COVID-19 SPECIAL PUBLIC HEALTH SURVEILLANCE BULLETIN

NATIONAL INSTITUTE FOR COMMUNICABLE DISEASES
Division of the National Health Laboratory Service

VOLUME 19. SUPPLEMENTARY ISSUE 3 | 04 AUGUST 2021

FOREWORD

The third COVID-19 wave in South Africa has been dominated by the SARS-CoV-2 Delta variant, evidently the most infectious variant to date. In addition to the immediate illness caused by the initial infection, there is increasing evidence of and concern for the long-term effects of a SARS-CoV-2 infection post recovery. The data presented here detail new, returning or ongoing health problems more than four weeks after the initial infection as experienced by COVID-19 survivors who suffered acute illness and were hospitalized. The majority of patients unfortunately reported persistent symptoms at one month following hospital discharge, often impacting on their functional and occupational status. This condition is now referred to as Long Covid.

We trust you will find this important information useful as we grapple with the SARS-CoV-2 pandemic, and we encourage all eligible persons to get vaccinated as soon as possible as per National Department of Health directives.

Prof Basil Brooke - Editor

LONG COVID IN SOUTH AFRICA: FINDINGS FROM A LONGITUDINAL COHORT OF PATIENTS AT ONE MONTH AFTER HOSPITALISATION WITH SARS-CoV-2, USING AN ISARIC MULTI-COUNTRY PROTOCOL

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SUMMARY

Long COVID refers to a wide range of new, returning, or ongoing health problems experienced by COVID-19 survivors more than four weeks after initial infection with the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The aim of this study was to characterize physical and psychosocial sequelae in patients one month after discharge from hospital, and estimate the prevalence of and risk factors associated with Long COVID. In this prospective cohort study using an International Severe Acute Respiratory and emerging Infection Consortium (ISARIC) multi-country protocol, patients ≥18 years who had been hospitalized with confirmed SARS-CoV-2 between December 2020 and April 2021 underwent telephonic follow-up one month after hospital discharge. Baseline sociodemographic, health status and clinical data for the period of hospitalisation were retrieved from a national hospital surveillance system. All patients were interviewed at one month from hospital discharge with a standardised questionnaire for the evaluation of symptoms, functional status, health-related quality of life and occupational status. Multivariable logistic regression models were used to determine factors associated with persistent outcomes. In total, 1,448 of 61,038 eligible previously hospitalised COVID-19 survivors were enrolled. Patients had a median age of 51 (IQR 40 – 61) years and 784 (54.14%) were women. At one-month follow-up, 1,124 (82.2%) patients reported one or more persistent symptom(s). The most common symptoms reported were fatigue (69.8%), shortness of breath (32.0%), headaches

(17.5%), weakness in arms or legs (17.5%) and confusion or lack of concentration (16.0%). On multivariable analysis, factors associated with new or persistent symptoms following acute COVID-19 illness were ICU admission [adjusted odds ratio (aOR) 2.95; 95% Confidence Interval (CI) 1.02-2.27], and the presence of 1-3 acute symptoms [aOR 3.26; 95% CI 1.74-6.08] and ≥4 acute symptoms [aOR 5.83; 95% CI 2.83-9.75] compared to no symptoms. There were 128 (8.9%) patients who reported a change in occupational status after the acute illness, 85 (69.1%) of whom attributed this to Long COVID. It is concluded that the majority of patients reported persistent symptoms at one month from hospital discharge and that there is a significant impact of Long COVID on functional and occupational status. The large burden of Long COVID identified in this study should be addressed through development of clinical guidelines, establishment of multidisciplinary health services, training of health care workers and provision of information and support to patients who suffer from this condition.

INTRODUCTION

Since its emergence, the severe acute respiratory syndrome virus 2 (SARS-CoV-2) resulted in 191,148,056 confirmed infections and 4,109,303 deaths worldwide as of 21 July 2021.[1] South Africa reported 2,327,472 laboratory-confirmed cases and 68,192 deaths as of 21 July 2021.[2]

While there is a greater understanding about acute coronavirus diseases 2019 (COVID-19) and risk factors for severity and mortality, less is known about the long-term complications that may arise in patients infected with SARS-CoV-2. There is currently much debate surrounding the most appropriate terminology and clinical criteria, with many different names proposed including *"Post-Acute Sequelae of SARS-CoV-2 Infection (PASC)"* or *"Post COVID-19 Condition"*. Patients and advocacy groups have preferred "Long COVID" and so we have adopted the term 'Long COVID' for the purposes of this manuscript until a universally accepted name and definition is produced. Although the formal World Health Organization (WHO) definition is currently under review, the US Centers for Disease Prevention and Control (CDC) describes post-COVID conditions as a wide range of new, returning or ongoing health problems people can experience four or more weeks after SARS-CoV-2 infection.[3]

Cases of persistent symptoms were described as early as May 2020, and our understanding of the condition continues to improve through increasing numbers of published studies. From these studies to date, between 29% and 93% of patients may report persistent symptoms after one to seven months following acute COVID-19.[4-17] The high degree of variability in the reported prevalence of the condition in previous studies may result from methodological inconsistencies between them, the absence of a well-established definition for the condition, differences in the societal attitude to post-viral illness and differences in the local epidemiology of acute COVID-19 at the study sites.[18] Currently, there is no published data on Long COVID in South Africa and Africa as a whole. As part of a multi-country study coordinated by the International Severe Acute Respiratory and emerging Infection Consortium (ISARIC), we established a prospective cohort of SARS-CoV-2 infected patients for serial follow-up after hospitalisation. The aim of this study was to determine the prevalence of and risk factors for Long COVID in South Africa.

METHODS

Study design

This was a prospective, observational cohort study. We used an ISARIC open-access tool that can be locally adapted for the follow-up of patients with COVID-19, with the aim to facilitate standardized data collection globally and enable pooled analysis.[19]

Study population

The DATCOV national hospital surveillance system developed by the National Institute for Communicable Diseases (NICD) and the National Department of Health (NDoH) was used to identify SARS-CoV-2-infected hospitalised patients for follow-up, and to obtain baseline patient data on demographics, comorbidities and hospital admission to compare associations with long-term sequelae. The study population included individuals hospitalised in the public and private health sectors and from all provinces, with a positive reverse transcriptase polymerase chain reaction (RT-PCR) assay or rapid antigen test for SARS-CoV-2, admitted to a hospital for one day or longer, and discharged alive between the period 1 December 2020 to 27 April 2021. Patients were eligible for inclusion irrespective of reason for admission including COVID-19 symptoms, isolation, incidental finding on admission for other reason, or nosocomial infection with SARS-CoV-2, and therefore included both those who were diagnosed with COVID-19 and those who were asymptomatic. Patients 18 years and older with capacity to consent to participate in the study were included. Of all eligible discharged, contactable patients, a random selection of patients was contacted for participation in this follow-up study. Randomisation was done through selection of participants using a computer-generated list of eligible participants.

Measurements instruments

A standardized case reporting form (CRF) developed by ISARIC was used for demographic variables, COVID-19 vaccination status, symptoms during hospitalisation, current health status, acute COVID-19 complications, new or persistent symptoms, lifestyle and socioeconomic variables. The CRF contains validated tools to establish quality of life (measured by EQ-5D-5L), dyspnoea (assessed using modified MRC dyspnoea scale) and difficulties in functioning (UN/Washington disability score). Changes in disability, breathlessness and health state (EQ5D index) were calculated by comparing patients before SARS-CoV-2 infection to the one-month assessment. The Washington Group Short Set on Functioning (WG-SS) questions[20] were used to measure changes in short term disability (seeing, hearing, walking, remembering, communication and self-care).

Data collection

Follow-up surveys were conducted by telephonic interview at one month, with additional follow-up scheduled at 3, 6 and 12 months following discharge from hospital. Verbal consent was obtained and recorded and, where possible, interviews were conducted in the language of the patients' choice.

Statistical analysis

Data was entered and stored on a secure online REDCap repository hosted by the University of Oxford on behalf of ISARIC. Descriptive statistics such as frequencies and percentages were used for summarising categorical data, and continuous data were expressed using medians and interquartile ranges (IQR). Frequency distribution tables and graphs were used to describe demographics, prevalence of symptoms, prevalence of comorbidities and changes in health and occupational status. Five multivariable logistic regression models were implemented to assess factors associated with the following outcomes: 1) new or persistent symptoms, 2) self-reported non-recovery, 3) new or worsening breathlessness, 4) new or worsening disability, and 5) anxiety/depression. The outcome variables were obtained as follows:

- New or persistent symptoms: obtained from the number of persistent symptoms the patients have. Those who did not have any symptoms were classified as "No persistent symptoms" and those with 1 or more symptoms were classified as "New or persistent symptoms".
- Self-reported non-recovery: obtained from the question "Do you feel fully recovered from your COVID-19?". The five possible responses to this question were collapsed to two categories in order to implement the logistic regression. Responses "Agree", "Slightly agree" or "Strongly agree" were classified as "Recovered". Responses of "Disagree" or "Slightly disagree" were classified as "Not recovered", whilst "Neither agree or disagree" was treated as neutral and excluded from the analysis.
- New or worsening breathlessness: obtained from the question "How breathless you feel TODAY and how breathless you felt BEFORE your COVID-19 illness". Responses were coded from a value of 1 to 5 where "Not troubled by breathlessness except on strenuous exercise" = 1; "Short of breath when hurrying or when walking up a slight hill" = 2; Walk slower than most people of my age because of breathlessness, or have to stop for breath when walking at own pace" = 3; "Stop for breath after walking 100 yards/ 90-100 metres, or after a few minutes on level ground" = 4; and "Too breathless to leave the house, or breathless when dressing/undressing" = 5. The output obtained from difference between breathlessness before and breathlessness after (breathless before – breathless after) was classified into two categories. A difference greater or equal to zero was classified as "No new or worsening breathlessness" = 0 (breathing better or no change in breathlessness) and a difference of less than zero was classified as "New or worsening breathlessness" = 1.
- New/worse disability: constructed from the Washington short set tool[20] which includes questions on changes in vision, hearing, mobility, remembering, self-care and communication (comparing before and after contracting COVID-19). Responses to these questions were coded from 1 to 4, where "No - no difficulty" = 1, "Yes - some difficulty" = 2, "Yes - a lot of difficulty" = 3, and "Cannot do at all" = 4. Change in any disability was classified as "Better" = 1, "No Change" = 2 and "Worse/New disability" = 3. The outcome variable "New/worse disability" was constructed if worse change or a new disability was noted in any one of the stated Washington disability categories ("No disability" = 0 and "At least one disability" = 1).
- Anxiety/Depression: constructed from the EuroQol Research Foundation EQ-5D™ tool v2.1.[21] The Anxiety/Depression question was coded as follows: 1 = "I am not anxious or depressed", 2 = "I am slightly anxious or depressed", 3 = "I am moderately anxious or depressed" 4 = "I am severely

anxious or depressed" and 5 = "I am extremely anxious or depressed". The responses were collapsed in two categories, "no anxiety/ depression" (option 1) and anxiety/ depression" (options 2 – 5). The outcome variable "Anxiety/ Depression" was constructed if there was any level of anxiety or depression reported ("No anxiety/ depression" =0, "Anxiety/ Depression" = 1).

Predictor variables included in the model were age, sex, race, health sector where patient was admitted (public or private), presence of individual comorbid conditions (asthma, diabetes, hypertension, chronic cardiac disease, chronic kidney disease, malignancy, tuberculosis, HIV and obesity), number of symptoms during acute infection, treatment in ICU and treatment with oxygen or ventilation. For each multivariable model, variables that were significant at $p<0.2$ in the univariate analysis were included for multivariate analysis. Some variables such as age, sex and race were included in the model *a priori* on the basis of clinical plausibility. Manual backward elimination was implemented and the final model selection was guided by minimisation of the Akaike information criterion (AIC) or Bayesian information criterion (BIC). Statistical significance for the multivariable analysis was assessed at $p<0.05$. Statistical analyses were performed using Stata software version 16 (StataCorp Limited, College Station, Texas, USA).

Ethics and approvals

The study was approved by the University of the Witwatersrand Human Research Ethics Committee (HREC M201150). Approvals were obtained from all provinces via the National Health Research Database (NHRD).

RESULTS

Study population

Of the 117,573 COVID-19 admissions reported to DATCOV, 61,038 were eligible for inclusion and 1,448 patients were randomly enrolled in the study (Figure 1). The patients who were enrolled and those that were not enrolled in the study had similar characteristics with respect to age, sex and the distribution of comorbidities. There was, however, a higher proportion of participants enrolled who had been admitted in the private health sector (66.0%) compared to the public sector, and there were higher proportions recruited among patients aged 40-64 years, and those treated in ICU and requiring supplemental oxygen. A lower proportion of patients were recruited from Western Cape Province (Supplementary Table 1).

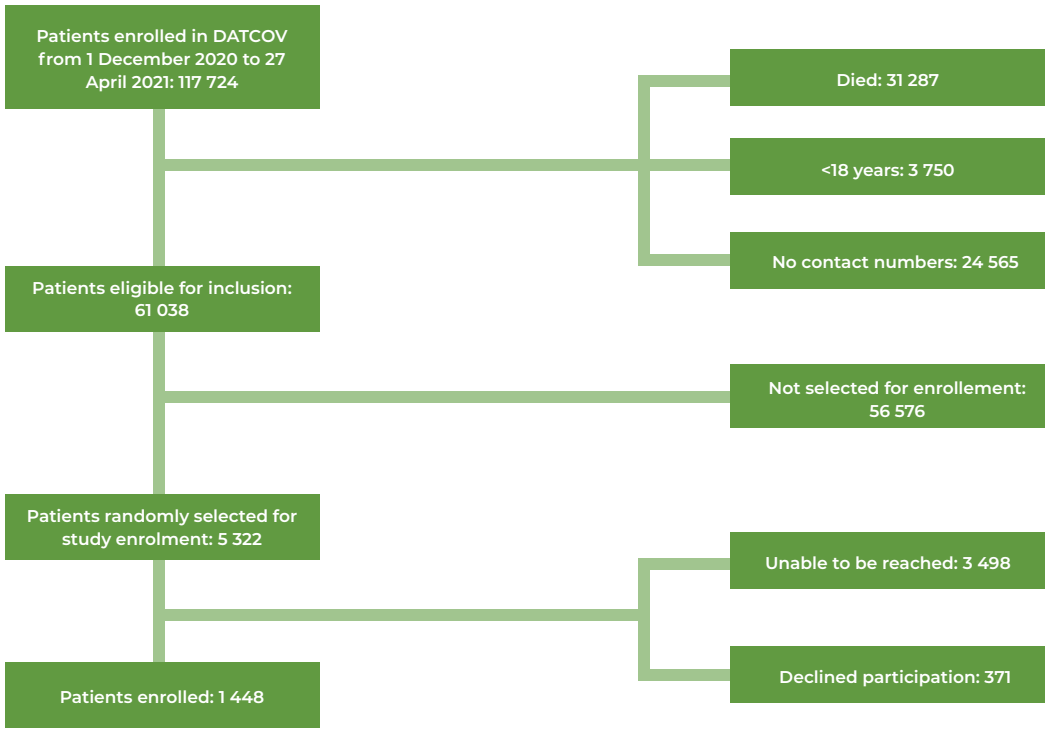

Figure 1. Study population based on processes and criteria for inclusion, NICD Long COVID Study, South Africa, 1 December 2020 - 27 April 2021.

Socio-demographic characteristics

The median time between hospital discharge and telephonic follow-up was 28 days (IQR=28-29). Of the 1,448 patients recruited, 784 (54.1%) were female. Among patients aged <40 years (n=349; 24.1%), there were 223 (28.4%) females and 126 (18.9%) males, and among patients aged >40 years (n=1,098; 75.8%) there were 560 (71.4%) females and 538 (81.0%) males. The median age of the patients was 51 years [interquartile range (IQR) 40 -61] and most patients were aged 40-64 years (n=857; 59.2%). There were 866 (59.8%) patients who were black, 321 (22.2%) white, 119 (8.2%) mixed race and 96 (6.6%) of Indian ancestry (Table 1). Approximately 932 (64.4%) of the patients reported having at least one comorbid condition. The most commonly self-reported comorbidities were hypertension (n=489; 33.8%), diabetes (n=308; 21.3%), obesity (n=294; 20.3%) and HIV (n=101; 7.0%). There were 493 (34.0%) patients hospitalized in the public sector. The majority (n=795; 54.9%) of patients required supplemental oxygen therapy during hospitalisation, whilst 406 (28.0%) required admission to an intensive care unit (ICU) and 85 (5.9%) required invasive mechanical ventilation (Table 1).

Table 1. Baseline and hospitalisation characteristics, NICD Long COVID Study, South Africa, 1 December 2020 - 27 April 2021.

Characteristic	Female n (%)	Male n (%)	Total n (%)
	784 (54.14%)	664 (45.86%)	1448
Median age (IQR)	50 [38 - 60]	52.5 [43 - 62]	51 [40 - 61]
Age group (years)			
<40 years	223 (28.4)	126 (18.9)	349 (24.1)
40-64 years	445 (56.8)	412 (62.1)	857 (59.2)
≥65 years	115 (14.7)	126 (19.0)	241 (16.6)
Unknown	1 (0.1)	0	1 (0.1)
Race			
Black	516 (56.8)	350 (52.7)	866 (59.8)
White	139 (17.7)	182 (27.4)	321 (22.2)
Mixed race	60 (7.7)	59 (8.9)	119 (8.2)
Indian	51 (6.5)	45 (6.8)	96 (6.6)
Other/Asian	2 (0.3)	0	2 (0.1)
Unknown	16 (2.0)	28 (4.2)	44 (3.0)
Number of comorbidities			
No comorbidities	272 (34.7)	244 (36.8)	516 (35.6)
1 comorbidity	260 (33.2)	230 (34.6)	490 (33.8)
2 comorbidities	185 (23.6)	115 (17.3)	300 (20.7)
≥ 3 comorbidities	67 (8.6)	75 (11.3)	142 (9.8)
Comorbidity			
High blood pressure	258 (32.91)	231 (34.79)	489 (33.77)
Calculated obesity	160 (20.41)	134 (20.18)	294 (20.30)
Diabetes – Type II	127 (16.20)	127 (19.13)	254 (17.54)
Other	91 (11.61)	75 (11.30)	166 (11.46)
HIV	77 (9.82)	24 (3.61)	101 (6.98)
Heart disease	24 (3.06)	38 (5.72)	62 (4.28)
Asthma	49 (6.25)	15 (2.26)	64 (4.42)

Diabetes- Type I	32 (4.08)	22 (3.31)	54 (3.73)
Kidney disease	6 (0.77)	10 (1.51)	16 (1.10)
Cancer	11 (1.40)	7 (1.05)	18 (1.24)
Rheumatological disorder	9 (1.15)	4 (0.60)	13 (0.90)
Neurological condition	5 (0.64)	7 (1.05)	12 (0.83)
Chronic lung disease	5 (0.64)	6 (0.90)	11 (0.76)
Dementia	2 (0.26)	2 (0.30)	4 (0.28)
Liver disease	3 (0.38)	0	3 (0.21)
Blood disorder	1 (0.13)	1 (0.15)	2 (0.14)
Asplenia	0	0	0
Province			
Eastern Cape	68 (8.67)	62 (9.34)	130 (8.98)
Free State	51 (6.51)	20 (3.01)	71 (4.90)
Gauteng	237 (30.23)	213 (32.08)	450 (31.08)
KwaZulu-Natal	162 (20.66)	125 (18.83)	287 (19.82)
Limpopo	15 (1.91)	18 (2.71)	33 (2.28)
Mpumalanga	63 (8.04)	44 (6.63)	107 (7.39)
North West	68 (8.67)	52 (7.83)	120 (8.29)
Northern Cape	16 (2.04)	17 (2.56)	33 (2.28)
Western Cape	104 (13.27)	113 (17.02)	217 (14.99)
Sector			
Private	482 (61.48)	473 (71.23)	955 (65.95)
Public	302 (38.52)	191 (28.77)	493 (34.05)
Required admission to ICU	198 (25.3)	208 (31.3)	406 (28.0)
Required supplemental oxygen	416 (53.1)	379 (57.1)	795 (54.9)
Required invasive mechanical ventilation	35 (4.5)	50 (7.5)	85 (5.9)

Half of the patients (n=713; 49.2%) reported that they had consulted with a general practitioner or local clinic subsequent to their hospital discharge, and 75 (5.2%) patients were re-admitted to hospital. Weight loss was reported by 932 (64.4%) of patients. Only 13 (0.9%) patients had been vaccinated against COVID-19 at the time of follow-up.

Acute and persistent symptoms

There were 1,258 (86.9%) patients who reported symptoms during the acute phase of their COVID-19 illness, while the remaining patients were asymptomatic and required hospital admission for reasons other than COVID-19. The median number of acute symptoms reported was 4 (IQR 2 – 6). Among the patients reporting acute symptoms, 125 (8.7%) reported one, 182 (12.6%) reported two, 202 (14.0%) reported three and 748 (51.7%) reported four or more. The most commonly reported symptoms on admission during the acute COVID-19 illness were fatigue/malaise (57.0%), shortness of breath (48.8%), fever (44.8%), cough (42.3%), myalgia (32.7%) and headaches (32.3%).

One month after hospital discharge, 1,187 (82.0%) patients reported new or persistent symptoms. Among the patients reporting persistent symptoms, 317 (21.9%) reported one, 235 (16.2%) reported two, 161 (11.1%) reported three and 474 (32.73%) reported four or more. The most commonly reported symptoms at one month post-hospital discharge were fatigue (69.8%), shortness of breath (32.0%), headaches (17.5%), weakness in arms or legs (17.5%) and confusion or lack of concentration (16.0%) (Figure 2).

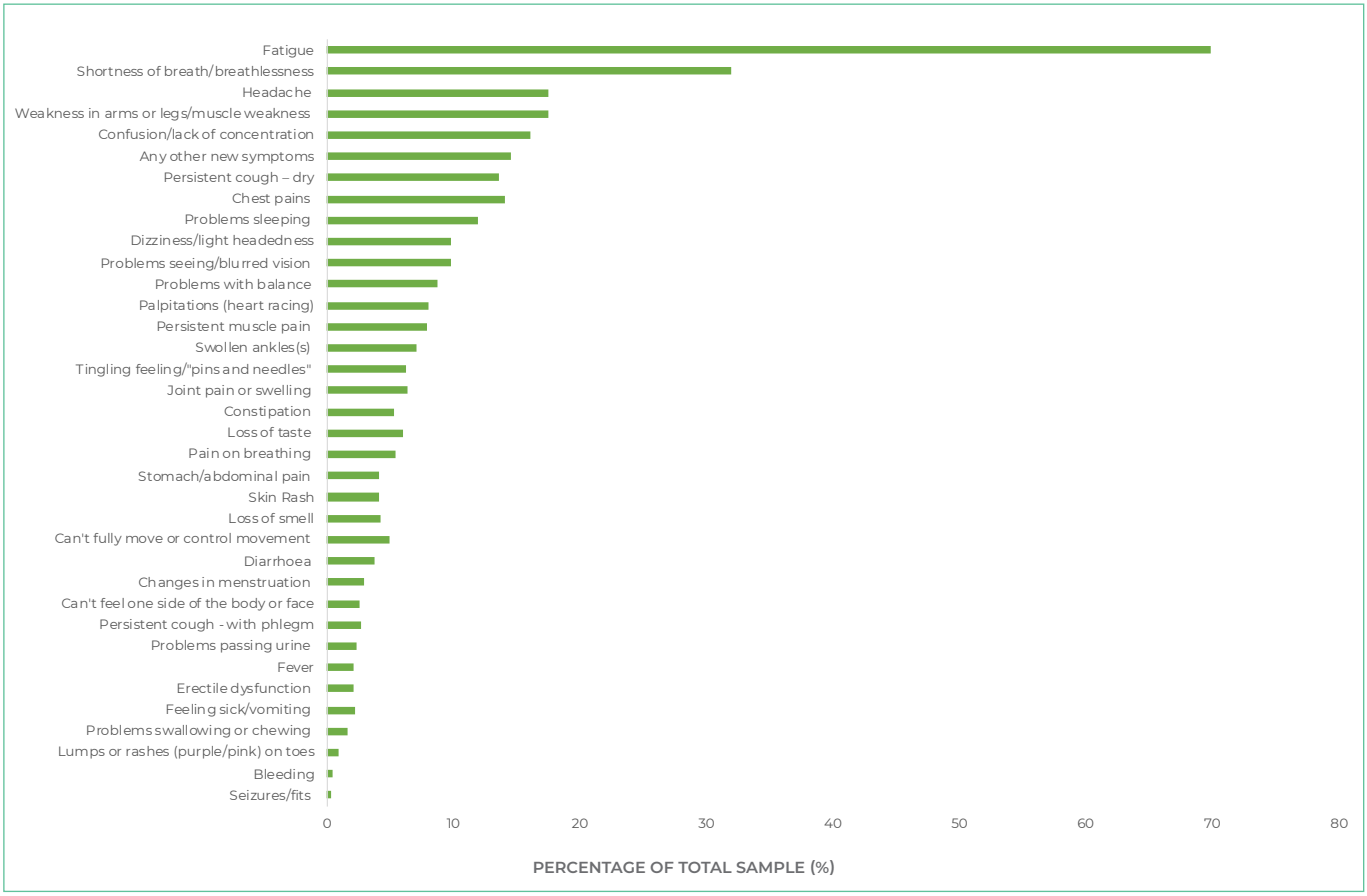

Figure 2. Post-COVID symptoms reported in the last 7 days at one month post-discharge from hospital, NICD Long COVID Study, South Africa, 1 December 2020 - 27 April 2021, N=1,448.

Acute versus new or persistent symptoms

From acute infection to one month following hospital discharge, there was a decrease in the number of patients reporting acute infection symptoms (fever, cough, myalgia, headache, chest pains etc.) but there was a significant increase in patients who reported fatigue/malaise (p<0.001) and skin rashes (p<0.001) (Figure 3).

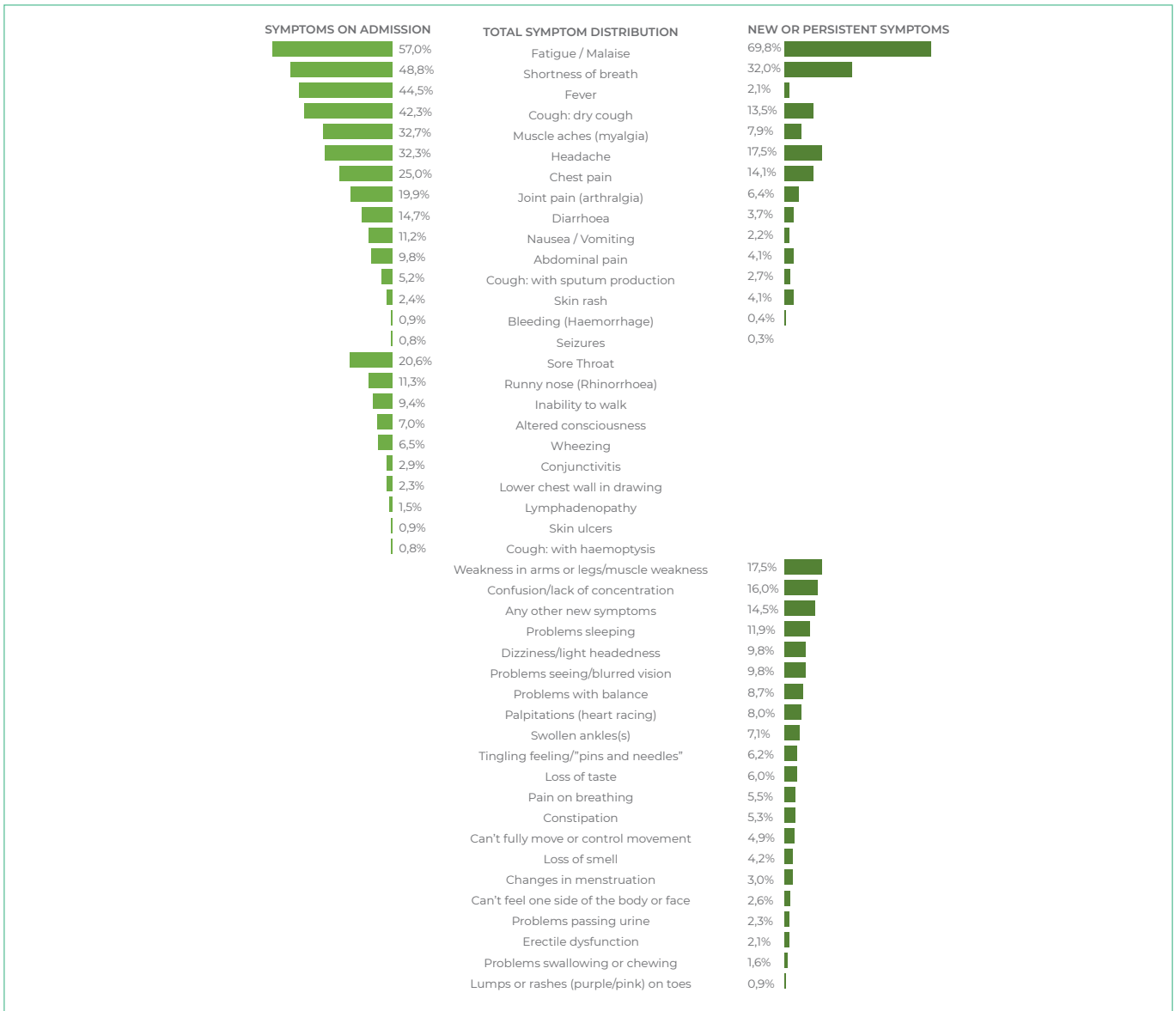

Figure 3. Acute symptoms during hospitalisation versus persistent symptoms at one month follow-up, NICD Long COVID Study, South Africa, 1 December 2020 - 27 April 2021. The second series of symptoms were only surveyed during acute infection and the third series of symptoms were only surveyed at one month post-discharge from hospital.

Based on a scale of 1 – 10, the median self-perceived general health score was 9 IQR [7 - 10] at one month post discharge from hospital. Most (n=1,078; 74.4%) patients reported a health score of ≥8 and 123 (8.5%) reported perceived health score ≤5 (Figure 4).

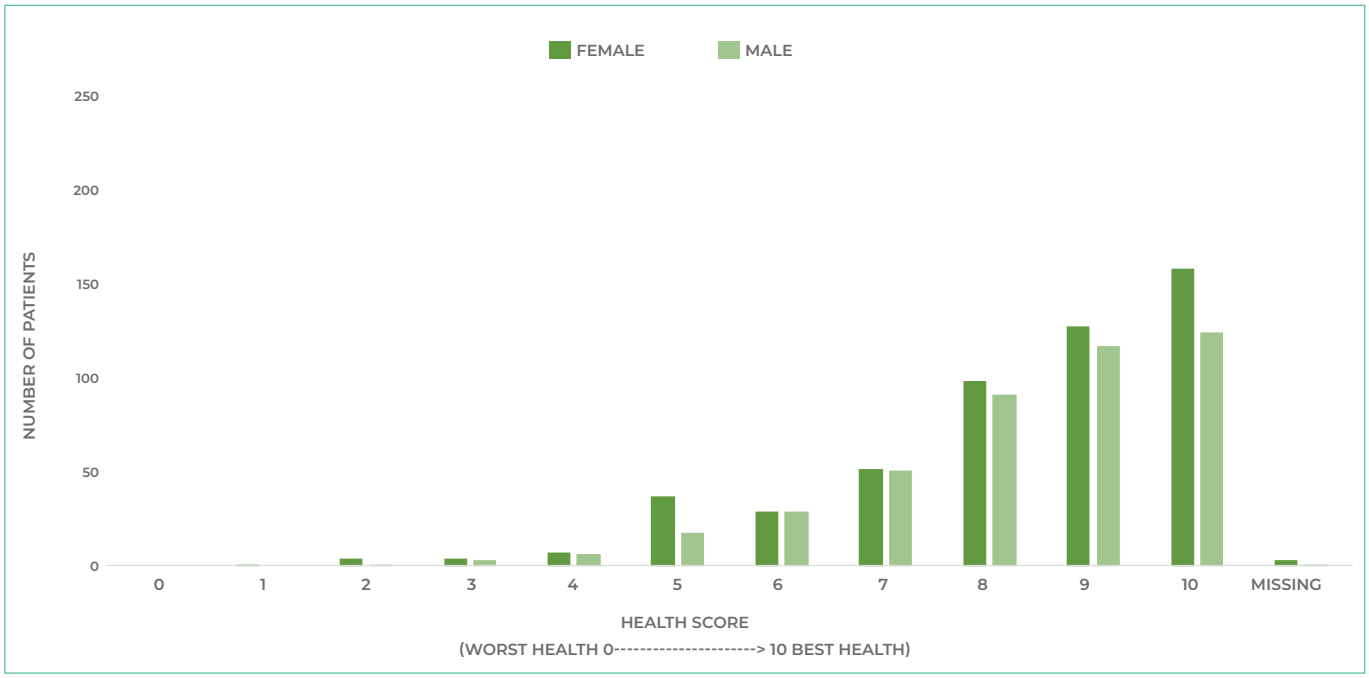

Figure 4. Self-perceived health score at one month post-discharge from hospital, NICD Long COVID Study, South Africa, 1 December 2020 - 27 April 2021, N=1,448.

Enrolled patients were asked to rate their level of fatigue from 0 (no fatigue) to 10 (worst possible fatigue). The majority of patients reported no fatigue and 508 (35.1%) reported a fatigue rating ≥5 at one month post discharged from hospital (Figure 5).

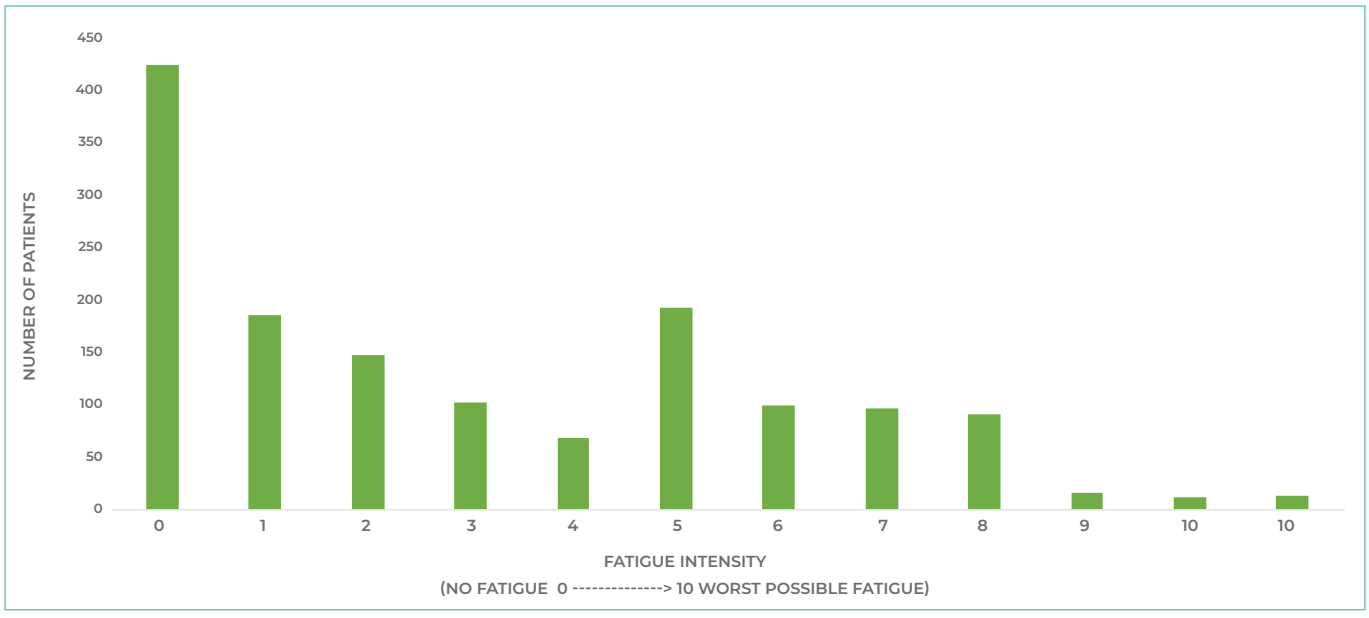

Figure 5. Fatigue intensity among participants (N=1,448) at one month post-discharge from hospital, NICD Long COVID Study, South Africa, 1 December 2020 - 27 April 2021, N=1,448.

Patients were asked to grade their current level of experienced dyspnoea on the modified Medical Research Council (mMRC) Dyspnoea Scale. The proportion of patients reporting mMRC dyspnoea grade 1 decreased from 1,347 (93.0%) before COVID illness to 908 (62.7%) at one month following COVID illness; grade 2 increased from 28 (1.9%) to 262 (18.1%); grade 3 increased from 13 (0.9%) to 137 (9.5%); grade 4 increased from 2 (0.1%) to 93 (6.4%); and grade 5 increased from 3 (0.2%) to 29 (2.0%) (Figure 6).

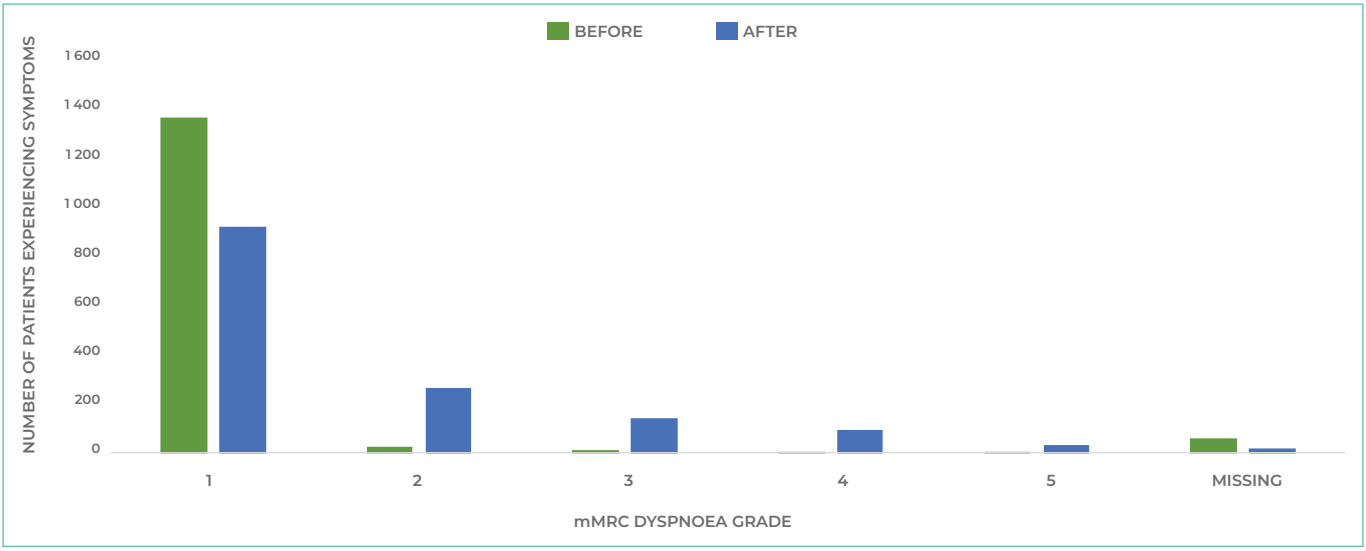

Figure 6. Percentage of patients experiencing shortness of breath prior to acute COVID-19 (green) and one month following discharge from acute illness (blue), NICD Long COVID Study, South Africa, 1 December 2020 - 27 April 2021, N=1,448.

Key
1 - Not troubled by breathlessness except on strenuous exercise
2 - Short of breath when hurrying or when walking up a slight hill
3 - Walked slower than most people of my age because of breathlessness, or had to stop for breath when walking at own pace
4 - Stopped for breath after walking 100 yards/ 90-100 meters, or after a few minutes on level ground
5 - Too breathless to leave the house, or breathless when dressing/undressing

Impact of persistent symptoms on daily living

Most patients reported no problems with mobility, self-care, usual activities, pain/discomfort or anxiety/depression. However, 379 (26.2%) reported problems with mobility, which was similar for females and males. There were 153 (10.3%) patients who reported problems with self-care, which was similar for females and males. There were 402 (27.8%) patients who reported problems with performing their usual activities including work, study, housework and family or leisure activities, which was similar for females and males.

There were 113 (7.8%) patients who experienced moderate, severe or extreme pain. More females (n=190; 24.2%) reported pain than males (n=127; 19.1%). There were 214 (14.8%) patients who reported slight anxiety/depression, 130 (9.0%) reported moderate anxiety/depression and 40 (2.8%) reported having severe to extreme anxiety/depression. More females (269, 34.3%) than males (147, 22.1%) reported having anxiety/depression (Table 2).

Table 2. Impact of persistent symptoms on activities of daily living measured using the EuroQol Research Foundation EQ-5D™ tool v2.1, NICD Long COVID Study, South Africa, 1 December 2020 - 27 April 2021, N=1,448.

Activities of Daily Living	Female n (%)		Male n (%)		Total n (%)	
	Number	Percentage	Number	Percentage	Number	Percentage
	784	54%	664	46%	1448	100%
Mobility						
No Problems	575	73%	493	74%	1068	74%
Slight Problems	112	14%	104	16%	216	15%
Moderate Problems	65	8%	45	7%	110	8%
Severe Problems	18	2%	10	2%	28	2%
Unable	14	2%	11	2%	25	2%
Missing	0	0%	1	0%	1	0%
Self-Care						
No Problems	698	89%	596	90%	1294	89%
Slight Problems	52	7%	43	6%	95	7%
Moderate Problems	16	2%	11	2%	27	2%
Severe Problems	7	1%	5	1%	12	1%
Unable	11	1%	8	1%	19	1%
Missing	0	0%	1	0%	1	0%
Usual Activities						
No Problems	560	71%	482	73%	1042	72%
Slight Problems	131	17%	107	16%	238	16%
Moderate Problems	63	8%	44	7%	107	7%
Severe Problems	13	2%	15	2%	28	2%
Unable	15	2%	14	2%	29	2%
Missing	2	0%	2	0%	4	0%
Pain / Discomfort						
No Pain	594	76%	532	80%	1126	78%
Slight Pain	121	15%	88	13%	209	14%
Moderate Pain	51	7%	31	5%	82	6%
Severe Pain	16	2%	7	1%	23	2%
Extreme Pain	2	0%	1	0%	3	0%
Missing	0	0%	5	1%	5	0%
Anxiety/ Depression						
No Anxiety/Depression	513	65%	513	77%	1026	71%
Slight Anxiety/Depression	133	17%	81	12%	214	15%
Moderate Anxiety/Depression	84	11%	46	7%	130	9%
Severe Anxiety/Depression	25	3%	15	2%	40	3%
Extreme Anxiety/Depression	27	3%	5	1%	32	2%
Missing	2	0%	4	1%	6	0%

Most patients reported no change in ability to see, hear, walk, remember and self-care (Figure 7). However, 302 (20.9%), 250 (17.3%) and 125 (8.6%) reported worsening in walking, remembering and seeing, respectively.

Figure 7. Changes in activities of daily living measured using the WG-SS Tool, NICD Long COVID Study, South Africa, 1 December 2020 - 27 April 2021, N=1,448.

Occupation

Among all patients, 802 (55.4%) were working full-time before contracting COVID-19, while 276 (19.1%), 206 (14.2%) and 58 (4.0%) were retired, unemployed or working part-time respectively. There were 128 (8.9%) patients who reported a change in occupation after COVID-19 acute infection. Of these, 85 (69.1%) attributed the changes in occupation to the effects of Long COVID.

Lifestyle changes

Patients were surveyed about their social habits before and after COVID-19 diagnosis. It was noted that 57 (3.9%) were smoking less, 293 (20.2%) were consuming less alcohol, 769 (53.1%) were eating healthier food, 331 (22.9%) were exercising more whilst 486 (33.6%) were exercising less (Table 3).

Table 3. Lifestyle changes following COVID-19 illness, NICD Long COVID Study, South Africa, 1 December 2020 - 27 April 2021.

	Smoking N (%)	Drinking alcohol N (%)	Eating healthy food N (%)	Physical activity N (%)
I do this more often	19 (1.3)	17 (1.2)	769 (53.1)	331 (22.9)
I do this less often	57 (3.9)	293 (20.2)	86 (5.9)	486 (33.6)
No difference	235 (16.2)	319 (22.0)	583 (40.3)	609 (42.1)
I did not do this before COVID-19	1133 (78.3)	812 (56.1)	-	-
Missing	4 (0.3)	7 (0.5)	10 (0.7)	22 (1.5)

Factors associated with Long COVID

On multivariable analysis, factors associated with new or persistent symptoms were ICU admission [aOR 2.95; 95% CI 1.60-5.43], and presence of 1-3 symptoms [aOR 3.26; 95% CI 1.74-6.08] and ≥4 symptoms [aOR 5.25; 95% CI (2.83-9.75] compared to 0 symptoms during acute COVID-19 illness (Table 4).

Factors associated with self-reported non-recovery were pre-existing obesity [aOR 1.52; 95% CI 1.02-2.27] and the presence of ≥4 symptoms [aOR 4.38; 95% CI 1.52-12.59] compared to 0 symptoms during acute COVID-19 illness. Black Africans were less likely to report non-recovery [aOR 0.49; 95% CI 0.30-0.79] (Table 4).

Factors associated with persistent breathlessness following acute COVID-19 illness were admission to ICU [aOR 3.45; 95% CI 2.43-4.90]; pre-existing asthma [aOR 2.12; 95% CI 1.01-4.48] and obesity [aOR 1.94; 95% CI 1.38-2.73] as well as 1-3 symptoms [aOR 2.32; 95% CI 1.11-4.86] and ≥4 symptoms [aOR 3.55; 95% CI 1.74-7.26] compared to 0 symptoms during acute COVID-19 illness. Black Africans were less likely to report breathlessness [aOR 0.57; 95% CI 0.38-0.84] (Table 4).

Factors associated with new or worse disability were ICU admission [aOR 2.03; 95% CI 1.46-2.84], pre-existing obesity [aOR 1.28; 95% CI 0.93-1.77], type 2 diabetes mellitus [aOR 1.49; 95% CI 1.01-2.22], and the presence of 1-3 symptoms [aOR 2.04; 95% CI 1.05-3.97] and ≥4 symptoms [aOR 3.81; 95% CI 2.01-7.22] compared to 0 symptoms during acute COVID-19 illness. Males were less likely to have new or worsening disability [aOR 0.60; 95% CI 0.44-0.82] (Table 4).

Factors associated with anxiety/depression one month after hospital discharge included mixed race [aOR 1.94; 95% CI 1.09-3.43], ICU admission [aOR 1.64; 95% CI 1.15-2.34], pre-existing obesity and 4 or more symptoms [aOR 2.40; 95% CI 1.27-4.54] compared to 0 symptoms during acute COVID-19 illness. Males [aOR 0.39; 95% CI 0.28-0.54] were less likely to report anxiety/depression (Table 4).

Table 3. Lifestyle changes following COVID-19 illness, NICD Long COVID Study, South Africa, 1 December 2020 - 27 April 2021.

Characteristic	New or persistent symptoms aOR (95% CI)	Self-reported non-recovery aOR (95% CI)	Breathlessness aOR (95% CI)	New or worsening disability aOR (95% CI)	Anxiety and/or depression aOR (95% CI)
Age group					
<40 years	Reference	Reference	Reference	Reference	Reference
40-64 years	1.40 (0.90-2.18)	1.21 (0.70-2.09)	1.26 (0.80-1.99)	1.25 (0.82-1.90)	1.10 (0.71-1.69)
≥65 years	1.00 (0.54-1.84)	0.68 (0.31-1.49)	0.93 (0.50-1.73)	0.86 (0.48-1.53)	0.58 (0.30-1.11)
Sex					
Female	Reference	Reference	Reference	Reference	Reference
Male	0.98 (0.68-1.39)	1.13 (0.76-1.70)	1.02 (0.72-1.43)	0.60 (0.44-0.82)	0.39 (0.28-0.54)
Race					
White	Reference	Reference	Reference	Reference	Reference
Black	0.72 (0.47-1.09)	0.49 (0.30-0.79)	0.57 (0.38-0.84)	0.76 (0.52-1.10)	1.15 (0.78-1.72)
Mixed Race	1.66 (0.81-3.40)	0.58 (0.28-1.19)	1.14 (0.65-2.03)	0.89 (0.51-1.53)	1.94 (1.09-3.43)
Indian	0.93 (0.48-1.82)	1.66 (0.88-3.14)	0.58 (0.31-1.09)	0.79 (0.43-1.44)	0.99 (0.52-1.88)
Unknown	1.29 (0.55-3.06)	0.70 (0.27-1.81)	1.20 (0.57-2.54)	2.12 (1.03-4.36)	3.25 (1.53-6.89)
Required supplemental oxygen					
No	Reference	Reference	Reference	Reference	Reference
Yes	1.07 (0.74-1.54)	1.15 (0.76-1.74)	1.40 (0.99-1.98)	0.99 (0.72-1.37)	0.93 (0.66-1.30)
Required admission in ICU					
No	Reference	Reference	Reference	Reference	Reference
Yes	2.95 (1.60-5.43)	1.33 (0.85-1.96)	3.45 (2.43-4.90)	2.03 (1.46-2.84)	1.64 (1.15-2.34)

Required invasive mechanical ventilation No Yes	Reference 0.83 (0.32-2.17)	Reference 1.30 (0.63-2.68)	Reference 1.22 (0.64-2.32)	Reference 0.73 (0.39-1.35)	Reference 0.83 (0.43-1.61)
Individual Comorbidities Asthma Obesity Diabetes Type 2 High Blood Pressure	 5.21 (0.65-41.50) 1.37 (0.85-2.21) - -	 1.91 (0.91-4.02) 1.52 (1.02-2.27) - -	 2.12 (1.01-4.48) 1.93 (1.38-2.73) - -	 - 1.28 (0.93-1.77) 1.49 (1.01-2.22) -	 - 1.58 (1.13-2.20) - 1.36 (0.95-1.94)
Symptoms before admission No symptoms 1-3 symptoms ≥4 symptoms	 Reference 3.26 (1.74-6.08) 5.25 (2.83-9.75)	 Reference 1.99 (0.66-5.95) 4.38 (1.52-12.59)	 Reference 2.32 (1.11-4.86) 3.55 (1.74-7.26)	 Reference 2.041 (1.05-3.97) 3.809 (2.01-7.22)	 Reference 1.47 (0.75-2.87) 2.40 (1.27-4.54)

DISCUSSION

We report new or persistent symptoms in 82% of patients at one month following discharge from hospital with laboratory confirmed SARS-CoV-2, in a cohort of 1,448 patients. This is the first study, to our knowledge, which presents an evaluation of the extent and characteristics of Long COVID in South Africa or the WHO Africa region. Our findings fall within the range of other international published studies that have reported small cohorts, with follow-up periods of 1 to 7 months and with varied prevalence of persistent symptoms from as high as 93% to as low as 26%.[4-17] Similar to other published studies, the most common symptoms reported in this cohort of COVID-19 survivors were shortness of breath, headaches, fatigue and confusion or lack of concentration.[4-17] The high burden of persistent symptoms is concerning for South Africa due to the potential for placing an additional burden on an already overwhelmed health care system, a decline in work productivity and the resultant decline in production, and an increased need for economic support amongst those affected.

On multivariate analysis, we found that age had no significant association with all outcomes analysed. Some literature showed a significant association between patients under the age of 65 years and persistence of symptoms[6,8], whilst others found that increasing age was related to persistence of symptoms.[16,22]

Males were less likely to report disability and anxiety/depression. Sex was not associated with breathlessness, new or persistent symptoms or self-reported non-recovery. Female sex was found to have a significant association with Long COVID in other studies[11,22], including associations with fatigue and breathlessness[6] and incomplete recovery, greater disability, worse fatigue and breathlessness.[8]

Black Africans were less likely to report breathlessness and non-recovery. Individuals of mixed race were more likely to report anxiety/depression. We have not found other studies that have reported on associations of race or ethnicity with Long COVID. The reasons for differences in persistent symptoms by race are unclear and require further investigation.

Pre-existing asthma, obesity and diabetes were associated with post-COVID outcomes. The risk factors for Long COVID are poorly described in the current literature and at least one study reported no association between comorbid disease and persistence of symptoms.[13] Asthma has been shown to have a significant association with Long COVID.[22]

There were significant associations between the presence and number of acute symptoms and breathlessness, persistent symptoms, non-recovery, disability and anxiety/depression. These findings

suggest that those with symptoms and those who had a greater number of symptoms during the acute infection are at greater risk for Long COVID. Sudre *et al*[22] found that fatigue, headache, dyspnoea, hoarse voice and myalgia were most predictive of Long COVID and that patients who presented with >5 symptoms in the first week of acute illness had a significant association with Long COVID. We plan to test associations with specific symptoms during acute illness that have significant association with Long COVID in future analyses.

Admission to ICU was significantly associated with persistent breathlessness, new or worsening disability and anxiety/depression. Post-intensive care syndrome (PICS), which is a collection of physical, mental and emotional symptoms that continue to persist after a patient leaves the ICU, is well described in the literature.[23-27] In this study there were no significant associations with the need for ventilation during acute illness and any of the outcomes. This differs in relation to a study by Scott, *et al*.,[8] which found that patients who had required invasive ventilation were nearly four times more likely to report an incomplete recovery compared to those who had not required oxygen.

Finally, 6% of patients reported that they had experienced a change in occupation since their illness due to persistence of symptoms or Long COVID. These rates are lower than those in the current literature that have reported 8% to 20% of patients whose occupation was impacted following COVID-19.[4,9] This lower rate of change in occupation may be due to relatively low full-time employment pre-COVID-19 in our study population, which was at 55%. The studies listed above were performed in Sweden and France where unemployment was 9.1% and 8.6% respectively[28,29] whereas the current unemployment rate in South Africa is 28.2%.[30] This difference in employment rates may account for lower rates of change in occupational status. The findings support the need for development of appropriate occupational health responses that would include determination of sick leave and compensation due to ill health.

Only a very small proportion of our cohort had been vaccinated at the time of this study and, as a result, we are unable to identify any association between administration of these vaccines and persistence of symptoms or other measured outcomes. As of 21 July 2021, 5,831,389 COVID-19 vaccine doses had been administered in South Africa. Only 5.1% of adults have been fully vaccinated and 9.5% have had one dose of a two-dose vaccine.[31] A small, early cohort from the United Kingdom found that vaccination caused a significant decrease in persistent symptoms and an increase in symptom resolution.[32] We plan to further investigate the impact of COVID-19 vaccination as our study progresses and as the vaccination coverage in South Africa increases.

STRENGTHS

This is a large national representative longitudinal cohort study and the first of its kind in South Africa. As part of the global ISARIC collaboration, we used standardised and validated tools, which allow comparison across participating countries. The alignment to the DATCOV hospital surveillance system and national SARS-CoV-2 case list allowed us to identify potential participants, and to verify key demographic and clinical data related to their hospital admission. These are preliminary results of an ongoing study. The study will continue to recruit patients and will follow them up for 12 months from hospital discharge.

LIMITATIONS

The study has several important limitations. Firstly, the study was limited to patients who were hospitalised with SARS-CoV-2, and it would be useful, in future, to add a comparison group of patients with SARS-CoV-2 who did not require hospitalisation, or a control group of hospitalised patients with a lower respiratory tract infection who did not test positive for SARS-CoV-2. However, the inclusion of patients admitted for other reasons who were asymptomatic for COVID-19 does allow some comparison of symptomatic and asymptomatic COVID-19 and Long COVID. Beyond the need for comparative analysis, the inclusion of only previously hospitalised patients may result in over-reporting of symptoms not specifically attributable to acute COVID-19 or Long COVID, and which may be better explained by PICS or complications arising directly from hospitalisation. Secondly, many patients did not have contact details available (21% of the total sample) or could not be reached (65% of the eligible population) and this could have potentially biased the sample towards individuals from higher socio-economic strata. We enrolled a disproportionate number of patients from the private healthcare sector of South Africa, which caters for a more affluent segment of the South African population. The over-representation of this group in the study is due to the greater degree of completeness of the contact details for patients testing in the private sector.

Patients who experienced symptoms may have been more likely to participate than those who did not. We have compared demographic characteristics of the patients and the hospitalised patients from the sample drawn and found similar distribution by age, sex, race and province, except for a higher proportion of study patients aged 40-64 years and a lower proportion recruited from Western Cape Province, and higher proportions of patients who were treated in ICU and required supplementary oxygen - which is believed to be related to underreporting on DATCOV (Supplementary Table 1).

The possibility of recall and response bias and the subjective rating of symptoms may affect the outcomes of the study.

Race was self-identified by the patient and categorised in line with the Statistics South Africa classification including black African, white, mixed, Indian and other.

CONCLUSIONS

The findings of this national survey demonstrated a high prevalence of new or persistent symptoms at one month post-discharge from hospital following SARS-CoV-2 illness, with resultant limitations to the activities of daily living, new or worsening disabilities and negative changes to occupational status. These findings will inform public health measures to address Long COVID, including identifying those who are at risk of developing Long COVID, providing patient support and messaging, developing clinical pathways and guidelines for the care of these patients, and for informing other aspects of health service planning. Long-term follow-up of this cohort will provide further insights to the evolution of Long COVID in South Africa. Future analyses will also be able to assess the effect of COVID-19 vaccination on persistent symptoms, and to compare Long COVID between South Africa's first, second and third wave, when different virus lineages predominated.

ACKNOWLEDGEMENTS

We would like to acknowledge all members of the research team (namely Ashrina Kandier, Bawinile Hlela, Bibianna Chikowere, Claudette Kibasomba, Dorcas Magorimbo-Njanjeni, Jeniffer Nagudi, Khadija Shangase, Khutso Maphoto, Lindelwa Ngobeni, Manana Sibanda, Menzi Mbonambi, Ncamsile Mavundla, Okaeng Plaatjie, Salaminah Mhlang, Thandeka Kosana and Zelna Jacobs) responsible for the recruitment of participants into the study and their continued involvement in subsequent follow ups. We are grateful to the Bill and Melinda Gates Foundations (especially Georgina Murphy and Keith Klugman) for their continued support of the project. We thank the ISARIC team (especially Daniel Plotkin, Laura Merson and Louise Sigfrid) for their help in developing the CRF and supporting the REDCap database. Finally, we would like to acknowledge all members of the NICD and DATCOV Team (especially Richard Welch) who have provide technical support and assisted with data management.

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SUPPLEMENTAL MATERIAL

Supplementary Table 1. Characteristics of study patients and hospitalised patients in DATCOV, a hospital-based COVID-19 surveillance network coordinated by the National Institute for Communicable Diseases, South Africa.

Median age (IQR)	Long COVID Study			DATCOV		
	Private	Public	Total	Private	Public	Total
	955 (66.0%)	493 (34.1%)	N=1 448	42,531 (50.0%)	42,551 (50.0%)	N=85,082
	53 [44 - 61]	46 [34 -59]	51 [40 - 61]	52 [42 - 62]	52 [37 - 64]	52 [40 - 63]
Age group						
<40 years	161 (16.86)	188 (38.13)	349 (24.10)	8,572 (20.15)	12,263 (28.82)	20,835 (24.49)
40-64 years	621 (65.03)	236 (47.87)	857 (59.19)	25,099 (59.01)	20,113 (47.27)	45,212 (53.14)
≥65 years	172 (18.01)	69 (14.00)	241 (16.64)	8,738 (20.55)	10,071 (23.67)	18,809 (22.11)
Unknown	1 (0.10)	0	1 (0.07)	122 (0.29)	104 (0.24)	226 (0.27)
Sex						
Female	482 (50.47)	302 (61.26)	784 (54.14)	22,304 (52.44)	25,991 (61.08)	48,295 (56.76)
Male	473 (49.53)	191 (38.74)	664 (45.86)	20,226 (47.56)	16,523 (38.83)	36,749 (43.19)
Unknown				1 (0.00)	36 (0.08)	37 (0.04)
Race						
White	449 (47.02)	417 (84.58)	866 (59.81)	10,576 (24.87)	28,802 (67.69)	39,378 (46.28)
Black	293 (30.68)	28 (5.68)	321 (22.17)	4,616 (10.85)	733 (1.72)	5,349 (6.29)
Mixed Race	86 (9.01)	33 (6.69)	119 (8.22)	2,184 (5.14)	1,620 (3.81)	3,804 (4.47)
Indian	84 (8.80)	12 (2.43)	96 (6.63)	2,697 (6.34)	691 (1.62)	3,388 (3.98)
Other/Asian	-	2 (0.41)	2 (0.14)	27 (0.06)	150 (0.35)	177 (0.21)
Unknown	43 (4.50)	1 (0.20)	44 (3.04)	22,431 (52.74)	10,555 (24.81)	32,986 (38.77)
Province						
Eastern Cape	75 (7.85)	55 (11.16)	130 (8.98)	2,761 (6.49)	5,434 (12.77)	8,195 (9.63)
Free State	34 (3.56)	37 (7.51)	71 (4.90)	1,796 (4.22)	2,038 (4.79)	3,834 (4.51)
Gauteng	305 (31.94)	145 (29.41)	450 (31.08)	12,862 (30.24)	9,354 (21.98)	22,216 (26.11)
KwaZulu-Natal	206 (21.57)	81 (16.43)	287 (19.82)	10,310 (24.24)	7,893 (18.55)	18,203 (21.39)
Limpopo	20 (2.09)	13 (2.64)	33 (2.28)	1,932 (4.54)	2,078 (4.88)	4,010 (4.71)
Mpumalanga	63 (6.60)	44 (8.92)	107 (7.39)	1,955 (4.60)	1,956 (4.60)	3,911 (4.60)
North West	48 (5.03)	72 (14.60)	120 (8.29)	2,044 (4.81)	2,504 (5.88)	4,548 (5.35)
Northern Cape	26 (2.72)	7 (1.42)	33 (2.28)	795 (1.87)	536 (1.26)	1,331 (1.56)
Western Cape	178 (18.64)	39 (7.91)	217 (14.99)	8,076 (18.99)	10,758 (25.28)	18,834 (22.14)
Number of comorbidities						
No comorbidities	300 (31.41)	216 (43.81)	516 (35.64)	27,140 (63.81)	7,204 (16.93)	34,344 (40.37)
1 comorbidity	329 (34.45)	161 (32.66)	490 (33.84)	7,411 (17.42)	10,728 (25.21)	18,139 (21.32)
2 comorbidities	214 (22.41)	86 (17.44)	300 (20.72)	3,753 (8.82)	6,745 (15.85)	10,498 (12.34)
≥ 3 comorbidities	112 (11.73)	30 (6.09)	142 (9.81)	453 (1.07)	2,826 (6.64)	3,279 (3.85)
Unknown	-	-	-	3,774 (8.87)	15,048 (35.36)	18,822 (22.12)
Required admission to ICU						
No	600 (62.83)	396 (80.32)	996 (68.78)	36,703 (86.30)	41,269 (96.99)	77,972 (91.64)
Not sure	16 (1.68)	25 (5.07)	41 (2.83)			
Yes	337 (35.29)	69 (14.00)	406 (28.04)	5,828 (13.70)	1,282 (3.01)	7,110 (8.36)
Missing	2 (0.21)	3 (0.61)	5 (0.35)			
Required supplemental Oxygen						
No	395 (41.36)	258 (52.33)	653 (45.10)	20,921 (49.19)	25,714 (60.43)	46,635 (54.81)
Yes	560(58.64)	235 (47.67)	795 (54.90)	21,610 (50.81)	16,837 (39.57)	38,447 (45.19)
Required invasive mechanical ventilation						
No	883 (92.46)	480 (97.36)	1,363 (94.13)	40,821 (95.98)	41,778 (98.18)	82,599 (97.08)
Yes	72 (7.54)	13 (2.64)	13 (2.64)	1,710 (4.02)	773 (1.82)	2,483 (2.92)