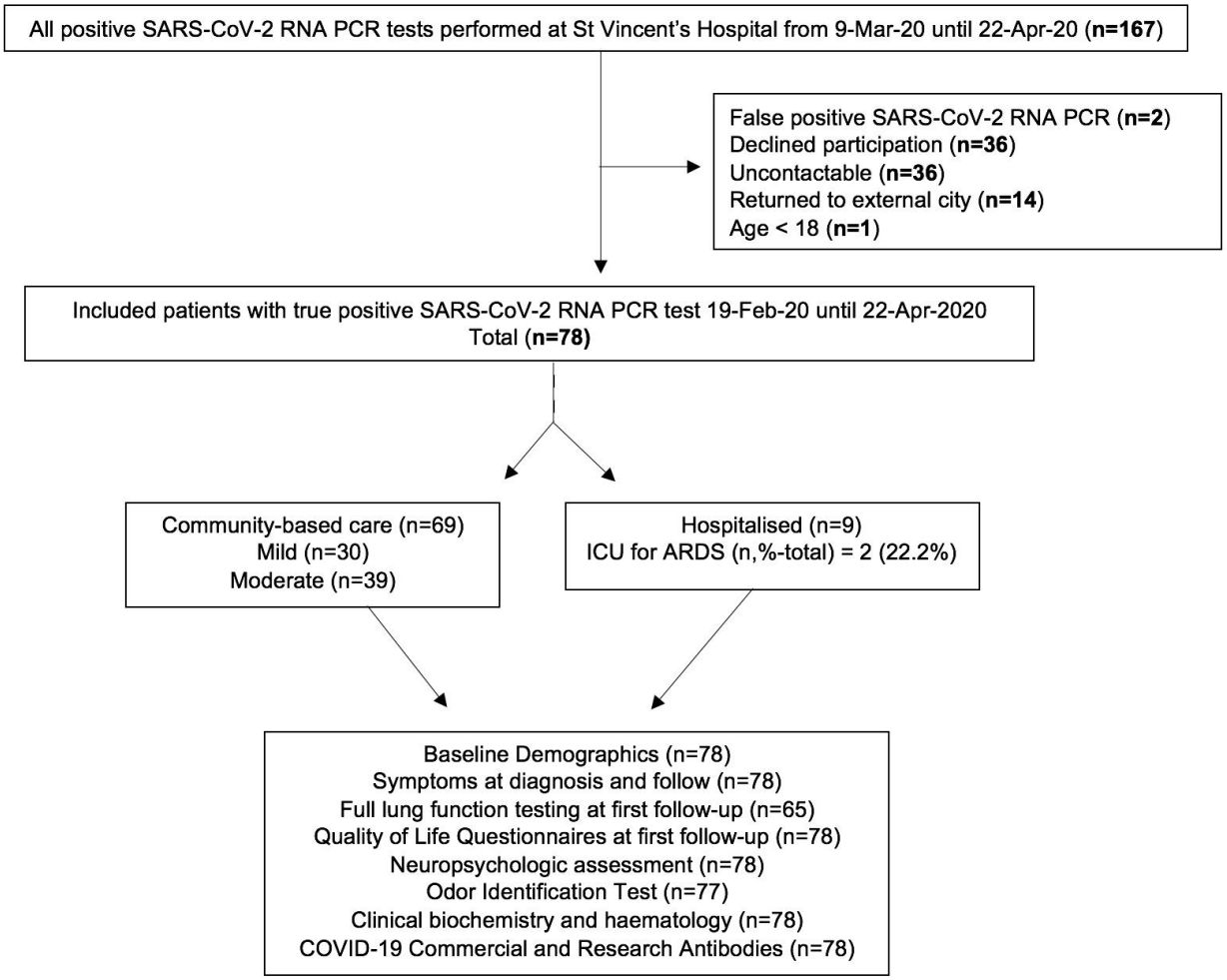


Table 1. Results of first complex lung function testing after COVID-19 (n=65).

Parameter	Total (n=65)	Community (n=56)	Hospitalised (n=9)
Median (IQR) days from COVID-19 diagnosis to first lung function	113 (105-131)	115 (107-139)	74 (63-98)
Median Pre-BD FEV_1 %-Predicted (IQR) - FEV_1 < LLN (n)	99 (84-104) 5	99 (84-105) 4	97 (78-103) 1
Median Pre-BD FVC %-Predicted (IQR) - FVC < LLN (n)	106 (97-117) 3	105 (97-117) 2	106 (89-118) 1
Mean FEV_1/FVC Ratio (SD)	74 (9)	74 (8.7)	71 (11)
Median TLC %-Predicted (IQR) - TLC < LLN (n)	101 (91-107) 8	102 (92-107) 6	91 (78-99) 2
Median $DLCO_{cor}$ %-Predicted (IQR) - $DLCO_{cor}$ < LLN (n)	92 (84-103) 11	93 (85-103) 8	89 (62-99) 3
Mean Capillary blood gas pO2 mmHg (SD)	86 (9.6)	87 (9.5)	82 (9.8)
Mean Capillary blood gas A-a Gradient mmHg (SD)	24 (9.6)	23 (9.3)	29 (10)

TLC = Total lung capacity; $DLCO_{cor}$ = Diffusing capacity for carbon monoxide adjusted for concurrent haemoglobin; FEV_1 = Forced expiratory volume in 1 second; FVC = Forced vital capacity; LLN=Lower Limit Normal; Pre-BD = Pre-Bronchodilator. Descriptive statistics are summarised by mean and standard deviation (SD) or median with interquartile range (IQR) for continuous variables, and counts (%) for categorical variables. Global Lung Function Initiative (GLFI) reference equations were used for spirometry and diffusion capacity. Quanjer et al. reference equations were used for static lung volumes.

Supplementary Table 1. Definition of ADAPT cohort sub-populations.

Cohort sub-population definitions	
Mild	Managed in the community with minor, largely upper respiratory tract viral symptoms including sore throat, rhinorrhoea, headache and anosmia/ageusia.
Moderate	Managed in the community with fever/chills **AND** 1 of the following organ-localising symptoms, **OR** ≥ 2 of the following organ-localising symptoms; cough, haemoptysis, shortness of breath, chest pain, nausea/vomiting, diarrhoea or altered consciousness/confusion.
Severe	Patients requiring inpatient care on the wards or in the intensive care unit (ICU).

Supplementary Table 2. Patient characteristics at the time of COVID-19 presentation (n=78).

Patient Characteristic	Total (n=78)	Community (n=69)	Hospitalised (n=9)
Mean age (y) at diagnosis (SD)	47 (16)	45 (15)	62 (8.6)
Female sex (n, %)	27	27	0
Caucasian Ethnicity (n, %)	65	57	8
Epidemiology			
- Overseas travel	39	35	4
- Known close contact	38	32	6
- Presence in a high-risk setting	15	12	3
Without co-morbidity (n, %)	37	36	1
Co-Morbidities			
- Hypertension	14	12	2
- Diabetes Mellitus	7	3	4
- Chronic Cardiac Disease	8	5	3
- Chronic Lung Disease	1	1	0
- Asthma	9	8	1
- Chronic Kidney Disease	3	2	1
- Cancer	7	6	1
- Immune Disorders	3	3	0
- Obesity	3	2	1
- Obstructive Sleep Apnoea	1	1	0
- Psychiatric Diagnosis	6	6	0
Smoking (Ever)	29	21	8
Highest Education Level			
- University	61	54	7
- High School	14	13	1
ICU Admission for ARDS	2	N/A	2

Counts are presented as n (%); Means are presented with standard deviations; Presence in a high-risk setting (Hospitals, aged care facilities, residential care facilities, correctional facilities, boarding schools, cruise ships); Psychiatric Diagnosis (Anxiety, Depression, Bipolar Affective Disorder, Attention Deficit Disorder); Immune Disorders (HIV infection, Solid-Organ Transplant, Auto-Immune Disease). Descriptive statistics are summarised by mean and standard deviation (SD) and counts (%) for categorical variables.