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Analysis of clinical symptoms, radiological changes and pulmonary function data 4 months after COVID-19

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Abstract

Background: Coronavirus disease 2019 (COVID-19) ranges from asymptomatic disease to respiratory failure and requires invasive mechanical ventilation (IMV). Data about the sequelae after infection are scarce. The study aims to describe the prevalence of symptoms, pulmonary function tests (PFTs), and radiological changes after four months of follow-up.

Methods: A prospective, cross-sectional, multicentre study was performed. Patients with different illness severities were consecutively included (mild; moderate: hospitalized without IMV; severe: hospitalized with IMV). Clinical variables, health-related quality of life (HRQoL), PFT (spirometry, diffusing capacity of the lungs for carbon monoxide (DLCO)), and (CT) scans of the chest were obtained. The association between the risk of sequelae (DLCO <80%) and altered CT was analysed using logistic regression adjusted for confounding variables.

Results: 60 patients (18 mild, 17 moderate, and 25 severe) were included. Fatigue was found in 11% of the mild, 47% of the moderate and 36% of the severe group. Altered DLCO (mild: 5.5%, moderate: 41%, severe: 28%, $p < .05$) and change in HRQoL (mild: 50%, moderate: 94%, severe: 60%), while the severe group showed a higher prevalence of altered CT (88% vs. 64%). Awake prone position (APP) and high-flow nasal cannula (HFNC) was independently associated with altered DLCO, Odds ratio (OR) 7.28 (CI, 1.10-47.81; $p < .05$), and altered CT, OR 9.50 (CI, 1.26-71.5; $p < .05$). Besides, prolonged time in IMV was associated with altered CT, OR 1.24 (CI, 1.05-1.46; $p < .05$).

Discussion: It is common to find sequelae in symptoms, radiology, and PFT. In our series, the use of APP+HFNC and days on IMV were associated with an increased risk of sequelae.

KEYWORDS
coronavirus, COVID-19, pulmonary function test, SARS-CoV-2

Study register: ISRCTN16865246.

1 | INTRODUCTION

According to the World Health Organization (WHO), SARS-CoV-2 has caused a total of 113 274 506 confirmed cases, including 2 512 407 deaths.[1,2] The 2019 coronavirus infection (COVID-19) varies from asymptomatic infection to acute respiratory distress syndrome (ARDS). These cases require connection to invasive mechanical ventilation (IMV) and admission to the intensive care unit (ICU).[3,4]

The high prevalence of severe symptoms and increased demand for IMV have led to the incorporation of new therapeutic interventions such as the awake prone position (APP) and the high-flow nasal cannula (HFNC).[3,5,6] However, during the acute phase of COVID-19, the severity and mortality of the condition are higher than those of other respiratory diseases such as the influenza virus.[7,8]

Few data in the literature describe the recovery phase of the disease. Regarding mental health, there has been an increase in depressive and anxious presentations.[9] On the other hand, pulmonary sequelae of SARS-CoV-2 are common in the early stages.[10,11] Preliminary studies have focused on the first months after infection and have shown a decrease in distance covered in the walking test, a reduction in diffusing capacity of the lung for carbon monoxide (DLCO),[11,12] and alterations in imaging tests, such as computed tomography (CT) scans of the chest.[10] On this last point, previous studies have reported that pulmonary fibrosis is a possible sequela among SARS survivors (CoV-2).[13]

This study's objective was to evaluate the radiological sequelae, lung function impairment, and HRQoL of patients who presented with SARS-CoV-2 infections of different clinical severities after four months of follow-up in Chile.

2 | METHODS

2.1 | Study design

This study was performed according to the current recommendation from the STROBE statement.[14] We conducted a cross-sectional analysis including two academic hospitals located in Chile (Hospital Regional Dr Guillermo Grant Benavente, Concepcion, and Complejo Asistencial Dr Victor Rios Ruiz, Los Angeles). The protocol of this study was previously published in the ISRCTN register (ID: ISTCTN16865246). This study was approved by the institutional review board (IRB) of Servicio de Salud Biobio (Code: CEC113) and Servicio de Salud Concepcion (Code CEC-SSC: 07-20-26), and written informed consent was obtained previously for inclusion in the study.

We included patients aged ≥18 years with previous positive PCR for SARS-CoV-2 infection from April to July 2020. As exclusion criteria, patients characterized by the following: (1) presenting with active cancer during follow-up, (2) being a patient in palliative care during follow-up, (3) being lost to follow-up or having transferred to another hospital or city during the follow-up, and (4) having a severe mental disability during follow-up.

For study purposes, we developed three study groups according to the COVID-19 acute phase, following the WHO recommendations[3]:

- Severe COVID-19: Severe hypoxemia and medical records of ARDS according to the Berlin criteria.[15] This group was admitted to the ICU.
- Moderate COVID-19: Clinical or radiographic evidence of lower respiratory tract disease; this group required hospitalization without connection to IMV.
- Mild COVID-19: Mild symptoms (eg, fever, cough, and change in taste or smell, without dyspnea); this group received clinical outpatient monitoring and supportive care. Mild cases were determined according to $PaO_2/FiO_2 > 250$ when measured and when the patient reported mild symptoms (eg, fever, cough, and change in taste or smell) without dyspnea according to the initial telephonic evaluation and during follow-up clinical evaluation.

For the moderate and severe groups, we identified patients from our REDCAP database, and for the mild group, participants were telephonically invited to participate as a control group.

2.2 | Data extraction

2.2.1 | Baseline and ICU stay

We extracted data detailing a patient's previous medical records and COVID-19 illness during the acute phase. At baseline, we pulled data describing demography (age, sex, year of schooling, rural area); anthropometry (weight, health, body mass index (BMI) (kg/m^2)); social habits (alcohol, tobacco history); comorbidities (arterial hypertension, insulin resistance, diabetes mellitus, hypothyroidism, arrhythmia, coronary heart disease); and current medications. During the acute phase, we extracted data detailing a patient's COVID-19 symptoms. The poorest values of each of the following laboratory parameters were reported: ferritin (mg/dl), C-reactive protein (CRP) (mg/dl), leukocyte count ($\times 10^9$), lymphocyte count ($\times 10^9$), D-dimer (mg/dl), fibrinogen (mg/dl), and PaO_2/FiO_2 ratio. Also, we extracted data on medical interventions performed during hospitalization (antibiotics, HFNC, APP), use of steroids (dexamethasone), anti-interleukin 6 (Tocilizumab), use of IMV, days in IVM, neuromuscular blockade (NMB), prone position, tracheostomy, full days in ICU, and total days in the hospital.

2.2.2 | Four months follow-up

Details of the protocol and procedures in the follow-up visit are available in E-Appendix 1 in Supplementary Information. After four months of follow-up, all participants underwent a clinical evaluation exploring current COVID-19 symptoms and new symptoms, such as muscle fatigue measured by the binary Chalder fatigue questionnaire.[16] A cut-off point of ≥4 points was considered severe fatigue. Additionally, we asked about the following symptoms: self-report of decreased libido, alopecia, new paraesthesia, or paresis of the lower or upper extremities. Dyspnea was achieved by the modified medical research council (mMRC), and depression was assessed using the Beck Depression Inventory.[17] During the evaluation, the participants completed the following questionnaires: The Hospital Anxiety and Depression Scale (HDAS)[18] and the Short Form 12 Health Survey (SF-12), the latter used to evaluate HRQoL and included both physical and mental domains.[19] Finally, the personal change in HRQoL was assessed using a visual analog scale with a range of 0% (worst HRQoL) and 100% (best HRQoL) before SARS-CoV-2 infection during the follow-up. A change ≥of 10% was indicative of a change in HRQoL, similar to previous reports.[20]

2.2.3 | Pulmonary function tests (PFTs)

During the follow-up, an arterial blood sample was obtained for arterial blood gas analysis. The procedure was performed at room temperature, with an FIO2 of 21% and a barometric pressure of 760 mm Hg. All participants underwent forced spirometry at baseline and 15 min after inhalation of 400 μg of salbutamol (CPF-S/D; Medical Graphics Inc, USA). The procedure followed the current guidelines of the American Thoracic Society (ATS).[21] We extracted data from the forced vital capacity (FVC, %), forced expiratory volume in the first second (FEV1, %), FEV1/FVC ratio, and forced expiratory flow 25-75% (FEF 25-75, %).

Besides, DLCO and a six-minute walk test (6MWT) were performed. DLCO (Elite PlatinumDL; Medical Graphics Inc, USA) was corrected using the barometric pressure described above. We extracted data corrected by haemoglobin (DLCOc), % ml/min/mm Hg, DLCOc 80%, alveolar volume (AV, %), and DLCO/AV ratio (%). The 6MWT was performed following current ATS guidelines (meters, %).[22] Finally, all PFTs were reported as percentages (%) of predictive value, following the Chilean population's predictive values.[23-26] (E-Appendix-1 in Supplementary Information).

2.2.4 | CT scan of the chest

All images were acquired using a high-resolution CT scan (SOMATOM, Siemens, Germany). In a cephalic-caudal direction, the patients in a supine position with slices achieved at the end of inspiration and end of expiration (E-Appendix-1 in Supplementary Information). A radiologist blinded to the medical records evaluated the images and classified them as normal or abnormal chest CTs. The following findings were extracted according to the Fleischner Society[27]: ground-glass opacities, mixed ground-glass opacities, consolidation, interlobular thickening, bronchiectasis, atelectasis, solid nodules, nonsolid nodules, reticular lesions, fibrotic lesions, air trapping, and the number of lobes affected. In addition, the abnormalities on chest CT were quantified using the total severity score (TSS). This score includes the visual inspection of each lobe, reporting the % impairment of each lobe (0-25%: 1 point; 26-50%: 2 points, 51-75%: 3 points, and 76-100%: 4 points), and the sum of each lobe represents the TSS. This method was previously reported in patients with ARDS by Ooi et al.[28]

2.2.5 | Statistical analysis and confounder assessment

The means (standard deviations) and medians [interquartile range] were estimated for quantitative variables with normal and nonnormal distributions. The absolute and relative frequencies will be used for qualitative variables. The Shapiro-Wilk test was used to analyse the normality of distributions. The appropriate tests established differences between the groups: t-test, ANOVA, chi-squared (for parametric variables), Mann–Whitney U-test, or Fisher's exact test (for nonparametric variables). In the case of significant intergroup differences, we performed a post hoc analysis following the Bonferroni method.

The association between PFT and abnormal chest CT was evaluated using unadjusted and adjusted analyses. The results were reported as odds ratios (ORs) with their respective confidence intervals (95%-CIs) using a logistic regression model following a stepwise analysis. We predefined demographic and medical interventions during acute COVID-19 as potential confounding variables (age, sex, hypertension, BMI, tobacco history, ferritin levels, D-dimer, weeks since SARS-CoV-2 diagnosis, the severity of COVID-19 illness, ARDS, ICU stay, HFNC, APP, IMV, BNM, tracheostomy, and days in IMV). All analyses were performed using SPSS version 25.0 software (IBM statistics, Chicago, USA), and a p value $< .05$ was considered statistically significant.

2.2.6 | Sample size

We hypothesized that the risk of pulmonary sequelae after four months is associated with COVID-19 severity. We used the previous data from Torres-Castro et al,[29] who reported a

66% of sequelae among patients with severe COVID-19 and using a baseline prevalence of 15%, a 90% of potency, and a *p* value of 0.05 (type 1 error), the estimated sample size was 16 per group.

3 | RESULTS

The study flowchart is shown in Figure 1. A total of 18 patients were included in the mild, 17 in the moderate, and 25 in the severe COVID-19 classifications. Patients classified as severe were significantly older than those classified as mild (50.0 (±10.3) vs. 39.2 (±14.3) years old). We found no differences in tobacco history within groups. Regarding comorbidities, the moderate group included significantly more patients with diabetes mellitus (35.2%) and insulin resistance (29.4%). Concerning current medication, a higher percentage of patients in the moderate group reported metformin (47%) and insulin (29.4%) than in the other groups. Table 1 shows the baseline characteristics according to the level of severity.

Regarding COVID-19 illness during the acute phase, we found differences between the severe group regarding the total days of hospitalization (29.9 days ± 23.4), days in the ICU (13.0 days ± 13), and days of IMV (10.2 days ± 7.5). Furthermore, this group presented lower PaO_2/FIO_2. In contrast, the moderate group presented lower lymphocyte counts. Both groups reported using systemic dexamethasone as a corticosteroid following the RECOVERY trial.[30] Sixteen patients with mild COVID-19 were discharged without supplementary O_2. Those with moderate COVID-19 received O_2 therapy in the medical ward. We did not use CPAP-BiPAP therapy in these patients. Moreover, any patient-reported additional O_2 or CPAP-BiPAP therapy after discharge. Regarding other clinical characteristics of COVID-19 patients, there were no statistically significant differences (Table 2).

Figure 2 shows symptoms associated with COVID-19 during the acute period and follow-up. Diarrhoea and fever were only reported in the critical stage of the disease. Symptoms such as headache (38%) and dyspnea (24%) continued to manifest during follow-up. We found that fatigue was reported in 46% of the moderate group, 36% of the severe group, and 11% of the mild group. Compared to other groups, the moderate group reported an increased score on the HDAS (anxiety domain; 8.58 points ± 3.9) and a decreased score on the SF-12 (physical domain; 37.0 points ± 14.2). We found individual changes in HRQoL for 94% of the moderate group, 60% of the severe group, and 50% of the mild group. Finally, we found a nonsignificant difference in the Beck Depression Inventory. Table 3 shows the symptom and psychosocial questionnaire values collected during follow-up.

3.1 | PFTs and CT scan of the chest

During follow-up, the moderate group showed lower FVC (82.5% (±17.2) vs. 87.7% (±15.4) vs. 97.4% (±17.3)) and lower AV (87.3% (±15.7) vs. 89.9% (±12.6) vs. 100.8% (±16.4)) than the other groups. Furthermore, the moderate group showed worse PFT than the severe group (35.3% of FEV1/FVC <70% vs. 12%; and 41% DLCO <80% vs. 28%). There were no statistically significant differences in other lung function variables (Table 4).

Regarding chest CT at follow-up, 88% of abnormal CTs were found in the severe group compared to 64.7% in the moderate group and 22% in the mild group. The main finding was ground grass opacities (72% in the severe group) and solid nodules (32%) were significantly different. In addition, the total severity score (TSS) was 0.38 (±0.7) in the mild group, 2.59 (±3.0) in the moderate group and 3.2 (±2.3) in the severe group. No statistically significant differences were found for the other pulmonary findings by CT (Table 5).

Finally, Table 6 shows the association of having a DLCO <80% and an altered CT given by variables related to a greater risk of sequelae of COVID-19. The unadjusted model showed that patient age, the development of ARDS, the use of APP+HFNC, and corticosteroids were associated with

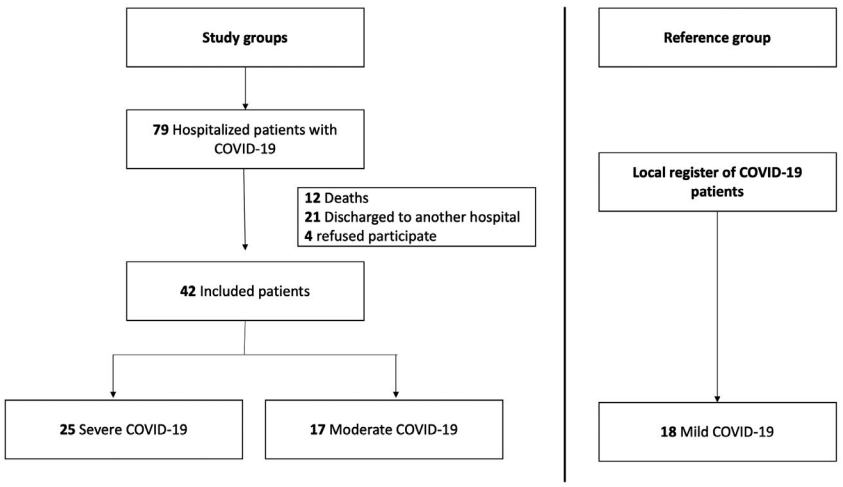

FIGURE 1 Study flowchart

TABLE 1 Baseline characteristic of the included participants (total = 60)

Variable	Mild ($n = 18$)	Moderate ($n = 17$)	Severe ($n = 25$)
Sex male, *n* (%)	6 (33.3)	11 (64.7%)	15 (60)
Age (years), (SD)	39.2 (±14.3)	47.4 (±11)	50.0 (±10.3)[a,b]
Years of schooling, *n* (%)			
<8 years	4 (22.2)	5 (29.4)	14 (56)
8-12 years	6 (33.3)	3 (17.6)	4 (16)
≥12 years	8 (44.5)	9 (52.9)	7 (28)
Rural area, (%)	1 (5.6)	3 (17.6)	2 (8)
Comorbidities			
Hypertension, (%)	2 (11.1)	8 (47)	9 (36)
Diabetes mellitus, (%)	1 (5.5)	6 (35.2)[a,c]	5 (20)[a]
Insulin resistance, (%)	0 (0)	5 (29.4)[a,c]	1 (4)[a]
Hypothyroidism, (%)	1 (5.5)	0 (0)	4 (16)
BMI (kg/m^2), (%)	29.8 (5.7)	30.9 (2.3)	32.1 (5.7)
Obesity (BMI ≥30 kg/m^2), (%)	6 (33.3)	9 (52.9)	15 (60)
Tobacco			
Nonsmoker, *N* (%)	17 (66.6)	20 (52.9)	20 (58.8)
Current, *N* (%)	4 (22.2)	1 (5.8)	3 (8.8)
Former, *N* (%)	2 (11.1)	7 (38.8)	11 (32.3)
Pack/year, mean (SD)	5.6 (±7.5)	8.1 (±9.3)	8.6 (±9.3)
Diuretics, (%)	1 (5.5)	2 (11.7)	2 (8)
Metformin (%)	2 (11.1)	8 (47)[a,c]	7 (28)[a]
Insulin, (%)	0 (0)	5 (29.4)[a,c]	1 (4)[a]
Hypolipemiant drugs, (%)	2 (11.1)	6 (35.2)	4 (16)
Hypnotic drugs, (%)	2 (11.1)	4 (23.5)	4 (16)
Antidepressants, (%)	1 (5.5)	1 (5.8)	3 (12)

Abbreviations: ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin II receptor blocker; BMI, body mass index; SD, standard deviation.

[a]Statistical difference compared to mild group, p value < .05.

[b]Statistical difference compared to moderate group, p value < .05.

[c]Statistical difference compared to severe group, p value < .05.

a risk of DLCO <80% and an increased risk of having an altered CT scan. After multivariable analysis adjusted for confounding variables, the use of APP+HFNC had an OR of 7.28 (95%-CI, 1.10-47.81, $p = .03$) for a DLCO <80% and an OR of 9.5 (95%-CI, 1.26-71.5, $p = .04$) for having an altered CT compared to those who did not use APP+HFNC. Additionally, we found that IMV was associated with an OR of 1.24 (95%-CI, 1.05-1.46, $p = .4$) for an altered chest CT scan.

4 | DISCUSSION

This study's main findings are as follows (1) After four months of follow-up, the prevalence of severe fatigue is frequent among patients with different severities of COVID-19 illness. (2) Hospitalized patients with moderate SARS-CoV-2 have a higher prevalence of anxiety symptoms and alterations in the physical activity domain. (3) In the same group, we found a higher prevalence of altered PFT (spirometry and DLCO). (4) In severe COVID-19, radiological sequelae's presence is significant and predominantly consists of ground glass persistence. (5) In our cohort, the multivariate analysis resulted in an independent association between the use of APP+HFNC therapy and the risk of radiological and pulmonary function sequelae.

After COVID-19 infection, patients report a high prevalence of symptoms related to increased tiredness and fatigue, which is correlated with a subjective appreciation of a lower quality of life. In a study by Carfi et al[20] carried out in Italy, 60% of the patients presented significant alterations in their HRQoL. Other studies ranged between 1 and 3 months, confirming these findings.[31,32] In our study, we separated our population by the severity of COVID-19. As a result, we

TABLE 2 Clinical characteristic during the acute COVID-19 illness (total = 45)

Variable	Mild ($n = 3$)[d]	Moderate ($n = 17$)	Severe ($n = 25$)
Days in hospital (days), (SD)	0	9.4 (±6.2)[a]	29.9 (±23.4)[a,b]
Days in ICU (days), (SD)	0	2.6 (±5.6)[a]	13.0 (±8.3)[a,b]
Days in IMV (days), (SD)	0	0	10.2 (±7.5)[a,b]
Ferritin (mg/dl) (days), (SD)	190 (±186)	1614 (±1511)[a]	2390 (±1591)[a]
CRP (mg/dl) (days), (SD)	2.0 (±5.2)	138 (±82.4)[a]	172 (±135)[a]
Leukocyte count (×109), (SD)	6955 (±1254)	8864 (±43.1)[a]	11 931 (±5.452)[a]
Lymphocyte count (×109), (SD)	2880 (±982)	863 (±355)[a]	872 (±321)[a]
D-Dimer (mg/dl), (SD)	215 (±312)	900 (±422)[a]	1871 (±1248)[a,b]
Fibrinogen (mg/dl), (SD)	319 (±184)	652 (±59)[a]	732 (±262)[a]
PaO_2/FIO_2 ratio, (SD)	350 (±26.0)[a]	246 (±80.2)[a]	179 (±44.1)[a,b]
HFNC, *n* (%)	0 (0%)[a]	8 (53.3)[a,c]	9 (36)[a]
Awakening prone position, *n* (%)	0 (0%)[a]	11 (73.3)[a,c]	9 (36)[a]
Antibiotics, *n* (%)	0 (0%)	15 (100)[a]	25 (100)[a]
Steroids, *n* (%)	0 (0%)	11 (73.3)[a]	14 (56)[a]
Anti-interleukin 6, *n* (%)	0 (0%)	0 (0%)	2 (8)[a]
NMB, *n* (%)	0 (0%)	0 (0%)	18 (72)[a,b]
Prone, *n* (%)	0 (0%)	0 (0%)	14 (56)[a,b]
Tracheostomy, *n* (%)	0 (0%)	0 (0%)	7 (28)[a,b]

Abbreviations: CPR, C- reactive protein; HFNC, high flow nasal cannula; ICU, intensive care unit; IMV, invasive mechanical ventilation; NMB, neuromuscular blockage; PaO_2/FiO_2, ratio arterial oxygen pressure/inspiratory oxygen fraction; SD, standard deviation.

[a]Statistical difference compared to mild group, p value < .05.

[b]Statistical difference compared to moderate group, p value < .05.

[c]Statistical difference compared to severe group, p value < .05.

[d]Data from 3 patients in mild group was used as reference value.

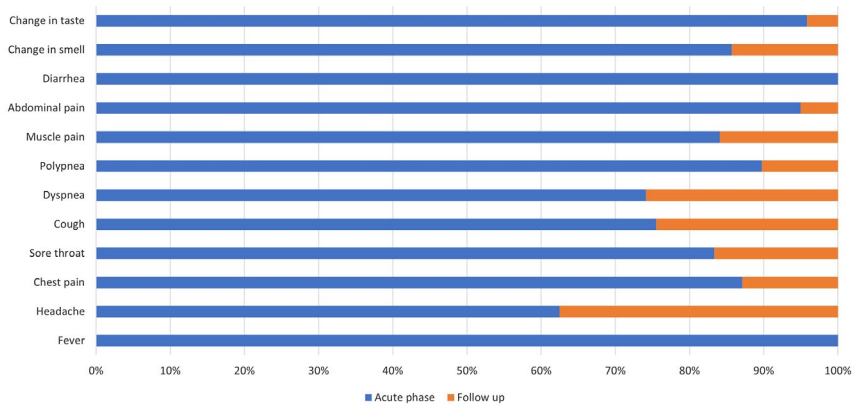

FIGURE 2 Prevalence of COVID-19 related symptoms during the acute infection and the follow-up visit

found a high prevalence of symptoms without significant differences among groups.

We found a significant difference between patients with moderate COVID-19 regarding HRQoL and psychosocial health in contrast to mild and severe COVID-19. We consider this finding innovative since it suggests that this group of patients exposed to new therapies such as the awakening prone position and HFNC during the acute phase presented an increased psychosocial sequelae prevalence. Moreover, we found that this group showed an increased risk of alteration in PFT. In our series, this group included 41% of those patients with altered DLCOc, compared to 28% of severe patients who required IMV. Additionally, this association was not associated with tobacco history. Compared with other COVID-19 studies, our prevalence is similar to that reported by studies from China[11,12] and extrapolated data from other viral infections such as influenza, SARS, and MERS viruses.[33,34] Huang et al during follow-up at one month after hospital discharge,

TABLE 3 Clinical and questionnaire score 4 months after SARS-CoV-2

Variable	Mild ($n = 18$)	Moderate ($n = 17$)	Severe ($n = 25$)
Tiredness, (*N*) (%)	13 (72)	16 (94.1)[a,b]	19 (76.0)
Fear to get infected again, (*N*) (%)	4 (22.2)	10 (58.8)	11 (44.0)
Decreased libido, (*N*) (%)	0 (0)	4 (23.5)	3 (12.0)
Paresthesias, (*N*) (%)	2 (11.1)	8 (47)	8 (32.0)
Alopecia, (*N*) (%)	2 (11.1)	2 (11.7)	4 (16.0)
Paresis, (*N*) (%)	0 (0)	1 (5.8)	4 (16.0)
Questionnaires			
mMRC, (*N*) (%)			
Grade 0, (*N*) (%)	7 (38.9)	5 (29.4)	4 (16.0)
Grade 1, (*N*) (%)	10 (55.6)	11 (64.7)	19 (76.0)
Grade 2, (*N*) (%)	1 (5.5)	0 (0)	1 (4.0)
Grade 3, (*N*) (%)	0 (0)	1 (5.9)	1 (4.0)
Grade 4, (*N*) (%)	0 (0)	0 (0)	0 (0)
Chalder (points), (SD)	4.4 (±3.4)	6.5 (±2.2)	5.1 (±2.6)
Severe fatigue, (%)	5 (11.1)	10 (47)[a]	10 (36%)[a]
HDAS- Anxiety, (points), (SD)	5.87 (±4.8)	8.58 (±3.9)[a,b]	5.60 (±3.6)
HDAS- Depression, (points), (SD)	5.5 (±4.6)	5.94 (±3.6)	3.4 (±2.9)
Beck depression (points), (SD)	9.3 (±9.9)	12.1 (±8.1)	8.9 (±6.8)
SF-12 (physical domain) (points), (SD)	50.3 (±7.7)	37 (±14.2)[a,b]	41.2 (±10)[a]
HRQoL at baseline (%), (SD)	89 (±12.7)	88 (±7.8)	89.9 (±10.2)
HRQoL final (%), (SD)	74.4 (±24.3)	60 (±18.6)	70.6 (±23.2)
Change in HRQoL >10%, *N* (%)	9 (50)	16 (94)[a,b]	15 (60)

Abbreviations: HDAS, hospital anxiety and depression scale; HRQoL, health related quality of life; mMRC, modified medical research council; SF-12, short form-12.

[a]Statistical difference compared to mild group, p value < .05.

[b]Statistical difference compared to severe group, p value < .05.

observed 30 individuals (52.6%) with abnormal diffusion capacity among the 57 patients participating in the study.[35] A similar observation was reported by Shah et al. A 12-week follow-up study showed abnormal DLCO in 52% of patients, with 45% of these patients also having an abnormal total lung capacity indicating a concurrent restrictive ventilatory deficit.[36] In a systemic review and meta-analysis, Torres-Castro et al. found a prevalence of altered diffusion capacity of 39% (CI 24-56%). In the severity analysis, the prevalence found was 66% (CI 31-94%, $p < .01$).[29] An exciting observation on the possible mechanisms related to alteration of DLCO after COVID-19 pneumonia was reported by Chapman et al. The reduction of DLCO is explained by reduced Alveolar Volume (VA) and abnormal gas exchange. Lung fibrosis associated with acute respiratory distress syndrome in COVID-19 patients would likely damage alveolar-capillary units, leading to loss of alveolar units and impaired gas exchange.[37]

Although to date, we have found no explanation for this association, we hypothesize that the combination of novel interventions,[5] such as the hyperoxia provided by APP and HFNC therapy, in association with lung damage secondary to spontaneous ventilation and the different connections to IMV in patients with ARDS, can be a possible mechanism for this association. However, these findings should be investigated in future studies. In other research, Vianello et al demonstrated that HFNC played an essential role in reversing hypoxemia in approximately two-thirds of the patients with SARS-CoV-2 with severe hypoxemic acute respiratory failure unable to achieve SaO2 ≥ 92% under standard oxygen therapy.[38] This improvement in oxygenation was explained on varied mechanisms, such as matching of delivered flow with increased ventilatory demand, the achievement of high and stable FIO2 (up to 100%), upper airway washout, generation of positive pressure at end-expiration, and delivery of air heated and humidified.

Finally, the persistence of altered chest CT after four months was more common in the group of patients with severe infection requiring IMV, which is consistent with lower oxygenation in the acute phase and a collateral effect from management in the ICU. However, after the

TABLE 4 Changes in the pulmonary function test 4 months after COVID-19 pneumonia

Variable	Mild ($n = 18$)	Moderate ($n = 17$)	Severe ($n = 25$)
Arterial blood gas			
pH, (SD)	7.4 (±0.01)	7.39 (±0.02)	7.39 (±0.02)
PaO_2 (mm Hg), (SD)	104.3 (±8.4)	97.7 (±6.7)	100 (±9.4)
pCO_2 (mm Hg), (SD)	38.6 (±3.1)	40.0 (±3.4)	38.7 (±2.8)
HCO_3^- (mEq/L), (SD)	23.6 (±1.7)	24.1 (±1.5)	22.9 (±1.4)
Base excess	−0.9 (±1.0)	−0.9 (±1,6)	−1.2 (±1.4)
A-a difference	9.2 (±7.1)	9.3 (±6.6)	9.4 (±10.6)
Spirometry			
FVC (%), (SD)	97.4 (±17.3)	82.5 (±17.2)[a,c]	87.7 (±15.4)[a]
VEF_1 (%), (SD)	99.5 (±26.8)	87.7 (±15.4)	93.6 (±13)
VEF_1/CVF (%), (SD)	101.7 (±8.6)	105.4 (±9.3)	107.3 (±9.7)
VEF_1/CVF <70%, (*N*, %)	1 (5.5)	6 (35.3)[a,c]	3 (12)[a]
FEF 25-75 (%), (SD)	104.1 (±27.0)	94.5 (±29.1)	114.3 (±40.6)
DLCO (ml/min/mm Hg)			
DLCOc (%), (SD)	92.6 (±20.4)	82.3 (±19.7)	88.9 (±21.8)
DLCOc <80%, (*N*, %)	1 (5.5)	7 (41.2)[a,c]	7 (28.0)[a]
Alveolar volume (%), (SD)	100.8 (±16.4)	87.3 (±15.7)[a,c]	89.9 (±12.6)[a]
Ratio DLCO/AV (%), (SD)	82.4 (±15.2)	80.3 (±14.2)	85.3 (±18.8)
6MWT			
Distance (meters), (SD)	545 (±87)	521 (±106)	506 (±123)
Predicted distance (meters), (SD)	618 (±102)	567 (±62)[a]	548 (±80)[a,b]
Predicted (%), (SD)	88.9 (±10.5)	91.9 (±15.9)	92.7 (±209)

Abbreviations: 6MWT, six minutes walking test; A-a, alveolar-arterial oxygen difference; c, corrected by hemoglobin; DLCO, diffusing capacity of the lung for carbon monoxide; FEV_1, forced expiratory volume in the first second; FEV_1/FVC ratio, FEF 25-75, forced expiratory flow at 25-75% of forced vital capacity; FVC, forced vital capacity; SD, standard deviation.

[a]Statistical difference compared to mild group, p value < .05.

[b]Statistical difference compared to moderate group, p value < .05.

[c]Statistical difference compared to severe group, p value < .05.

multivariate analysis, we found that the risk of presenting an altered CT was independently associated with the use of APP+HFNC and days of IMV during the acute phase. Additionally, the use of APP+HFNC therapy was associated with an increased risk of altered DLCOc. Based on our results, we consider that using awake prone decubitus and HFNC as an alternative therapy to orotracheal intubation and connection to IMV in patients with severe COVID-19 pneumonia may increase the prevalence of sequelae after four months. However, these findings have to be confirmed in subsequent studies, including many patients and longer follow-ups.

This is the first study to have focused on the analysis of radiological sequelae, quality of life, and lung function in Latin America to the best of our knowledge. The main limitations of our study are the small number of patients. Another limitation is our sample's follow-up, which was focused four months after COVID-19, which could lead to bias due to the potential effect of time since infection and the risk of sequelae. However, our analyses were adjusted for weeks from diagnosis, reducing this possible confounding effect. Finally, we consider that it is essential to study sequelae after COVID-19 recovery to identify patients with impaired lung function to apply therapeutic strategies to reduce long-term sequelae and improve quality of life.

In conclusion, patients diagnosed with COVID-19 presented a high prevalence of symptoms and impaired quality of life, regardless of infection severity. In those with COVID-19 pneumonia, which required hospital admission, the use of an APP and HFNC was associated with an increased risk of presenting altered DLCOc and chest CT during follow-up. Additionally, prolonged IMV stay was also associated with an increased risk of altered chest CT. Longer follow-up

TABLE 5 Changes in the computed tomography (CT) scan of the chest 4 months after SARS-CoV-2 infection

Variable	Mild ($n = 18$)	Moderate ($n = 17$)	Severe ($n = 25$)
Abnormal CT, *n* (%)	4 (22.2)	11 (64.7)[a]	22 (88)[a,b]
Ground-glass opacities, *n* (%)	2 (11.1)	7 (41.2)[a]	18 (72)[a,b]
Mixed ground-glass opacities, *n* (%)	0 (0)	2 (11.8)	1 (4)
Consolidation, *n* (%)	0 (0)	1 (5.9)	0 (0)
Interlobular thickening, *n* (%)	1 (5.5)	5 (29.4)[a]	8 (32)[a]
Bronchiectasis, *n* (%)	0 (0)	2 (11.8)	4 (16)
Atelectasis, *n* (%)	0 (0)	1 (5.9)	6 (24)
Solid nodules, *n* (%)	0 (0)	3 (17.6)[a]	8 (32)[a,b]
Non-solid nodules, *n* (%)	0 (0)	3 (17.6)[a]	6 (24)[a]
Reticular lesions, *n* (%)	1 (5.5)	3 (17.6)[a]	1 (4)
Fibrotic lesions, *n* (%)	0 (0)	3(17.6)[a]	5 (20)[a]
Air trapping, *n* (%)	2 (11.1)	6 (35.3)[a]	7 (28)
Number of lobes affected, *n* (±)	0.5 (±0.8)	1.4 (±1.2)	1.9 (±1.5)
TSS (mean), (±)	0.38 (±0.7)	2.58 (±3.0)	3.2 (2.3)[a]

Abbreviation: TSS, total severity score.

[a]Statistical difference compared to mild group, p value < .05.

[b]Statistical difference compared to moderate group, p value < .05.

TABLE 6 Unadjusted and adjusted risk of radiological sequelae and DLCO <80%

	Non adjusted model	Adjusted model
	OR (95%-CI)	OR (95%-CI)
DLCO <80%		
Age	1.05 (1.01-1.11)[a]	1.03 (0.96-1.10)
ARDS	4.18 (1.03-16.58)[a]	1.28 (0.14-11.53)
APP+HFNC	8.92 (2.13-37.33)[a]	7.28 (1.10-47.81)[b]
Steroids usage[c]	4.71 (1.10-20.20)[a]	0.85 (0.08-9.0)
Abnormal chest CT		
Age	1.07 (1.02-1.12)[a]	1.07 (0.99-1.16)
ARDS	11.50 (3.18-41.56)[a]	6.06 (0.20-175.7)
APP+HFNC	86.61 (1.55-28.16)[a]	9.50 (1.26-71.5)[b]
Steroids usage[c]	10.0 (2.56-39.06)[a]	3.48 (0.22-54.26)
IMV	3.50 (1.03-11.92)[a]	1.94 (0.2-15.0)
Days in IMV	1.16 (1.03-1.30)[a]	1.24 (1.05-1.46)[b]

Abbreviations: ARDS, acute respiratory distress syndrome; APP, awake prone position; CT, computed tomography; HFNC, high flow nasal cannula; IMV, invasive mechanical ventilation.

[a]Statistically significant variable with a p value < .05.

[b]Adjusted analysis after controlling for confounders in the logistic regression analysis (Age, sex, hypertension, BMI, smoking, ferritin levels and D-dimer levels, time since the diagnosis of SARS-CoV-2 [weeks], and for the interventions performed during the hospital stay [severity of COVID-19, hospital stay in ICU, CNAF, prone vigil, steroids, IMV, BNM, tracheostomy, and days in IMV]) with a p value < .05.

[c]Dexamethasone according to RECOVERY trial.

studies with larger numbers of patients will be required to validate these findings.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

AUTHOR CONTRIBUTIONS

GL, EN, MH, FL, JL, LL, VO: Contributed to study design and study execution; MH, JL, CR, FF, NC, EE: Data extraction and analysis. GL, MH, EN: Drafting of the manuscript. GL, EN, MH, FL, JL, LL, VO, GH, SF: Critical review and final approval.

All authors approved the final version of the manuscript.

ETHICAL APPROVAL

This study was approved by the institutional review board (IRB) of Servicio de Salud Biobio (Code: CEC113) and Servicio de Salud Concepcion (Code CEC-SSC: 07-20-26), and written informed consent was obtained previously for inclusion in the study.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the Supporting Information section.

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