

The Impairment of Respiratory Gas Transport Due to SARS.CoV-2 Pneumonia Persists Essentially Unchanged Over At Least 52 Weeks Despite the “Apparent” CT Complete Recovery

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Received: September 29, 2026; **Published:** October 12, 2026

Abstract

Background: The pulmonary capillary rarefaction and the consequent drop in lung blood volume (Vc) have been identified as major pathogenetic factors underlying SARS.CoV-2 pneumonia, resulting the respiratory gas transport affected at variable degree.

Aim: To investigate over fifty-two-week the duration of troubles in respiratory gas transport occurring in patients radiologically (CT) recovered from COVID-19 pneumonia, but still complaining persistent dyspnea.

Methods: This secondary longitudinal analysis included 30 untreated adults previously hospitalized for COVID-19 pneumonia. Spirometry, DL_{CO}, simultaneous single-breath diffusing capacities for nitric oxide and carbon monoxide (sDL_{NO} and sDL_{CO}), sDL_{NO}/sDL_{CO} ratio, pulmonary capillary blood volume (Vc), oxygen saturation, and the mMRC dyspnea score were assessed at baseline and after 4, 12, 24, and 52 weeks. Continuous outcomes were analyzed by linear mixed-effects models while the mMRC scores by mixed-effects ordered logistic regression.

Results: Lung volumes and DL_{CO} remained broadly stable over 52 weeks. Vc, that was markedly reduced at baseline (39.5% predicted), remained unchanged after 52 weeks (38.9%; global time effect p = 0.165). The sDL_{NO}/sDL_{CO} ratio remained abnormally high despite a slight decrease over time from 131.4% to 127.4% predicted (p = 0.008). After 52 weeks, the mMRC score slightly improved in 43.3% of patients, while remained unchanged in 43.3%, and further worsened in 13.3%.

Conclusion: Abnormalities in respiratory gas transport persist essentially unchanged for at least 52 weeks after CT recovery from COVID-19 pneumonia, being the symptomatic improvement quite limited. These findings confirm the long lasting impairment of pulmonary capillary function in respiratory Long COVID.

Keywords: Long COVID; Pulmonary Capillary Blood Volume; Dyspnoea; Nitric Oxide

Introduction

The impact of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) infection on lung structures is characterized by alveolar involvement together with the occurrence of vascular endothelial damage and microvascular occlusion in the lung due to activation of platelets and several mediators that stimulate coagulation and micro-thrombosis [1-6].

Citation: Povero Massimiliano., et al. “The Impairment of Respiratory Gas Transport Due to SARS.CoV-2 Pneumonia Persists Essentially Unchanged Over At Least 52 Weeks Despite the “Apparent” CT Complete Recovery”. *EC Pulmonology and Respiratory Medicine* 15.11 (2026): 01-11.

Growing interest had developed in this field of research as the consequences of this complex tissular injury [7] were presumed to cause substantial troubles in respiratory gas transport. Actually, the persisting dyspnea reported by a large proportion of patients after their hospital discharge following complete radiological recovery from COVID-19 pneumonia (Long Covid) still represents the most frequent clinical sign complained for long time [8,9], although usually investigated for limited duration (usually for one to six months only) [10,11].

Unfortunately, the pathogenesis of this long-lasting dyspnea remained frequently undefined as both spirometric lung volumes and current DL_{CO} proved of limited diagnostic value in these cases [12-19]. The pathophysiology underlying the dyspnea that characterizes for long time the post-COVID-19 pneumonia recovery phase was investigated since 2021 [20]. It was clarified in 2022 when the persistence of a substantial drop in the pulmonary capillary blood volume (V_c) was assessed for the first time by means of the single-breath simultaneous assessment of diffusing capacity of carbon oxide (sDL_{CO}) and of nitric oxide (sDL_{NO}) also in the absence of visible CT parenchymal lesions [21]. This investigational method was later recommended as the most sensitive and specific lung function test to perform in these cases, particularly when dyspnea persists despite normal or near-normal lung volumes [22-24].

Aim of the Study

Aim of the present study was to investigate the spontaneous duration of changes in pulmonary blood volume and in dyspnea score over 52 weeks in patients officially defined by CT as completely recovered from COVID-19 pneumonia, but still complaining long-lasting dyspnea following their hospital discharge (i.e. respiratory Long-COVID syndrome).

Methods

Study design

Out-patients aged ≥ 18 years recovered for COVID-19 pneumonia, but still complaining dyspnea for several months since their hospital discharge were investigated between September 1, 2021 and October 30, 2024, after their informed consent.

All patients had originally suffered from COVID pneumonia affecting $\geq 50\%$ of their lung volume (CT documented). At recruitment, patients provided a CT scan performed in the previous four weeks that confirmed the absence of any visible COVID-related parenchymal residual lesions.

Subjects aged < 18 years, current and former-smokers, with main comorbidities affecting lung diffusion (i.e. blood hemoglobin [Hb] < 12 g/L; heart failure; lung fibrosis; vasculitis; chronic obstructive pulmonary disease [COPD]; diabetes; renal and liver failure), with visible residual COVID-related parenchymal lesions, with physical and/or cognitive limitations enabling lung function assessment, those who refused to sign the informed consent, and those with an incomplete data set were excluded.

Endpoints and assessments

General variables collected were: age, gender, body mass index (BMI), Hb (in g/L) and reported comorbidities. Variables collected at baseline and during the follow-up at pre-specified timepoints (such as, at 4, 12, 24, and 52 weeks) were: the Forced Expiratory Volume in 1sec (FEV_1), the FEV_1 and Forced Vital Capacity (FVC) ratio (FEV_1/FVC), the current DL_{CO} , the simultaneous diffusing capacity of carbon oxide (sDL_{CO}) and of nitric oxide (sDL_{NO}), the sDL_{NO}/sDL_{CO} ratio, the pulmonary capillary blood volume (V_c), the peripheral oxygen saturation (SpO_2) at rest. All these parameters had been reported as % predicted. The modified British Medical Research Council (mMRC) dyspnea score was also recorded over time [25]. At recruitment, the duration (in weeks) of dyspnea lasting after hospital discharge had been also considered.

Spirometric volumes and current DL_{CO} had been assessed by a Platinum DX Elite Plethysmography (MedGraphics, Saint Paul, MN, USA), while sDL_{NO} , sDL_{CO} , The sDL_{NO}/sDL_{CO} ratio and V_c were assessed by means of the “Stand-Alone” Hypair Compact System (MGC

Diagnostics International, Sorinnes, Belgium). This equipment consents the non-invasive simultaneous assessment of DL_{CO} (sDL_{CO}) and DL_{NO} (sDL_{NO}) during usual single breath maneuvers [26,27]. While procedures for current measures of DL_{CO} require a breath-hold times of 10, measures of sDL_{NO} and sDL_{CO} require a breath-hold times of 5 sec [20,26,27]. As DL_{CO} is mainly related to the lung blood capillary volume, the measures of Vc and of the sDL_{NO}/sDL_{CO} ratio are regarded as the most convenient parameters to assess for investigating this aspect [26-31]. A threshold value $>113\%$ pred. for the sDL_{NO}/sDL_{CO} ratio and $< 48\%$ pred for Vc indicate the occurrence of a significant drop in the lung capillary blood volume [32].

Statistics

The present analysis was a secondary longitudinal analysis restricted to the 30 untreated participants from the parent dataset; therefore, no new a priori sample-size calculation was performed for this single-cohort analysis. The available dataset was complete and balanced, with five observations per patient. Follow-up time was analyzed at 0, 4, 12, 24, and 52 weeks.

Continuous variables were summarized as mean and standard deviation (SD), and categorical variables as counts and percentages. Each continuous longitudinal outcome was analyzed by using a linear mixed-effects model with time entered as a categorical fixed effect and a patient-specific random intercept. Models were estimated by restricted maximum likelihood (REML) using Kenward-Roger degrees of freedom. The primary test was the global effect of time. Estimated marginal means with 95% confidence intervals were obtained at each visit, and contrasts between each follow-up visit and baseline were reported with Bonferroni adjustment for the four comparisons. Repeated-measures ANOVA was used as a sensitivity analysis. No adjustment for time-invariant baseline covariates was included in the primary models.

The mMRC score was analyzed as an ordinal outcome by using a mixed-effects ordered logistic regression with categorical time and a patient-specific random intercept. A global Wald test assessed the effect of time; visit-specific odds ratios were interpreted as the odds of being in a higher mMRC category relative to baseline. Predicted category probabilities and the proportions of patients improved, unchanged, or worsened versus baseline were also summarized.

All analyses were performed in Stata 15.1 (StataCorp, College Station, TX, USA).

Ethics

At recruitment, all subjects gave their informed consent to all procedures and to the anonymous use of their own data for research purposes. The study was approved by the Ethical and Scientific Commission of the National Centre for Respiratory Pharmacoeconomics and Pharmacoepidemiology during the session held on May 2nd, 2021 (n.: CES/NE02/2021).

Results

The analysis included 30 untreated patients, each with complete measurements at all five visits (Table 1 and 2). At recruitment, when compared to corresponding normal reference values, patients proved characterized by spirometric volumes within their normal ranges and by a slight reduction of current DL_{CO} mean values, while sDL_{NO}/sDL_{CO} and Vc mean values proved instead clearly pathologic (such as, abnormally high and quite low, respectively). In baseline, no patient had mMRC grade 0; while 14/30 (46.7%) had grade 1; 7/30 (23.3%) grade 2, and 9/30 (30.0%) grade 3. Mean SpO_2 value was also slightly low.

Most continuous outcomes showed no evidence of a global time effect: VC ($p = 0.979$), FEV_1 ($p = 0.635$), FEV_1/FVC ($p = 0.125$), DL_{CO} ($p = 0.514$), K_{CO} ($p = 0.933$), and Vc ($p = 0.165$) (Table 3 and figure 1). In contrast, the sDL_{NO}/sDL_{CO} ratio showed a slight statistically

Characteristic	Sample (N = 30)
Male sex, n (%)	16 (53.3%)
Age, years	60.8 ± 9.89
Blood Hb, g/L	13.4 ± 0.3
BMI, kg/m ²	25.3 ± 4.4
mMRC score	1.83 ± 0.87
Any comorbidity, n (%)	13 (43.3%)
Hypertension, n (%)	10 (33.3%)
Obesity, n (%)	1 (3.3%)
Atopy, n (%)	2 (6.7%)
SBP, mmHg	135.8 ± 4.9
DBP, mmHg	77.8 ± 6.1
Heart rate, beats/min	88.2 ± 5.2

Table 1: General characteristics of the untreated cohort at baseline (continuous data presented as mean ± standard deviation).

BMI: Body Mass Index; DBP: Diastolic Blood Pressure; Hb: Hemoglobin; mMRC: Modified British Medical Research Council; SBP: Systolic Blood Pressure.

Variable	Sample (N = 30)
SpO ₂ (%)	96.3 ± 0.7
VC (% predicted)	92.2 ± 10.7
FEV ₁ (% predicted)	87.8 ± 10.7
FEV ₁ /FVC (% predicted)	93.6 ± 8.0
DL _{co} (% predicted)	75.1 ± 12.2
K _{co} (% predicted)	88.3 ± 14.5
sDL _{NO} /sDL _{co} ratio (% predicted)	131.4 ± 9.2
Vc (% predicted)	39.5 ± 8.7
mMRC	
Dyspnea score = 1	14 (46.7%)
Dyspnea score = 2	7 (23.3%)
Dyspnea score = 3	9 (30.0%)

Table 2: Baseline pulmonary function and gas-transport variables in the untreated cohort at baseline (data presented as mean ± standard deviation).

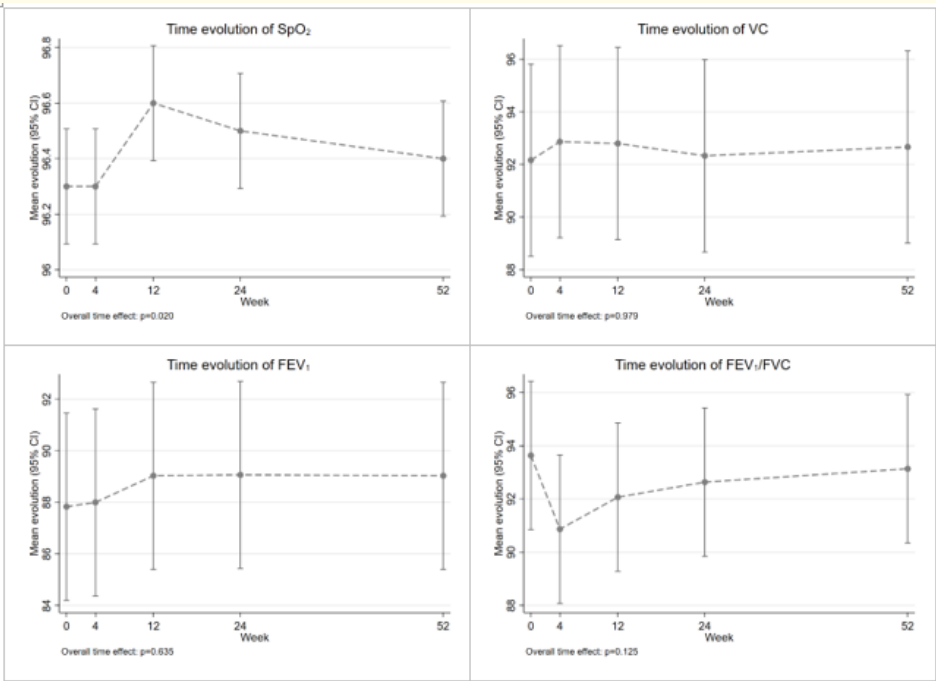
FEV₁: Forced Expiratory Volume in 1sec; FVC: Forced Vital Capacity; K_{co}: Carbon Monoxide Transfer Coefficient; mMRC: Modified British Medical Research Council; sDL_{co}: Simultaneous Diffusing Capacity of Carbon Oxide; sDL_{NO}: Simultaneous Diffusing Capacity of Nitric Oxide; SpO₂: The Peripheral Oxygen Saturation; Vc: Pulmonary Capillary Blood Volume; VC: Vital Capacity.

significant global time effect ($p = 0.008$) (Table 3 and figure 1). However, the mean sDL_{NO}/sDL_{CO} ratio decrease over time seems clinically negligible (from 131.4 at baseline to 126.4 at week 24, and 127.4% at week 52). Bonferroni-adjusted differences versus baseline were -5.00 percentage points at week 24 (95% CI -8.85 to -1.15; adjusted $p = 0.005$) and -3.97 at week 52 (95% CI -7.82 to -0.11; adjusted $p = 0.041$). SpO_2 also showed a global time effect ($p = 0.020$), driven by a small increase at week 12 (+0.30); the difference at week 52 was +0.10 and proved not significant after correction. Overall, such variations are clinically negligible. Despite some statistically significant variations, the overall distribution of each parameter over time seems quite stable (Figure S1 in the Supplementary materials) without a clear trend of improvement during the study period.

Outcome	Baseline	4 wk	12 wk	24 wk	52 wk	p-value
SpO_2 (%)	96.30	96.30	96.60	96.50	96.40	0.020
VC (% predicted)	92.17	92.87	92.80	92.33	92.67	0.979
FEV_1 (% predicted)	87.83	88.00	89.03	89.07	89.03	0.634
FEV_1/FVC (% predicted)	93.63	90.87	92.07	92.63	93.13	0.125
DL_{CO} (% predicted)	75.13	75.97	75.07	76.57	76.90	0.512
K_{CO} (% predicted)	88.30	88.17	87.53	87.63	88.50	0.933
sDL_{NO}/sDL_{CO} ratio (% predicted)	131.37	130.17	128.30	126.37	127.40	0.008
Vc (% predicted)	39.47	37.50	37.90	39.00	38.93	0.165

Table 3: Estimated marginal means over time from linear mixed-effects models in the untreated cohort.

FEV_1 : Forced Expiratory Volume in 1sec; FVC: Forced Vital Capacity; K_{CO} : Carbon Monoxide Transfer Coefficient; sDL_{CO} : Simultaneous Diffusing Capacity of Carbon Oxide; sDL_{NO} : Simultaneous Diffusing Capacity of Nitric Oxide; SpO_2 : The Peripheral Oxygen Saturation; Vc: Pulmonary Capillary Blood Volume; VC: Vital Capacity.



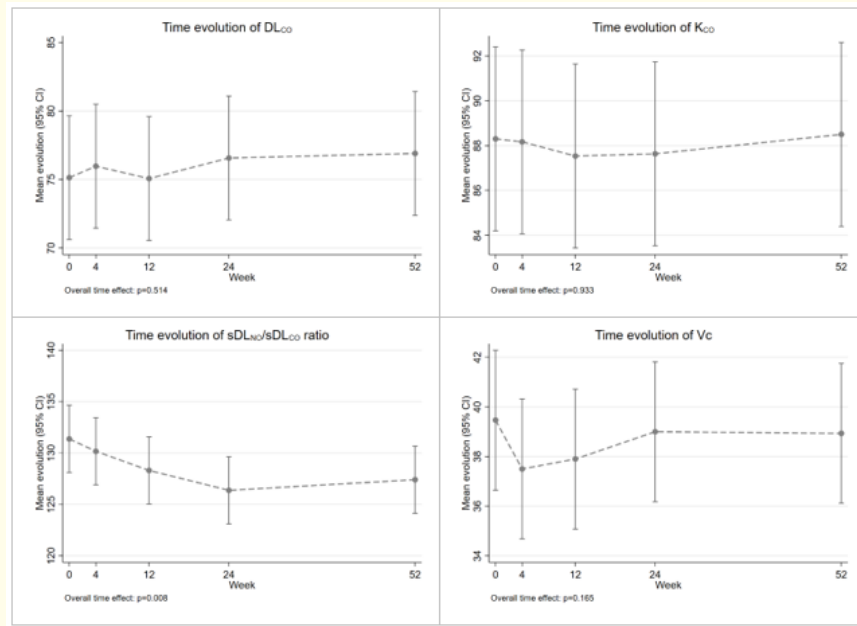


Figure 1: Adjusted longitudinal estimated means with 95% confidence intervals for pulmonary function and gas-transport variables.

FEV1: Forced Expiratory Volume in 1sec; FVC: Forced Vital Capacity; KCO: Carbon Monoxide Transfer Coefficient; sDLCO: Simultaneous Diffusing Capacity of Carbon Oxide; sDLNO: Simultaneous Diffusing Capacity of Nitric Oxide; SpO2: The Peripheral Oxygen Saturation; Vc: Pulmonary Capillary Blood Volume; VC: Vital Capacity.

The distribution of mMRC dyspnea score changed over time (Table 4, global Wald $p = 0.007$). Relative to baseline, the odds of being in a higher mMRC category were lower at week 24 (OR 0.13, Bonferroni-adjusted $p = 0.003$) and week 52 (OR 0.19, adjusted $p = 0.019$). At week 52, 13/30 patients (43.3%) had improved by at least one mMRC grade, 13/30 (43.3%) were unchanged, and 4/30 (13.3%) had worsened (Figure 2).

Week	mMRC 0, n (%)	mMRC 1, n (%)	mMRC 2, n (%)	mMRC 3, n (%)
0	0 (0.0)	14 (46.7)	7 (23.3)	9 (30.0)
4	0 (0.0)	14 (46.7)	12 (40.0)	4 (13.3)
12	0 (0.0)	18 (60.0)	9 (30.0)	3 (10.0)
24	3 (10.0)	14 (46.7)	13 (43.3)	0 (0.0)
52	5 (16.7)	9 (30.0)	15 (50.0)	1 (3.3)

Table 4: Observed distribution of mMRC dyspnea score over 52 weeks.

mMRC: modified British Medical Research Council.

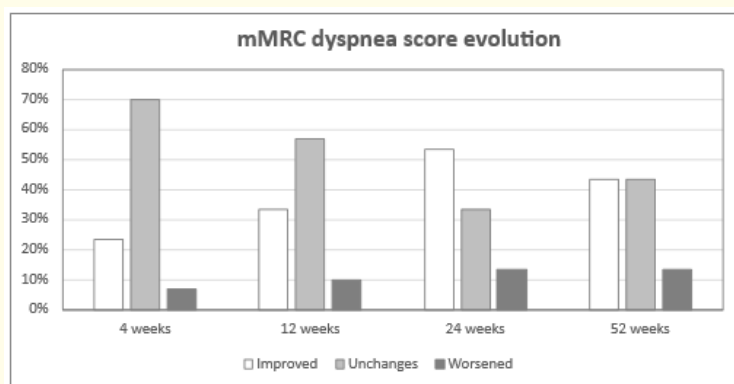


Figure 2: Observed evolution of mMRC dyspnea score over 52 weeks.

mMRC: modified British Medical Research Council.

Discussion

Alveolar damage, angiogenesis within inter-alveolar septa together with pulmonary microvascular thrombosis and occlusion represent the main pathogenetic events of SARS.CoV-2 acute infection [1-6].

This complex injury described at variable extent and duration in the deep lung also after less severe SARS.CoV-2 acute infections [32], frequently leads to the occurrence of long-lasting troubles in alveolar-blood gas transport that are associated with variable dyspnea persisting even long beyond the clinical and radiological recovering phase from COVID-19 pneumonia [24,33].

A few years ago, some studies investigated the underlying pathophysiology of troubles caused by SARS.CoV-2 infection within the deep lung. Persistent disorders in gas transport were firstly found in a non-homogeneous population and were mainly related to residual alveolar remodeling [20], while the relative role of lung microvasculature remained scarcely focused. The pathophysiological role of the microvascular lung injury was emphasized in 2022 when a substantial drop in lung capillary blood volume (Vc) was assessed for the first time in patients investigated for their dyspnea lasting for several weeks after clinical and radiological recovery from COVID pneumonia - Long-COVID) despite their normalized spirometrical lung volumes [21].

Data from that pivotal investigation carried out by means of the single-breath simultaneous assessment of sDL_{CO} and sDL_{NO} had been later confirmed by further physiological studies [22-24] that found the same kind of disorders in gas transport, although at variable degree, according to the peculiar severity of the original SARS.CoV-2 infection [32]. The hypothesis of the possible occurrence of a sustained lung capillary shortage was then presumed in all these cases. This hypothesis was confirmed by some anatomic studies published a few months later that proved the occurrence of a long-lasting capillary rarefaction and reduction in lung vascular density after COVID-19 pneumonia [34-36]. Nevertheless, some heterogeneity has been anatomically described in peripheral vascular lung injury [37] associated with variable physiological consequences that were both related to the severity of the original lung infection [24,32,33].

Based on the results of the present physiological study, the persistent reduction in pulmonary capillary blood volume (Vc) systematically observed after SARS-CoV-2 pneumonia does not appear to recover spontaneously and substantially over 52 weeks. Actually, Vc remained below the threshold limit of 48% predicted throughout the follow-up, while the sDL_{NO}/sDL_{CO} ratio always remained above the threshold limit of 113% predicted, thus clearly supporting the persistence of a substantial reduction in respiratory gas transport rather than the trend towards its time-dependent normalization. Moreover, all other physiological parameters investigated did not show significant time-effect

changes, regardless the slight decrease of the sDL_{NO}/sDL_{CO} ratio and of the mMRC dyspnea score, with the negligible transient increase of SpO₂ over the first 24 weeks. Given that the sustained reduction in Vc tends to reflect the occurrence of the persistent microvascular injury likely related to a reduction in pulmonary capillary density within the peripheral lung [34-36], this partial symptomatic improvement in dyspnea score observed despite the long-lasting abnormalities assessed in all parameters of lung diffusion tends to suggest that the trajectory of dyspnea does not probably run in parallel with that one of pulmonary microvascular abnormalities.

Limitation of the Study

The present study has some limitations: i) The study is a secondary analysis and was not prospectively powered to demonstrate equivalence or clinical stability; therefore, non-significant time effects should not be interpreted as proof of no change; ii) Multiple physiological endpoints were explored, multiplicity was controlled for the four visit-to-baseline contrasts within each endpoint but not across all different endpoints; iii) The pulmonary pressures were not measured, even if a specific study has been already planned. Point of strengths are: i) The strict selection of patients investigated; ii) Complete repeated measurements through 52 weeks; iii) The adoption of the most appropriate method presently available for detecting and assessing non-invasively the injury occurred in the deep lung at capillary level after SARS.CoV-2 infection; iii) The unprecedented long duration up to fifty-two weeks of the lung function monitoring of sDL_{NO}/DL_{CO} ratio and Vc after “apparent” complete clinical and radiological CT recovery from COVID-19 pneumonia; iv) The use of mixed-effects models that account for within-patient correlation, and ordinal modeling of the mMRC score.

Conclusion

The long-lasting troubles occurring in respiratory gas transport seem to remain essentially unchanged up to at least fifty-two weeks after recovery from COVID-19 pneumonia likely because due to the underlying capillary rarefaction and reduction in lung microvascular density. Further prospective studies are needed for investigating possible repair processes and related physiological consequences over longer time.

Recent diagnostic lung function tests (such as, the simultaneous single-breath assessment of DL_{CO} and DL_{NO}) are providing the opportunity to detect in short time and non-invasively the occurrence of these long-lasting changes in respiratory gas transport also in clinical practice.

Notably, as no residual parenchymal lesions were detected by conventional CT at recruitment after clinical recovery from COVID-19 pneumonia, more sensitive and specific CT algorithms would be implemented in order to better investigate the role of peripheral microvasculature structures of the deep lung.

Finally, data of the present study may suggest promising opportunities in terms of research for novel therapeutic options (unfortunately still inadequate [37-39]) against the Long-Covid respiratory syndrome.

Supplementary Material

Author’s Contributions

DNRW planned the study and wrote the manuscript; TP, provided the critical feedback and contributed to the final version of the manuscript; PM carried out all statistical calculations and contributed to the final version of the paper. All authors approved the final version of the manuscript.

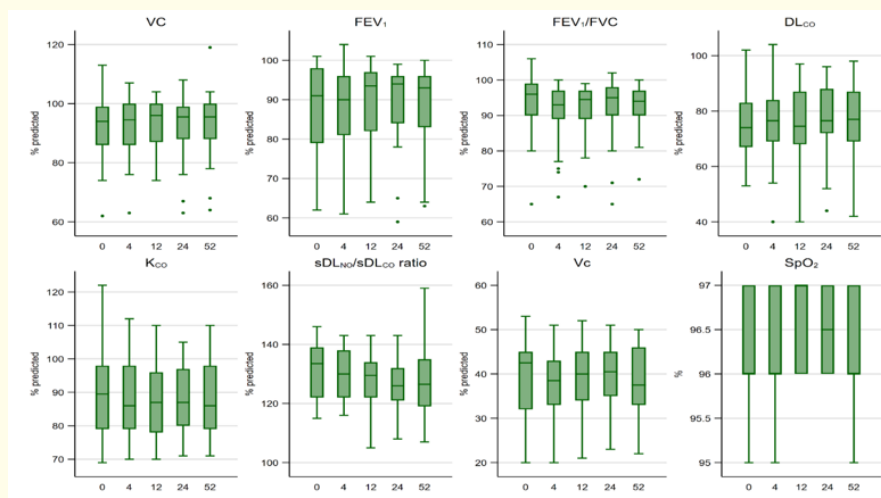


Figure S1: Box-plot of pulmonary function parameters and oxygen saturation over 52 weeks.

Conflict of Interest

All authors declare no conflict of interest in the present investigation.

Ethics Approval and Consent to Participate

The study was approved by the Ethical and Scientific Commission of the National Centre for Respiratory Pharmacoeconomics and Pharmacoepidemiology during the session of May 2nd, 2021. At recruitment, all subjects gave their informed consent also to the anonymous use of their own data for research purposes.

Availability of Data and Materials

The data-sets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Funding Support

The present study was a spontaneous investigation and did not receive any economic support.

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Citation: Povero Massimiliano, *et al.* "The Impairment of Respiratory Gas Transport Due to SARS.CoV-2 Pneumonia Persists Essentially Unchanged Over At Least 52 Weeks Despite the “Apparent” CT Complete Recovery". *EC Pulmonology and Respiratory Medicine* 15.11 (2026): 01-11.

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Volume 15 Issue 11 November 2026

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Citation: Povero Massimiliano., *et al.* “The Impairment of Respiratory Gas Transport Due to SARS.CoV-2 Pneumonia Persists Essentially Unchanged Over At Least 52 Weeks Despite the “Apparent” CT Complete Recovery”. *EC Pulmonology and Respiratory Medicine* 15.11 (2026): 01-11.