ORIGINAL ARTICLE

Symptom persistence and recovery among COVID-19 survivors during a limited outbreak in Canterbury, New Zealand: a prospective cohort study

Jeanette Cheung [ID],[1] Kim Nordmeier,[1] Sarah Kelland,[1] Michael Harrington,[2] Jonathan Williman,[3] Malina Storer,[1] Ben Beaglehole,[4] Lutz Beckert,[1] Stephen T Chambers,[5] Michael J Epton,[1] Josh Freeman,[2] David R Murdoch,[2,5] Anja M Werno[2] and Michael J Maze [ID][1,6]

[1]Respiratory Medicine Department, Canterbury District Health Board, [2]Microbiology Department, Canterbury Health Laboratories, and Departments of [3]Population Health, [4]Psychological Medicine, [5]Pathology and Biomedical Sciences, and [6]Medicine, University of Otago, Christchurch, New Zealand

Abstract

Background: In Canterbury, near complete identification of coronavirus disease 2019 (COVID-19) cases during a limited outbreak provides unique insights into sequelae.

Aims: The current study aimed to measure symptom persistence, time to return to normal activity, generalised anxiety and health-related quality of life (HrQoL) among COVID-19 survivors compared with uninfected participants.

Methods: The authors conducted a prospective cohort study of people tested for COVID-19 by reverse transcriptase polymerase chain reaction of nasopharyngeal swabs from 1 March to 30 June 2020. They enrolled participants who tested positive and negative at a 1:2 ratio, and administered community-acquired pneumonia, 7-item generalised anxiety disorder (GAD-7) and HrQoL (RAND-36) questionnaires.

Results: The authors recruited 145 participants, 48 with COVID-19 and 97 without COVID-19. The mean time from COVID-19 testing to completing the health questionnaire was 306 days. The mean age of patients was 46.7 years, and 70% were women. Four (8%) COVID-19–positive and eight (8%) COVID-19–negative participants required hospitalisation. Fatigue (30/48 [63%] vs 13/97 [13%]; $P < 0.001$), dyspnoea (13/48 [27%] vs 6/97 [6%]; $P < 0.001$) and chest pain (10/48 [21%] vs 1/97 [1%]; $P < 0.001$) were persistent in those with COVID-19. Fewer COVID-19–positive participants returned to normal activity levels (35/48 [73%] vs 94/97 97%; $P < 0.001$), with longer times taken (median 21 vs 14 days; $P = 0.007$). The GAD-7 and RAND-36 scores of both groups were similar across all anxiety and HrQoL subscales.

Conclusions: Persistent symptoms and longer recovery times were found in COVID-19 survivors, but not impaired generalised anxiety levels or HrQoL compared with COVID-19–uninfected participants.

Introduction

The coronavirus disease 2019 (COVID-19) pandemic has infected millions of people, but the long-term ramifications of this multisystem disease are yet to be fully understood.[1] The World Health Organization (WHO) recently released a clinical case definition of post–COVID-19 condition to aid further research and management.[2] This condition affects multiple organs and can be prolonged, fluctuates and new symptoms can emerge.[2–4] Patients will require extensive support and treatment as this condition may reduce their quality of life.[5]

Current literature on the post–COVID-19 condition are predominantly from hospitalised survivors,[3,4,6] though in New Zealand (NZ), only 6.3% of confirmed

cases were hospitalised.[7] The development of the condition is generally unrelated to the severity of initial illness and treatment.[3,8] Generalisation of many of these studies is limited because of potential selection bias, varied methods of diagnosing COVID-19, potential reinfection and lack of a control group, resulting in differing estimates of post–COVID-19 condition prevalence at various follow-up times.[3,4]

NZ is a geographically isolated island nation with a relatively low population density, enabling fast border control and enforcement of restricted population movement. Canterbury occupies the eastern central region of NZ's South Island and has a population of 599 694 (12.7% of NZ's total population).[9] During the initial COVID-19 outbreak (28 February to 22 May 2020), there were 165 confirmed and probable COVID-19 cases.

NZ initially adopted an aggressive elimination strategy with rapid COVID-19 diagnosis, contract tracing and swift isolation of confirmed or suspected COVID-19 cases. This led to near-complete case ascertainment as supported by a research study conducted in Otago, a neighbouring province. Craigie *et al.* found that almost all individuals who were not designated as COVID-19 cases but were at high epidemiological risk of infection were seronegative at a median of 14 weeks after first symptoms.[10] NZ's initial elimination approach led to a period without new or reinfection cases[7,11] and provided a unique natural experiment to further understand the post–COVID-19 condition in comparison to presentations with other respiratory illnesses.

We aimed to measure persistence of symptoms, time to return to normal activity levels, generalised anxiety levels and health-related quality of life (HrQoL) among COVID-19 survivors. We compared these outcomes with controls, who presented with similar acute symptoms and tested negative for COVID-19.

Methods

In this prospective cohort study, we approached patients who were tested for COVID-19 in Canterbury, NZ. We recruited participants in a 1:2 ratio of COVID-19 positive to COVID-19 negative (control group). Potential participants were identified by nasopharyngeal severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) reverse transcriptase polymerase chain reaction (RT-PCR) testing records at Canterbury Health Laboratories from 1 March 2020 to 30 June 2020. Inclusion criteria were: (i) age ≥18 years at the time of COVID-19 testing and (ii) able to consent for the study.

COVID-19–negative participants were selected from a chronologically ordered list of patients undergoing COVID-19 testing. We selected potential control participants as the next two patients tested following a patient testing positive. If control participants could not be contacted, we selected the subsequent patient on the list. A maximum of three attempts were made to contact potential participants.

An information and consent form was sent to those willing to partake in the study. Participants provided written consent to conduct the health questionnaire. The study was approved by the research ethics committee of the University of Otago (HE20/008) (Supporting Information).

A standardised health questionnaire (Appendix S1) was administered via phone. A case report form collected basic demographic information, symptoms at the time of COVID-19 testing and comorbidities considered risk factors for severe disease and/or delayed recovery. This form was based on the initial International Severe Acute Respiratory and Emerging Infections Consortium (ISARIC) – WHO Clinical Characterisation Protocol study[12] and clinical features of COVID-19 patients reported in Wuhan, China.[13] All participants completed a modified community-acquired pneumonia questionnaire to assess the persistence of symptoms and time to return to normal activity levels, which referred specifically to activities of daily living and physical activity.[14] The severity of persistent symptoms was recorded on a five-point Likert scale. Symptoms of generalised anxiety disorder (GAD) were evaluated using the 7-item generalised anxiety disorder (GAD-7) questionnaire, with a total score ≥10 used as the cutoff for the presence of GAD.[15] The RAND-36 questionnaire evaluates HrQoL[16] and comprises 36 items to appraise eight subscales. The sum scores for each subscale are from 0 to 100 with 100 representing maximal health. All data were uploaded to a Research Electronic Data Capture (REDCap) system.

Statistical analysis

Descriptive variables for COVID-19–positive and negative–participants were compared using chi-square tests for categorical and binary outcomes, and *t* tests or linear regression models for continuous outcomes. Risk ratios for persistence of symptoms and return to normal activity levels were determined.

For RAND-36 scores and return to normal activities levels, adjustments were made for confounders (age, sex, smoking status, asthma, hypertension, anxiety, post-traumatic stress disorder and elapsed time between COVID-19 testing and completion of questionnaire) by propensity analysis, with inverse weighting of propensity scores. The return to normal activities levels data were skewed. To minimise this, a log transformation was used

and geometric means were compared. The group comparisons are presented as ratios rather than differences. All statistical analyses were conducted using R version 4.0.3.[17]

Results

Participant flow and baseline characteristics

There were 852 eligible patients, of whom 110 (13%) were positive for SARS-CoV-2 on RT-PCR and 742 (87%) were negative. In total, 377 (44%) patients were excluded due to death, age < 18 years, not competent to consent or unable to contact. We contacted 475 potential participants, of whom 150 (150/475, 32%) declined to participate and 180 (180/475, 38%) could not be subsequently contacted to conduct the questionnaire. This study cohort comprised 145 (145/475, 30%) patients who completed the health questionnaire, 48 who were COVID-19 positive and 97 who were COVID-19 negative (control group). We enrolled 44% (48/110) of those diagnosed with COVID-19 and 53% (48/91) of cognitively able survivors (Fig. 1).

The mean time from COVID-19 testing to conducting the health questionnaire in the COVID-19–positive group was 251 days and in the control group was 333 days, giving a combined mean of 306 days. Demographic characteristics and comorbidities were generally

well balanced between cases and controls at baseline (Table 1). The mean age for both groups at the time of COVID-19 testing was 46.7 years, 70% were women and 90% were of European ethnicity. The mean NZ Index of Deprivation 2018 decile score was 4.3 ± 2.5 standard deviations (SDs) (1 = least deprived to 10 = most deprived). The most common comorbidities in both groups were anxiety or depression (36%), asthma (23%), hypertension (17%) and posttraumatic stress disorder (14%).

In the cohort, 10 of 145 patients were asymptomatic and of those 10 asymptomatic participants, two were COVID-19 positive and eight were COVID-19 negative. The majority of our participants did not require hospitalisation, apart from four (8%) of those with COVID-19 and eight (8%) without COVID-19 who required hospital admission. The presence of symptoms at the time of the illness is shown in Figure 2. Chest pain (16/45 [36%] vs 14/87 [16%]; $P = 0.011$), arthralgia (19/45 [42%] vs 14/87 [16%]; $P = 0.001$), shortness of breath (29/45 [64%] vs 34/88 [39%]; $P = 0.005$) and other symptoms (34/45 [76%] vs 41/88 [47%] $P = 0.001$) were significantly more prevalent in the COVID-19–positive group. Sore throat (64/88 [73%] vs 20/44 [45%]; $P = 0.002$) and rhinorrhoea (56/88 [64%] vs 19/45 [42%]; $P = 0.018$) were more frequent in the control group. During the illness, a greater proportion of COVID-19–positive participants were unable to shower and dress
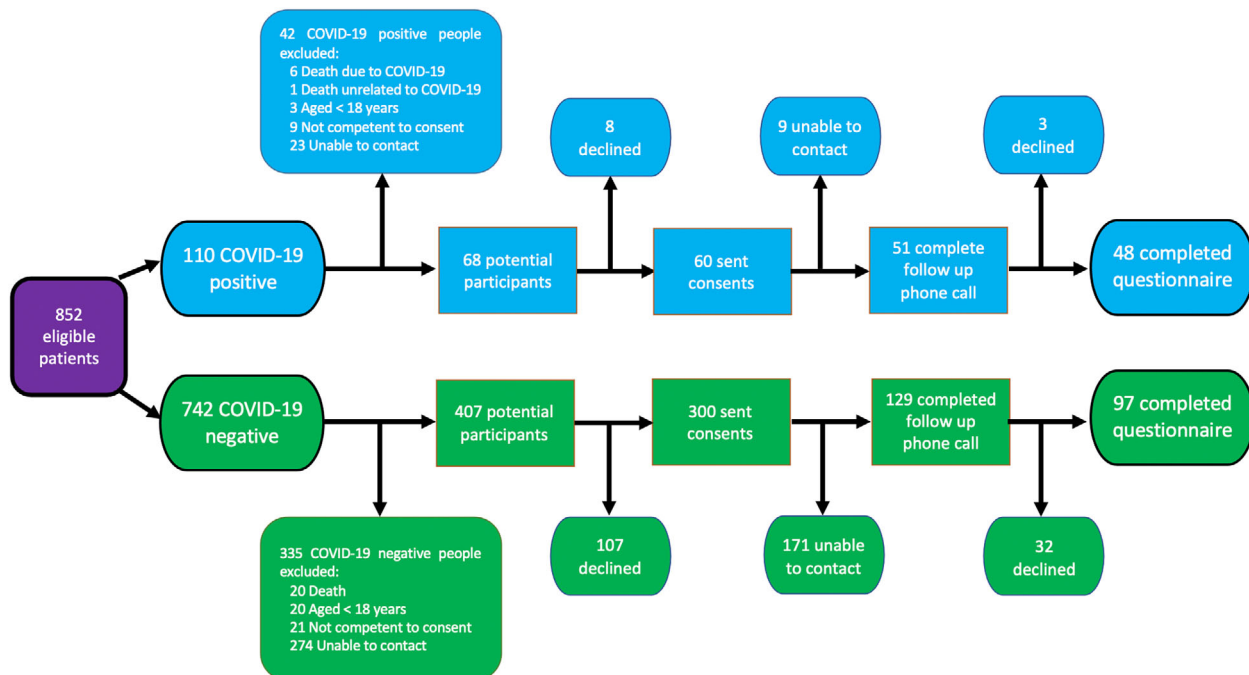

Figure 1 Flow chart of participant enrolment of patients tested for coronavirus disease 2019 (COVID-19), Canterbury, New Zealand, 2020.

Table 1 Baseline characteristics of patients tested for COVID-19, Canterbury, New Zealand, 2020

N	COVID-19 positive	COVID-19 negative	Total
	48	97	145
Age, mean (SD), (years)	43.2 (16.6)	48.6 (15.5)	46.7 (16.0)
Sex			
Women	33 (68.8)	69 (71.1)	102 (70.3)
Men	15 (31.2)	28 (28.9)	43 (29.7)
Ethnicity			
Maori	4 (8.3)	3 (3.1)	7 (4.8)
Pacific	0 (0.0)	0 (0.0)	0 (0.0)
Asian	3 (6.2)	2 (2.1)	5 (3.4)
MELAA	0 (0.0)	2 (2.1)	2 (1.4)
European	41 (85.4)	90 (92.8)	131 (90.3)
Smoking status			
Never	31 (64.6)	70 (72.2)	101 (69.7)
Ex-smoker	15 (31.2)	24 (24.7)	39 (26.9)
Current smoker	2 (4.2)	3 (3.1)	5 (3.4)
Physical activity (times per week)			
Never	3 (6.2)	2 (2.1)	5 (3.4)
<1	5 (10.4)	6 (6.2)	11 (7.6)
1	7 (14.6)	13 (13.4)	20 (13.8)
2–5	20 (41.7)	58 (59.8)	78 (53.8)
>5	13 (27.1)	18 (18.6)	31 (21.4)
NZ Dep (mean)	4.3	4.4	4.3
Comorbidities			
Anxiety and depression	17 (35.4)	35 (36.1)	52 (35.9)
Asthma	13 (27.1)	20 (20.6)	33 (22.8)
Hypertension	4 (8.3)	20 (20.6)	24 (16.6)
PTSD	6 (12.5)	15 (15.5)	21 (14.5)
Cancer	2 (4.3)	6 (6.2)	8 (5.6)
Diabetes	1 (2.1)	6 (6.2)	7 (4.8)
Chronic cardiac disease	3 (6.2)	3 (3.1)	6 (4.1)
Chronic pulmonary disease	2 (4.2)	2 (2.1)	4 (2.8)
Chronic kidney disease	0 (0.0)	4 (4.1)	4 (2.8)
Chronic liver disease	0 (0.0)	3 (3.1)	3 (2.1)
Chronic neurological disease	1 (2.1)	2 (2.1)	3 (2.1)

Values are number (percentage) unless stated otherwise.

MELAA, Middle Eastern Latin American and African; NZ Dep, New Zealand Index of Deprivation; PTSD, posttraumatic stress disorder.

themselves compared with the control group (8/45 [18%] vs 3/88 [3%]; $P = 0.004$). The contact source of their illness differed significantly ($P = 0.006$), with a predominance for foreign travel (21/45 [47%] vs 23/88 [26%]) and work as the source of infection (11/45 [24%] vs 11/88 [13%]) in the COVID-19–positive group.

Symptom persistence

A total of 34 of 45 (76%) COVID-19–positive participants had persistent symptoms compared with 17 of 97 (18%) in the control group. Figure 3 shows symptom persistence and severity. Fatigue (30/48 [63%] vs 13/97 [13%]; $P < 0.001$), dyspnoea (13/48 [27%] vs 6/97 [6%]; $P < 0.001$) and chest pain (10/48 [21%] vs 1/97 [1%]; $P < 0.001$) were persistent in the COVID-19–

positive group compared with the control group. The relative risk of developing fatigue, dyspnoea and chest pain in our COVID-19–positive group was 4.7 (95% confidence interval [CI], 2.7–8.1), 4.4 (95% CI, 1.8–10.8) and 20.2 (95% CI, 2.71–53.3) compared with those without COVID-19. The absolute risk of developing fatigue, dyspnoea and chest pain in COVID-19–positive participants was increased by 49%, 21% and 20% compared with the control group, respectively.

Time to return to normal activity levels

Fewer COVID-19–positive participants had returned to normal activity levels (35/48 [73%] vs 94/97 [97%]; $P < 0.001$) compared with control participants. Those infected with COVID-19 were 8.7 times (13/48 vs 3/97)
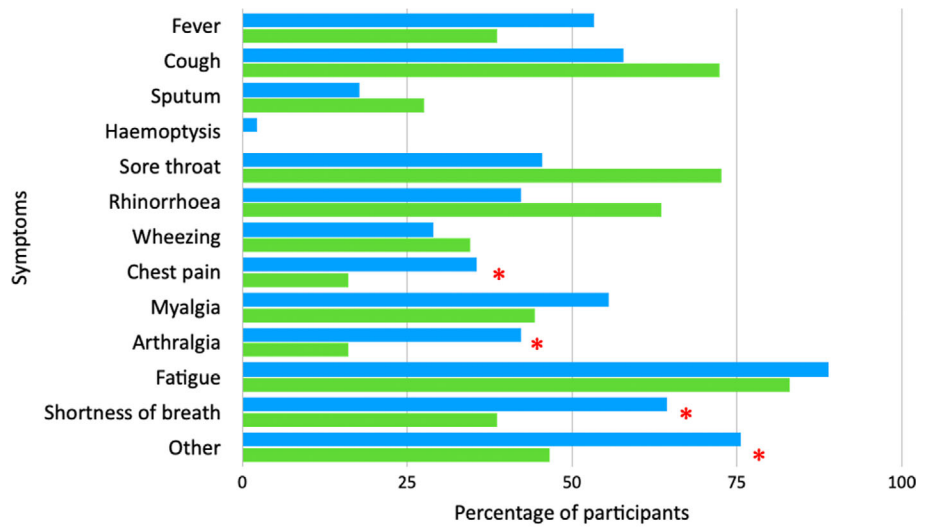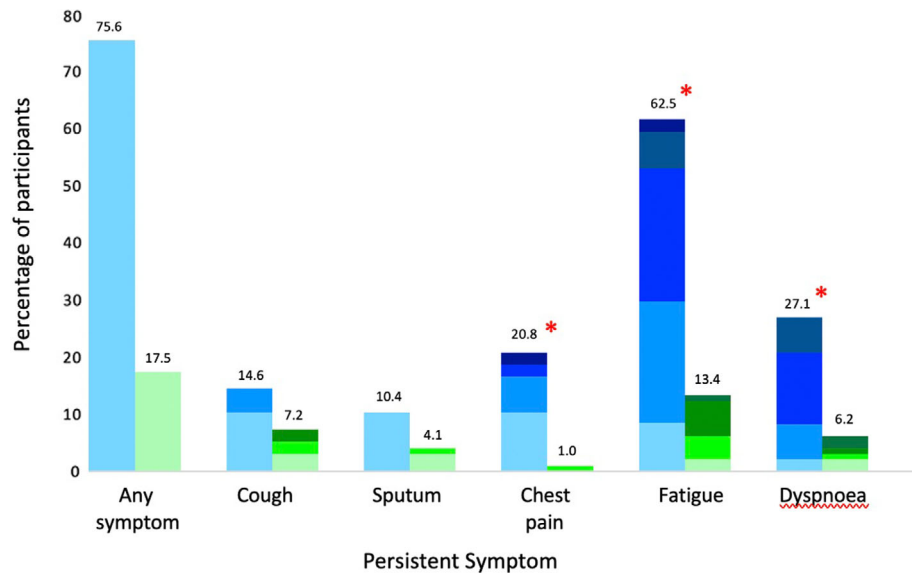
Figure 2 Initial symptoms during illness prompting coronavirus disease 2019 (COVID-19) testing, Canterbury, New Zealand, 2020. (■) COVID-19 positive and (■) COVID-19 negative.

* statistically significant

* Statistically significant

Severity scale key (1 least – 5 most severe)

Symptom severity	COVID-19 positive	COVID-19 negative
1		
2		
3		
4		
5		

Figure 3 Persistent symptoms and severity in those tested for coronavirus disease 2019 (COVID-19), Canterbury, New Zealand, 2020.
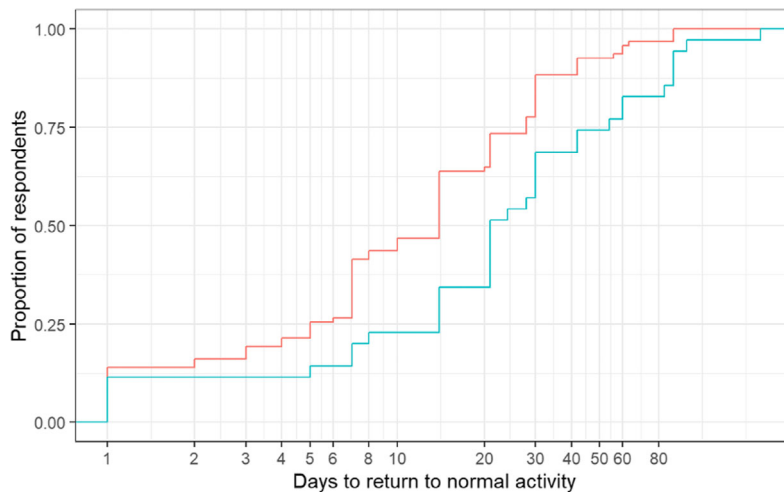
Figure 4 Time to return to normal activity levels following coronavirus disease 2019 testing, Canterbury, New Zealand, 2020. (——) FALSE and (——) TRUE.

more likely to have not returned to normal activity levels compared with those without COVID-19. After adjustment for confounders and skew in the data, the adjusted ratio COVID-19 positive/COVID-19 negative for return to normal activity levels was 0.75 ($P = 0.002$). This difference was seen in the time to return to normal activity levels, as shown in Figure 4, with a median of 21 days in those with COVID-19 and 14 days in those without COVID-19 (adjusted mean difference [MD], 2.03; $P = 0.007$).

Generalised anxiety

Levels of generalised anxiety were similar between both groups ($P = 0.747$). The combined prevalence of GAD ≥10 representing GAD was 18 of 145 (12%).

Health-related quality of life

For all eight subscales of the RAND-36 questionnaire, there was no significant difference between the groups. Physical function (MD, −5.04; $P = 0.093$), role limitation due to physical health (MD, −7.01; $P = 0.301$), bodily pain (MD, 4.61; $P = 0.255$), general health concepts (MD, −0.84; $P = 0.846$), role limitation due to emotional problems (MD, −5.19; $P = 0.347$), energy/fatigue (MD, −6.08; $P = 0.138$), emotional well-being (MD, 0.04; $P = 0.990$) and social functioning (MD, −5.71; $P = 0.110$). The lowest scores for both groups were for energy/fatigue (mean score of 60; SD ± 22) and general health concepts (mean score of 67; SD ± 24).

Discussion

This cohort study of ambulatory patients with COVID-19 showed long-term problems of fatigue, dyspnoea, chest pain and return to normal activity compared with patients presenting with similar respiratory symptoms who were COVID-19 negative. Our control group mostly represents people with acute non–-COVID-19–compatible symptoms. This facilitates comparisons of the relative risk of COVID-19 causing prolonged symptoms to a more severe degree compared with other respiratory infections.[18,19]

Our finding of approximately three quarters of COVID-19–positive participants describing persistent symptoms compares well with other studies where ongoing symptoms are reported in 27.8% to 78.6% of patients at 4 to 9 months of follow-up.[20–24] The persistence of fatigue, dyspnoea and chest pain is consistent with international studies.[6,25,26] In particular, fatigue and dyspnoea are the most prevalent enduring symptoms in both hospitalised and nonhospitalised survivors.[26,27] Although symptoms such as fatigue and chest pain are nonspecific and can occur in the general population, the high relative risks of these symptoms seen in the current study among those infected with COVID-19 suggest that high prevalence relates to infection.

We identified a wide variety of ongoing symptoms but the relatively low frequency of each symptom-limited relative risk assessment among those infected with COVID-19. Nevertheless, this highlights the diverse organ systems affected and is in keeping with existing descriptive studies of COVID-19 and other coronaviruses.[6,28,29]

Our study supports emerging data demonstrating a functional decline among survivors of mild COVID-19, including disruption in work, social and home life.[30] Existing literature identifies persistent challenges with activities of daily living with one third reporting

difficulties over 3 months.[31] The present study indicates that these challenges may extend to at least 6 months.

We found no difference in generalised anxiety levels between our groups but the presence of GAD in both groups was double prepandemic reports from the Mental Health Survey 2016/2017. This survey utilised the GAD-7 questionnaire to give a provisional diagnosis of GAD.[32] These results are similar to those seen among uninfected people during the initial COVID-19 pandemic, in NZ and internationally.[33,34]

We did not identify a difference in HrQoL in any of the eight subscales of the RAND-36 questionnaire between our groups. This is surprising given the high prevalence of persistent symptoms in those infected with COVID-19. It is also in contrast to most literature where HrQoL has been shown to be reduced compared with population norms in COVID-19 survivors.[5,35] Potential reasons for the discrepancy of our results with previous studies include a small sample size, a follow-up period 2 to 3 times longer than comparable studies[5,35] and the use of controls whose HrQoL may have been affected by non–-COVID-19 respiratory infection.[18,19]

The current study suggests that COVID-19 is associated with a higher frequency of persistent symptoms and a delayed return to normal activity levels when compared with those who tested COVID-19 negative. The characteristics of the population affected by COVID-19 and the multifaceted effects of COVID-19 infections are somewhat different from those seen in traditional rehabilitation programmes. This necessitates a strong multidisciplinary approach to rehabilitation. In addition, work is needed to identify vulnerable populations for whom rehabilitation programmes are needed. In NZ and elsewhere, indigenous and ethnic minorities have been disproportionally affected by COVID-19.[36,37] Although not addressed in the presen study, it is likely that this will also be seen with persistent COVID-19 symptoms and hence rehabilitation programmes need to be culturally appropriate.

Finally, since this study was conducted, vaccination against COVID-19 has been widely available for the eligible population in NZ. There is increasing evidence that vaccination may also reduce the risk of developing a post–COVID-19 condition in vaccinated individuals who subsequently become infected with COVID-19[38] and our findings may not be directly applicable to a vaccinated population.

Limitations

The current study has several limitations that may have influenced data interpretation. The relatively small sample size means that small differences in outcomes, particularly in HrQoL and generalised anxiety levels, may not have been detected. Although attempts were made to contact all patients diagnosed with COVID-19 in our region, we enrolled just over half of those eligible, which may have led to selection bias. There may be bias related to COVID-19 diagnosis as we did not collect data on the timing of symptom onset prior to COVID-19 testing. As virus detection is most sensitive in the first week of symptom onset[39] and serology testing was not performed, it is possible we may have misclassified a small number of participants. However, we do not expect that this will have meaningfully altered our results as previous work in NZ has indicated very few cases undetected by PCR even among those at high epidemiological risk.[10] The mean follow-up time between the groups differed and this may have exaggerated the apparent differences. Even so, we consider a decline in symptoms between 8 and 11 months in patients without COVID-19 unlikely to explain the substantial observed difference.

The external validity of the current study was limited by the fact that it was from one region of NZ. Our study included a high proportion of people identifying as being of NZ European ethnicity. This reflects the local epidemiology of COVID-19 during the study period. Furthermore, quality of life and mental health may have been affected by local variations in health services or pandemic-related social restrictions. Finally, the low risk of reinfection may influence symptom persistence.

Conclusion

This study demonstrates a high prevalence of persistent symptoms such as fatigue, dyspnoea and chest pain at 8 months and prolonged return to normal activity levels in those infected with COVID-19. This highlights the multifaceted and extended symptom burden caused by infection with COVID-19 and the need for a COVID-19–-specific holistic approach to rehabilitation of a relatively young patient group.

Acknowledgements

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Supporting Information

Additional supporting information may be found in the online version of this article at the publisher's web-site:

Appendix S1: Case Report Form
Appendix S2: STROBE Checklist