ABSTRACT

Introduction: COVID-19 resulted in an unprecedented worldwide spike in hospital and ICU admissions; predominantly for adult respiratory distress syndrome (ARDS). Survival rates for patients requiring mechanical ventilation in Cape Town during the waves driven by the ancestral strain and beta variant were approximately 30% during the first 3 waves of the pandemic. However, post-ICU admission sequelae and recovery trajectory in sub-Saharan Africa remain unknown.

Methods: We systematically evaluated a cohort of COVID-19 ICU survivors at three months following hospital discharge. A retrospective single-centre study enrolled all COVID-19 pneumonia patients who were admitted to ICU for mechanical ventilation and followed up at the post-COVID-19 Lung Disease Clinic between 1 July 2020 and 30 December 2021.

Results: A total of 26 patients were evaluated at 3 months after discharge from hospital following mechanical ventilation: 53% were male and 81% had at least one co-morbidity. Diabetes and hypertension were present in 42% and 54% of patients respectively. Persistent dyspnoea (89%) and fatigue (54%) were the most common post-COVID-19 symptoms. Median FEV_1 and FVC were 73% (IQR 65-83) and 71% (IQR 61-77) of predicted values respectively, whilst median DLCO was 59% (IQR 41-70) of predicted values. Abnormalities were confirmed in all patients (24/26) who underwent high resolution computer tomography (HRCT) of the chest, with ground glass opacities (46%) and interstitial thickening (58%) being most common. No significant risk factors for post-COVID-19 impairment were identified.

Conclusion: At 3 months after hospitalization, patients who received mechanical ventilation for COVID-19 pneumonia frequently reported ongoing symptoms. Lung function was moderately impaired with a disproportionate reduction in DLCO, and radiographic abnormalities were common. Long term follow up is required to determine the natural history post severe-COVID-19 lung disease.

Word count: 313

ACKNOWLEDGEMENTS

I would like to acknowledge and thank all the patients that were enrolled in this study at Groote Schuur Hospital.

I would also like to thank all colleagues in different disciplines, specifically the critical care units, for all their work, assistance, and management of these patients.

CONTRIBUTIONS

- **Professor Richard van Zyl-Smit (primary supervisor)**: Concept for thesis, planning, data synthesis, interpretation of results and manuscript preparation.
- **Dr Rubeshan Perumal**: Concept for thesis, planning, analysis and interpretation of data.
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PUBLICATION-READY MANUSCRIPT

Early sequelae of post COVID-19 lung disease in patients who were mechanically ventilated for severe COVID-19 pneumonia

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Word count: 3852

Key words: Post-COVID-19 lung disease, Post-COVID-19 ICU survival, respiratory sequelae post severe COVID-19 ARDS

Disclosures: Nil

Conflicts of interest: No conflicts of interest declared

Funding information: Nil

THESIS

Introduction

In late 2019, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) emerged in Wuhan, China, and spread rapidly, escalating to a global pandemic (1). Since the World Health Organisation declaration of COVID-19 as a global pandemic in March 2020 most of the attention focused on containment efforts and addressing the surge of cases with severe disease. Statistics from early on the pandemic indicated that whilst 1 in 5 patients required medical care and/or hospitalisation, 1 in 10 hospitalised patients required critical care in a dedicated intensive care unit (ICU) (2). This resulted in an unprecedented worldwide spike in ICU admissions, predominantly for adult respiratory distress syndrome (ARDS) secondary to COVID-19 pneumonia. In the already overburdened health care sector in South Africa, COVID-19 added enormous additional strain on the limited resources.

As the pandemic progressed and with the advent of vaccines and improved treatment strategies, the cumulative number of COVID-19 survivors increased. The focus is now increasingly shifting towards post-acute care and the management of mid- to long-term sequelae in these survivors (3). As the number of COVID-19 ICU survivors grows, there is increasing interest in the nature and extent of residual respiratory impairment and the long-term care needs of this population. A recently published article showed a 30% survival rate at discharge from ICU in a South African hospital in patients who required invasive mechanical ventilation (IMV) for severe COVID-19 pneumonia (4).

The respiratory tract is the most seriously affected system in severe COVID-19. The exact mechanisms underlying progression to severe pneumonia and respiratory failure are not fully elucidated, however, systemic inflammatory responses, host immune-associated injuries and inadequate adaptive immune response are central and are all implicated in disease progression.(5) What is not known, is how those with the most severe respiratory dysfunction requiring mechanical ventilation perform physiologically, radiologically, psychologically, and cognitively in the mid- and long-term (3,6). Following previous coronavirus epidemics such as Severe Acute Respiratory Syndrome (SARS) and Middle East Respiratory Syndrome (MERS),

persistent respiratory and systemic deficits have been reported, especially in those who experienced severe pneumonia or acute respiratory distress syndrome (ARDS) as a result (7). Persistent deficits across multiple domains including spirometry, diffusing capacity of the lung for carbon monoxide (DLCO), exercise capacity, mental. health, cognitive function, and overall quality of life have been reported in such patients (7). It is clear that post-COVID-19 lung disease is an evolving entity of public health significance and requires a well-coordinated health system response. With preliminary data confirming that various forms of post-COVID-19 lung disease are potential complications and consequences of severe COVID-19 pneumonia, it is advocated that survivors should be followed-up in centres which able to characterise the deficits, offer access to tailored therapeutic interventions, and develop strategies for managing these complications in the long term (3,8). Without systematic follow-up of these at-risk individuals, this entity of severe post-COVID-19 lung disease is likely to be under recognised and may result in excess morbidity (3,8).

At present, there is little data on the post-discharge trajectory of COVID-19 survivors who underwent invasive mechanical ventilation (IMV) for severe COVID-19 pneumonia in sub-Saharan Africa. To characterise the nature and extent of respiratory impairment in such patients, we systematically evaluated a cohort of mechanically ventilated ICU survivors three months after their discharge from hospital.

Methods

Study design and study population

This was a retrospective observational study performed at a single centre tertiary hospital in the Western Cape. It included all patients >18 years old with laboratory-confirmed severe COVID-19 pneumonia admitted to the ICU for invasive mechanical ventilation and seen at the post-COVID-19 Lung Disease Clinic between 1 July 2020 and 30 December 2021 were recruited. Patients referred during this time reflected the first, second and third waves of the pandemic in South Africa when B.1, Beta, and Delta variants were prevalent respectively. Our study population comprised ~20% of all COVID-19 ICU survivors over the study period.

Only patients with PCR-confirmed COVID-19 who were admitted to the ICU with COVID-19 ARDS as the primary diagnosis for IMV and who survived to three months post-discharge were included.

Demographic data, past medical history, COVID-19 ICU admission data (including mode(s) of respiratory support, duration of ICU admission and steroid exposure) as well as post-COVID-19 symptoms were extracted from clinical records. Key laboratory data, including peak C-reactive protein and D-dimer values, were extracted from laboratory records of the certified national laboratory service. Radiological data, including chest radiographs and computed tomography imaging, were accessed from a picture archiving and communication system, and reviewed by two pulmonologists. Pulmonary function testing was performed by a registered respiratory technologist according to ATS/ERS guidelines, including spirometry and diffusing capacity of the lungs for carbon monoxide (DLCO). Absolute values as well as values expressed as a percentage of predicted values as defined by the Global Lung Initiative were collected from the digital archive (9). The results of sub-maximal exercise testing using a standardised 6-minute walk test. when performed by capable patients, was captured from clinical records.

Study outcomes

The main outcomes were divided into 3 domains: symptoms, physiological data, and radiological findings 3 months after hospital discharge. Symptoms recorded were self-reported by the patients. Physiological outcomes were measured by pulmonary function tests (spirometry and DLCO), resting oxygen saturation by pulse oximetry in room air and 6-minute walk distance. Chest radiographs and computer tomography were reported for radiological outcomes. The presence or absence of abnormality was noted with documentation and further characterisation of the abnormalities.

Statistical analysis

Standard definitions and statistical methods were applied. Data are described using descriptive statistics and comparisons performed using the appropriate parametric and non-parametric tests.

Ethics Approval

Ethical approval for this study was granted by the human research ethics committee of the University of Cape Town (HREC 854/2020).

Results

Twenty-six mechanically ventilated COVID-19 survivors were seen over an 18-month period. The median age was 43 years ranging from the youngest at 29 to the oldest at 65 years, 54% (14/26) were male and ethnicity reflected that of the hospital referral catchment: 13 mixed ancestry, 6 black African, 5 Indian and 2 white.

The majority, 73% (19/26), of patients were self-reported non-smokers and 1 patient was a current smoker. At least one comorbidity was present in 81% (21/26) of all patients, with 38% having two or more co-morbidities. The most common co-morbid conditions were hypertension in 54% (14/26) patients and diabetes in 42% (11/26). Two patients were living with HIV; one was virologically suppressed on antiretroviral therapy whilst the other was a new diagnosis. The median (IQR) body mass index (BMI) was 29 (27-37) kg/m^2.

The median (IQR) length of stay in ICU was 32 (14-45) days with the longest stay in ICU being 121 days. Notably, 81% (21/26) of patients had received and failed high flow nasal oxygen respiratory support before requiring mechanical ventilation. All patients received systemic corticosteroids for COVID-19 related hypoxaemia. Baseline characteristics are shown in Table 1.

Table 1. Baseline characteristics of COVID-19 pneumonia ICU survivors at 3 months post-discharge

Characteristic	N=26
Age, years, median (range)	43 (29 – 65)
Sex, male, n (%)	14 (53.8)
Race, n (%) Black African Mixed ancestry Indian White	 6 (23.1) 13 (50) 5 (19.2) 2 (7.7)
Weight, kg, median (IQR)	84.5 (74.5 – 101.13)
Height, cm, median (IQR)	165.2 (159.9 – 171.2)
BMI, kg/m^2, median (IQR)	29 (27.2 – 37.1)
Smoking n (%) Current Former Non-smoker	 1 (3.8) 5 (19.2) 19 (73.1)
Comorbidities n (%) HIV Diabetes Mellitus Hypertension Chronic Kidney Disease Chronic Respiratory Disease Previous TB Chronic Cardiac Disease	 2 (7.7) 11 (42.3) 14 (53.8) 1 (3.8) 1 (3.8) 2 (7.7) 1 (3.8)
Days in ICU, median (IQR)	32 (IQR 14 - 45)
Modes of respiratory support during entire admission n (%) HFNC IMV	 21 (80.8) 26 (100)
Corticosteroid usage n (%) Dexamethasone Dexamethasone + prednisone Prednisone	26 (100) 11 (42.3) 14 (53.8) 1 (3.8)
Peak CRP, median (IQR)	83 (28.5 – 285)
Peak D-Dimer, median (IQR)	0.68 (0.41 – 0.68)
Pre-COVID mMRC dyspnoea n (%) 0 1 2	 20 (76.9) 5 (19.2) 1 (3.8)

Symptom outcomes

Median time from hospital discharge to the first appointment was 116 days (IQR 100-137). Persistent symptoms were reported by 96% (25/26) of patients at the ~3 months follow up visit. The most prevalent symptoms were dyspnoea 89% (23/26), fatigue 54% (24/26), chest tightness 42% (11/26) and cough 19% (10/26). Low mood was reported by 31% (8/26) of patients. 20 patients (77%) reported no dyspnoea at baseline pre-COVID-19. In those who did experience pre-COVID-19 dyspnoea, none reported greater than modified Medical Research Council (mMRC) II dyspnoea. In patients who experienced post-COVID-19 dyspnoea, 65% (17/26) reported mMRC I-II, whilst 23% (6/26) reported mMRC III-IV grade dyspnoea. Symptom outcomes are shown in Table 2.

Table 2. Post-COVID-19 symptoms at 3 months post-discharge

Characteristic	**N=26**
Time from discharge to assessment, days, median (IQR)	116 (99.7 – 137)
Post-COVID symptoms n (%)	
Shortness of breath	23 (88.5)
Cough	10 (38.5)
Chest tightness	11 (42.3)
Fatigue	14 (53.8)
Low mood	8 (30.7)
Chronic pain	7 (26.9)
Headaches	8 (30.7)
Post-COVID mMRC dyspnoea n (%)	
0	3 (11.5)
1	6 (23.1)
2	11 (42.3)
3	4 (15.4)
4	2 (7.7)

Physiological outcomes

The majority of patients 77% (20/26) had a normal clinical respiratory examination, and a median (IQR) resting peripheral O_2 saturation of 96% (90%-99%) and heart rate of 86 (65-105) beats minute. Abnormal auscultation with bilateral basal inspiratory crepitations was present in 23% (6/26) of patients. Cardiac examination was found to be abnormal in 19% (5/26) patients, with two patients having clinical features to

support pulmonary hypertension. Median length of ICU admission for mechanical ventilation was longer in those with abnormal examination (45 vs 26 days, p=0.06).

Spirometry was performed in all 26 patients. Only four patients (15%) had normal spirometry. Overall, dynamic lung volumes showed mild reductions with a median FEV_1 73% (IQR 64.8-83.3) and FVC 71% (IQR 61.3-77.3) of predicted values respectively. The median FEV_1/FVC ratio was non-obstructive: 84%. No individual patients had an FEV1/FVC ration less than 70%. Diffusing capacity of the lung for carbon monoxide (DLCO) was measured in 85% of patients. Median DLCO was moderately reduced at 59.5% (IQR 40.6-70.6) predicted values. A 6-minute walk test (6MWT) was conducted in 85% (22/26) patients with 4 patients being unable to walk unaided. The median distance walked was 440 (IQR 373-507) meters with median pre- and post-walk room air oxygen saturations of 97% and 94% respectively. There was no correlation between the length of ICU stay and FVC, DLCO or 6 min walk impairment (p=0.25 and p=0.08, p=0.77, respectively). These physiological and clinical findings are shown below in Table 3.

Table 3. Post-COVID-19 physiological and clinical findings at 3 months post-discharge

Parameter	**N=26**
Resting room air oxygen saturation mean (range)	96 (95-99)
Resting heart rate, median (IQR)	86 (65-105)
Respiratory examination n (%) Normal Abnormal	 20 (77) 6 (23)
Cardiac exam n (%) Normal Abnormal	 21 (81) 5 (19)
Spirometry, median (IQR) FEV_1 FEV_1 % predicted FVC FVC % predicted FEV_1/FVC	 2.26 (1.63 – 2.69) 72.5 (64.75 – 83.25) 2.74 (1.94 – 3.17) 70.5 (61.25 – 77.25) 84 (81.5 – 89.25)

DLCO, median (IQR) DLCO % predicted, median (IQR) DLCO <80% predicted (%)	13.71 (10.64 – 19.35) 59.50 (40.75 – 70.25) 86
6-minute walk test, median (IQR) Distance Pre-test saturation Post-test saturation	 440 (372.5 – 508.5) 97 (96 – 99) 94 (89.5 – 96.5)

Radiological outcomes

The majority, 85% (22/26) of patients had an abnormal chest x-ray at first visit. Seventy three percent had bilateral abnormalities, which were predominantly ground glass (46%) and reticular (31%). Volume loss was seen in 42% of patients. No pleural effusions or nodules were reported. Twenty-four patients had an HRCT Chest scan within 6 weeks of the first clinic visit. All chest CT scans were reported to be abnormal. CT findings were congruous with plain film radiography, with ground glass opacification in 46% and reticular interstitial thickening more common in 58% of patients. Disease was bilateral in 63% (15/24) and volume loss in 29% (7/24). Fibrosis was reported in 9/24 (38%) scans. These findings are summarised in Table 4.

Table 4. Post-COVID-19 radiographic findings at 3 months post-discharge

Characteristic	**N=26**
Chest radiograph n (%) Normal Bilateral disease Lower zone predominance Volume loss GGO Consolidation Reticular opacities	 4 (15.4) 19 (73.1) 17 (65.3) 11 (42.3) 12 (46.2) 2 (7.7) 8 (30.8)
Computed tomography, n=24(%) Normal Bilateral disease Lower zone predominance Volume loss GGO Interstitial thickening Fibrosis	 0 (0) 15 (62.5) 10 (41.6) 7 (29.1) 11 (45.8) 14 (58.3) 9 (37.5)

Discussion

Survival of patients in ICU with severe COVID-19 related ARDS requiring mechanical ventilation was low during our study period, approximately 30% (4). Survivors who followed up in the post-COVID-19 clinic had a high burden of symptoms, persistent radiological abnormalities, and lung function impairment. The duration of ICU stay was not associated with any physiological or radiological outcomes.

Persistent symptoms were reported in 96% of patients in our cohort at approximately 3 months after discharge from hospital. This is compatible with findings in similar studies conducted at 6 weeks, 2- 6- 9- and 12 months following discharge from ICU for severe COVID-19 pneumonia, where most patients experienced ongoing physical symptoms (1, 10-12). Although most of these studies included greater numbers of ICU survivors, not all these patients received invasive mechanical ventilation. The study by Wu X et al followed patients serially up to 12 months and demonstrated gradual symptom improvement over time (12). Long term follow-up of our cohort is planned for future review.

The most commonly reported symptoms at all time points in these comparative studies were fatigue, dyspnoea and chronic pain. The high prevalence of significant physical symptoms found in our cohort, most notably fatigue and dyspnoea, was ubiquitous in severe COVID-19 populations across the globe (1, 10-12). Similar symptoms of fatigue, dyspnoea and pain have also been reported in survivors of non-COVID-19 ARDS (13,14). The biological basis for persistent respiratory symptoms and physiological deficits after ARDS has been the subject of scientific research for many years prior to the COVID-19 related ARDS. ARDS, due to any cause, develops following injury and disruption to the alveolar–capillary barrier with persistent insults to the alveolar epithelium (15). This disruption sets in motion a series of inflammatory events which leads to impaired alveolar fluid clearance and alveolar oedema. With ongoing injury and/or failure to repair this damage in a timely manner a pathological temporary or permanent fibroproliferative response ensues in some patients (15). The reasons why only some patients have exuberant fibroproliferative responses remains uncertain and controversial. The impact of mechanical ventilation on lung injury has been explored in depth and it is widely accepted that the sheer forces exerted may

themselves be a form of ongoing lung injury, especially in patients whose lungs are already compromised with ARDS, thereby potentiating fibrosis (16,17). It is therefore plausible that patients such as ours, who were afflicted with the most severe COVID-19 pneumonia, ARDS and required invasive mechanical ventilation, were at high risk of lung injury that may not be fully reversible and therefore experienced a high burden of respiratory symptoms, as well as physiological deficits and radiological abnormalities during their post-discharge period.

To further understand the persistent symptoms and physiological changes noted in the post-acute COVID-19 phase, a British study evaluated the immune-proteomic profile in the airways (by means of bronchiolar-alveoli lavage fluid) and peripheral blood of healthy controls and post-COVID-19 patients 3-6 months after hospital discharge (18). Abnormal airway (but not serum) proteomes, with increased concentrations of proteins responsible for apoptosis, tissue repair pathways and epithelial injury were found in post-COVID-19 patients versus the healthy controls (18). Different cellular and proteomic profiles were linked to different phenotypes of abnormalities such as airways dysfunction and more diffuse parenchymal disease. This study provides further insights into an ongoing post-acute phase immune-inflammatory process underlying the prolonged course experienced by many post-COVID-19 survivors. Longer term follow-up of their patients at one year indicated that these immunological abnormalities resolved with time, which parallels the apparent improvements in post-COVID-19 symptoms reported in several studies (11-13, 18). Bronchoscopy was not performed in our setting as part of routine clinical care and our study was not able to identify any demographic or clinical predictors of persistent symptoms, in part due to the small number of survivors all with high burden of symptoms and physiological abnormalities.

Spirometry was less severely impaired than was initially expected in this cohort. A French study found more severe spirometric deficits in patients with severe COVID-19 pneumonia who required IMV, whilst many other studies confirmed only mild restrictive deficits in post-COVID-19 patients (12, 13, 19). A small group of our patients 15% (4/26) had normal spirometry with the majority having only mild/minor restrictions in lung volumes (median FVC 71%). None of our patients demonstrated an obstructive pattern (FEV_1/FVC <70%) on spirometry. At the time of our study, inclusion criteria for

ICU admission for severe COVID-ARDS excluded those with severe co-morbidities such as renal failure, ischaemic heart disease or severe COPD, etc. There were also a minority of smokers in our cohort, and how this might have impacted spirometric findings is unknown. Cho et. al. showed that air-trapping was prevalent in 58% of patients on thoracic CT 2-3 months after the diagnosis of COVID-19 pneumonia, with the highest prevalence in post-ICU patients (78%) (20). Quantitative analysis showed that 25-35% of the lung fields were involved in the post-COVID-19 patients compared to 7% in the control group. Despite the significant prevalence of confirmed air-trapping, no obstructive spirometry was demonstrated in their cohort either, suggesting that small rather than large airways were responsible for the radiographic findings (20).

Persistent abnormalities in DLCO (<80% of predicted) were seen in 86% of patients at 3 months. Reduced DLCO was less common in other 'post-COVID' studies where 56% patients had DLCO <80% predicted, but these again included patients with less severe disease receiving high flow nasal oxygen and non-invasive ventilation (21). Interestingly, the magnitude of impairment in DCLO was disproportionately greater than the severity of the deficit in lung volumes, with median DLCO of 59.5% compared to FVC of 71%. This pattern has been reported in several studies, some of which have shown an association between reduced DLCO and increasing severity of infiltrates on the CT scan (1, 19, 21-23). Matheson et. al. performed ^{129}Xe gas exchange magnetic resonance imaging (MRI) on post-COVID-19 patients, which provides a measure of alveolar-blood barrier integrity by calculating the Xe MRI red blood cell (RBC): alveolar tissue ratio (24). They showed a correlation between reduced DLCO and reduced Xe MRI RBC: alveolar tissue ratio, present in all their post COVID-19 patients, regardless of disease severity roughly 35 weeks post-acute infection (24). Thoracic CT demonstrated vascular pruning in post-COVID-19 patients who required hospitalisation compared to non-hospitalised patients and healthy controls, and they postulate that the abnormal MRI and CT findings were consistent with abnormal gas exchange stemming from the alveolar tissue barrier and pulmonary vascular compartments; the mechanism not defined. These findings may provide some explanation into the phenomenon of preserved spirometry with reduced DLCO reflected so widely throughout the literature.

We were not able to determine the impact of corticosteroid treatment on spirometry and DLCO as all our patients were managed with corticosteroid treatment during ICU admission. Furthermore, no identifiable predictors of impaired lung function were evident. An Italian study by Anastasio et al. found that patients who had severe COVID-19 pneumonia, including some who required IMV, had lower resting as well as post 6MWT oxygen saturation by pulse oximetry (22). Overall assessment of 6-minute walk test at 3 months post severe COVID-19 ARDS in our study revealed a preserved median distance of 440m with only 28% of patients recording distances below the lower limit of normal. No significant desaturation was noted in the majority (85%) of patients who were able to perform the test.

A 3-month chest x-ray was available in all patients, with over 90% having a CT chest imaging, but due to resource and lock-down restrictions not on the same day. This time delay (up to 6 weeks in some instances) may have contributed to some of the variations in distribution and pattern of abnormalities between the two modalities. Abnormal findings on chest radiograph were identified in 85% of patients. The prevalence of CT abnormalities at 3 months after severe COVID-19 pneumonia ranged from 71-80% in other including forms of ventilation other than IMV (12, 19, 23). Despite the lower incidence, the patterns of abnormality were very similar, with ground glass opacities, reticular infiltrates, traction bronchiolectasis and fibrosis being most common. Cho et al found that such changes were significantly more prevalent in post-ICU than non-ICU COVID-19 pneumonia patients (41% vs 91% $p<0.001$) (20). In our cohort, we found that despite all our patients having CT abnormalities, 16% maintained a preserved DLCO (>80% predicted value), whilst another showed correlation between the presence of CT abnormalities and reduced DLCO (19). A Spanish study performed flexible bronchoscopy on post-COVID-19 patients ~3 months following discharge and found that no histological patterns (organizing pneumonia, lymphoplasmacytic interstitial infiltrates for e.g.) of disease were associated with clinical factors (need for IMV, duration of ICU admission), nor did they correlate with specific radiographic patterns (25). Wu X et al reported CT findings on their patients at both 3 months and 12 months and found the prevalence of abnormalities dropped from 80% to 24% by one year and we postulate that many of the abnormalities in our patients may also resolve with time (12).

The post-COVID-19 lung disease clinic at Groote Schuur Hospital was the first of its kind on the African continent and attempted to follow up ICU survivors during the ongoing pandemic with limitations to investigations and patient movement (lockdown). It was not possible to recruit a control group of high-flow oxygen therapy or ward survivors given the restrictions. Furthermore, timing of follow up, treatment in ICU and access to rehabilitation services was not uniform. We also had no access to pre-COVID physiological testing and none in the acute phase of the illness. Long term outcomes at one year post ICU discharge would also provide more insight into the persistence of the radiological and physiological limitations seen both early and mid-term post ICU discharge.

Conclusion

Patients surviving mechanical ventilation for severe COVID-19 pneumonia spent on average a month in ICU and unsurprisingly had significant residual symptoms, radiological and physiological abnormalities at 3 months after discharge. The extent to which these abnormalities are ICU management-related rather than disease-related is unclear. Despite the severe disease and prolonged ventilation, most survivors had good functional capacity and exercise tolerance regardless of the persistent CT abnormalities. Long term follow up is required to determine the natural history of severe COVID ARDS changes and to describe whether they are static, improve with time, or evolve into a post-COVID-19 fibrotic lung disease.

Conflict of interest

There are no conflicts of interest to declare for any authors.

Funding source

This work did not receive any specific grant funding and all investigations were all performed as part of routine clinical workup.

LIST OF ABBREVIATIONS

ARDS	Acute respiratory distress syndrome
DLCO	Diffusing capacity of the lung for carbon monoxide
FEV1	Forced expiratory volume 1 second
FVC	Forced vital capacity
HRCT	High resolution computer tomography
HIV	Human immunodeficiency virus
ICU	Intensive care unit
IMV	Invasive mechanical ventilation
TB	Tuberculosis
WHO	World Health Organization

REFERENCES

1. Myall KJ, Mukherjee B, Castanheira AM et al., **Persistent Post-COVID-19 Interstitial Lung Disease. An Observational Study of Corticosteroid Treatment**. Ann Am Thorac Soc, 2021, **18**(5): p. 799-806

2. CDC. **COVID-19 Response Team. Severe outcomes among patients with coronavirus disease 2019 (COVID-19) - United States, February 12–March 16 2020** Morb. Mortal. Wkly Rep 2020, 69, 343–346

3 George, P.M, Barratt SL, Condliffe E et al., **Respiratory follow-up of patients with COVID-19 pneumonia.** Thorax, 2020, **75**(11): p. 1009-1016

4. Arnold-Day C, Van Zyl-Smit R, Joubert I et.al. **Outcomes of patients with COVID-19 acute respiratory distress syndrome requiring invasive mechanical ventilation admitted to an intensive care unit in South Africa**. SAMJ, 2022, 34-39, 112 (1)

5. Attaway, AH, Scherga R, Bhimraj A et al., **Severe covid-19 pneumonia: pathogenesis and clinical management.** BMJ, 2021;372: n436.

6. Tenforde, M.W., et al., **Characteristics of Adult Outpatients and Inpatients with COVID-19 - 11 Academic Medical Centers, United States, March-May 2020.** MMWR Morb Mortal Wkly Rep, 2020. **69**(26): p. 841-846.

7. Hassaan A, Patel K, Greenwood D et.al. **Long term clinical outcomes in survivors of severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS) coronavirus outbreaks after hospitiliisation or ICU admission: a systemic review and meta-analysis.** J Rehabil Med. 2020 May 31;52 (5).

8. Rai, D.K., P. Sharma, and R. Kumar. **Post covid 19 pulmonary fibrosis. Is it real threat?** Indian J Tuberc, 2021, **68**(3): p. 330-333.

9. Quanjer PH, Stanojevic S, Cole TJ et al. **Multi-ethnic reference values for spirometry for the 3-95-yr age range: the global lung function 2012 equations.** Eur Respir J. 2012;40(6):1324–43.

10. Logue, JK, Frank N, McCulloch D et al., **Sequelae in Adults at 6 Months After COVID-19 Infection.** JAMA Netw Open, 2021. **4**(2): p. e210830.

11. Carfì, A., Bernabi R, Landi F et al., **Persistent Symptoms in Patients After Acute COVID-19**. JAMA, 2020. **324**(6): p. 603-605.

12. Wu X, Liu X, Zhou Y et al. **3-month, 6-month, 9-month, and 12-month respiratory outcomes in patients following COVID-19-related hospitalisation: a prospective study.** Lancet Resp Med 2021;9: 747-54.

13. Heesakkers H, Van der Hoeven J, Corsten S et al. **Clinical Outcomes Among Patients With 1-Year Survival Following Intensive Care Unit Treatment for COVID-19.** JAMA. 2022;327(6):559-565.

14. Burnham EL, Janssen WJ, Riches DWH et al. **The fibroproliferative response in acute respiratory distress syndrome: mechanisms and clinical significance.** Eur Respir J 2014; 43: 276–285 [DOI 10.1183/09031936.00196412]

15. Huppert LA, Matthay MA, Ware LB et al. **Pathogenesis of Acute Respiratory Distress Syndrome**. Semin Respir Crit Care Med 2019;40:31–39.

16. Marini JJ. **Evolving concepts for safer ventilation**. Critical Care 2019, 23(Suppl 1):114 [DOI.org/10.1186/s13054-019-2406-9]

17. L. Gattinoni L, Tonetti T, Cressoni M et al. **Ventilator-related causes of lung injury: the mechanical power.** Intensive Care Med 2016 42:1567–1575 [DOI 10.1007/s00134-016-4505-2]

18. Vijayakumar B, Boustani K, Ogger PP et. al. **Immuno-proteomic profiling revelas aberrant immune cell regulation in the airways of individuals with ongoing post-COVID-19 respiratory disease.** Immunity 2022; 55 542-556. [DOI.org/10.1016/j-immuni.2022.01.017]

19. Frija-Masson J, Debray P, Boussouar A. **Residual ground glass opacities three months after Covid-19 pneumonia correlate to alteration of respiratory function: The post Covid M3 study.** Repair Med. 2021 Aug;184:106435. [DOI:10.1016/j.rmed.2021.106435].

20. Cho JL, Villacreses R, Nagpal P et. al. **Quantitative chest CT assessment of small airways disease in post-acute SARS-CoV-1 infection**. Radiology 2022; 304: 185-192. [DOI.org/10.1148/radiol.212170}

21. Huang C, Huang L, Wang Y et al. **6-month consequences of COVID-19 in patients discharge from hospital: a cohort study**. Lancet 2021;397:220-32. [DOI.org/10/1016/S0140-6736].

22 Anastasio F, Barbuto S, Scarnecchia E, et al. **Medium-term impact of COVID-19 on pulmonary function, functional capacity and quality of life.** Eur Respir J 2021; 58: 2004015 [DOI: 10.1183/13993003.04015-2020].

23. Qin W, Chen S, Zhang Y, et al. **Diffusion capacity abnormalities for carbon monoxide in patients with COVID-19 at 3-month follow-up.** Eur Respir J 2021; 58: 2003677 [DOI: 10.1183/13993003.03677-2020]

24. Matheson AM, McIntosh ML, Kooner HK et. al. **Persistent 129Xe MRI pulmonary and CT vascular abnormalities in symptomatic individuals with post-acute COVID-19 syndrome**. Radiology 2022; 305:466-476. [DOI.org/10.1148/radiol.220492]

25. Culebras M, Loor K, Sansano I et. al. **Histological findings in transbronchial cryobiopsies obtained from patients after COVID-19.** Chest 2021; 161(3):647-650. [DOI.org/10.1016/j.chest.2021.09.016]

ETHICS APPROVAL

UNIVERSITY OF CAPE TOWN
Faculty of Health Sciences
Human Research Ethics Committee

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21 January 2021

HREC REF: 854/2020

Prof K Dheda
Division of Pulmonology
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Dear Prof Dheda

PROJECT TITLE: A PROSPECTIVE OBSERVATIONAL STUDY OF POST-COVID-19 LUNG DISEASE IN PATIENTS PREVIOUSLY HOSPITALISED FOR SEVERE COVID-19

Thank you for your response letter, addressing the issues raised by the Faculty of Health Sciences Human Research Ethics Committee (HREC).

It is a pleasure to inform you that the HREC has **formally approved** the above-mentioned study.

This approval is subject to strict adherence to the HREC recommendations regarding research involving human participants during COVID -19, dated 17 March 2020 & 06 July 2020.

Approval is granted for one year until the 30 January 2022.

Please submit a progress form, using the standardised Annual Report Form if the study continues beyond the approval period. Please submit a Standard Closure form if the study is completed within the approval period.
(Forms can be found on our website: www.health.uct.ac.za/fhs/research/humanethics/forms)

Please quote the HREC REF 854/2020 in all your correspondence.

Please note that the ongoing ethical conduct of the study remains the responsibility of the principal investigator.

Please note that for all studies approved by the HREC, the principal investigator **must** obtain appropriate institutional approval, where necessary, before the research may occur.

Yours sincerely

PROFESSOR M BLOCKMAN
CHAIRPERSON, FHS HUMAN RESEARCH ETHICS COMMITTEE
Federal Wide Assurance Number: FWA00001637.
Institutional Review Board (IRB) number: IRB00001938
NHREC-registration number: REC-210208-007

HREC/REF 854/2020sa