

Assessment of the long-term consequences of COVID-19 pneumonia on pulmonary function, health-related quality of life, and immunological prognostic factors

COVID-19 PNEUMONIJOS ILGALAIKIŲ PADARINIŲ VERTINIMAS:
PLAUČIŲ BŪKLĖS, GYVENIMO KOKYBĖS IR IMUNOLOGINIŲ PROGNOSTINIŲ
VEIKSNIŲ ANALIZĖ

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Summary. Edita Strumilienė successfully defended a doctoral dissertation “Assessment of Long-Term Consequences of COVID-19 Pneumonia on Pulmonary Function, Health-Related Quality of Life, and Immunological Prognostic Factors” at a public meeting of the Dissertation Defense Panel at Vilnius University Faculty of Medicine on April 8, 2026. The dissertation has been prepared at the Department of Infectious Diseases and Dermatovenerology, Vilnius University Faculty of Medicine during the period of 2021–2025. This article presents the main results of the dissertation.

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INTRODUCTION

The COVID-19 pandemic has become one of the greatest public health crises of the 21st century, claiming millions of lives worldwide; Lithuania was among the EU countries with particularly high excess mortality rates, more than double the EU average [1–5].

While vaccination and advanced treatment options have significantly reduced severe disease forms and mortality [6, 7], long-term consequences of COVID-19 – commonly termed post-COVID syndrome or ‘long COVID’ – have emerged as a major concern. According to the World Health Organization (WHO), post-COVID syndrome is characterized by persistent or newly developed symptoms lasting at least 3 months after confirmed SARS-CoV-2 infection, without an alternative diagnosis, significantly impairing daily functioning [8]. Recent meta-analyses demonstrate that 10–40% or more of recovered individuals still experience at least one post-COVID symptom for one to two years after infection [9–17]. Respiratory impairment is among the most common components, manifesting as deteriorated pulmonary function tests, radiological lung changes, and reduced exercise tolerance, with some patients showing reduced diffusion capacity (DLCO) and persistent radiological abnormalities even 6–24 months post-illness [6, 11, 18–22]. Quality of life studies have similarly revealed significantly worse physical and mental health, limited work capacity, and reduced social activity even one year post-infection [23–26].

Immune system alterations play a crucial role in post-COVID syndrome pathogenesis: variable immunoglobulin responses (IgG, IgA, IgM), reduced or imbalanced T lymphocyte and NK cell counts, autoantibody formation, and complement (C3, C4) changes have all been implicated as possible prognostic markers or therapeutic targets [27–36]. However, the prognostic significance of these mechanisms remains insufficiently investigated, and standardized markers for post-COVID condition development are still being sought [10, 37]. Despite abundant international research, Lithuania has lacked systematic prospective studies comprehensively investigating the long-term consequences of COVID-19 across clinical, pulmonary function, radiological, immunological, and quality-of-life domains together [38, 39] – research that is essential for identifying risk groups, prognostic factors, and optimal long-term care strategies in our population.

AIM AND OBJECTIVES OF THE THESIS

Aim

To evaluate the long-term effects of COVID-19 on the respiratory system and health-related quality of life over a 12-month follow-up period, to identify risk

groups for post-COVID syndrome, and to determine potential immunological prognostic biomarkers.

Objectives

1. To assess the dynamics of pulmonary function parameters (FEV₁, FVC, FEV₁/FVC, DLCO) and radiological lung changes identified by computed tomography over 12 months following COVID-19 infection.
2. To analyze the longitudinal changes in immunological parameters, including immunogram markers (CD4+, CD8+, NK cells, B lymphocytes, activated T lymphocytes), components of the complement system (C3c, C4), and immunoglobulins (IgA, IgG, IgM, IgE), during the 12 months after SARS-CoV-2 infection.
3. To determine the associations between immunological parameters, pulmonary function measures, radiological lung abnormalities, and the clinical manifestations of post-COVID syndrome.
4. To evaluate changes in health-related quality of life using the SF-36 questionnaire over 12 months following COVID-19 infection, and to identify factors influencing the recovery process.

RESEARCH MATERIALS AND METHODS

Research environment, subjects, and selection criteria

The study was conducted at Vilnius University Hospital Santaros Klinikos (VUH SK). Participants were enrolled and followed up at the Center for Infectious Diseases; lung function tests were performed at the Pulmonology and Allergology Center, radiological examinations at the Radiology and Nuclear Medicine Center, and laboratory tests at the Laboratory Medicine Center of VUH SK. The study was approved by the Vilnius Regional Biomedical Research Ethics Committee (protocol No. 2020/6-1233-718; June 22, 2020) and conducted in accordance with the Declaration of Helsinki; all participants provided written informed consent.

Adult patients with SARS-CoV-2 infection confirmed by RT-PCR and treated at the VUH SK Center for Infectious Diseases between October 2021 and October 2022 were eligible if they had radiologically confirmed pneumonia, no known chronic lung disease, malignancy, or immunodeficiency at discharge, and were able to attend three follow-up visits (at 3, 6, and 12 months post-discharge) and complete the study assessments.

To address the aim and objectives, three research pathways were defined, and participants were allocated sequentially into three study groups (each planned to include 100 subjects). Group 1 underwent long-term

assessment of lung function, structural lung changes (chest CT), and cellular immunity. Group 2 was evaluated for long-term clinical symptoms and their associations with cellular and humoral immunological blood parameters. Group 3 underwent clinical assessment and health-related quality of life evaluation using the SF-36 questionnaire. All assessments were repeated at each follow-up visit, except chest CT, which was not repeated in patients without radiological abnormalities at the first visit.

Lung function tests, radiological examinations, and blood tests

Lung function tests (Vmax Encore, Viasys[®] Healthcare) measured FVC, FEV₁, the FEV₁/FVC ratio, TLC, VC, RV, and DLCO (adjusted for blood hemoglobin), presented as absolute values and/or percentages of the predicted norm. Chest CT (two spiral CT scanners, low-dose lung protocols) was evaluated by two independent radiologists for ground-glass opacity, consolidation, parenchymal bands, structural deformities, air bronchograms, and bronchiectasis, classified as inflammatory or fibrotic/reticular changes; each of the five lung lobes was scored 0–5 for severity per change type, following a method used in previous studies of SARS-induced pulmonary fibrosis [40, 41]. Peripheral blood lymphocyte subsets (CD3+, CD3+CD4+, CD3+CD8+, CD4/CD8 ratio, CD4+/CD28+/CD192+, CD8+/CD28+/CD192+, NK, CD19+, and activated CD3+HLA-DR+ T cells) were determined by flow cytometry (FACSCalibur, BD Biosciences); serum immunoglobulins (IgA, IgG, IgM, IgE) and complement components (C3c, C4) were measured by nephelometry (BN analyzer, Siemens Healthcare Diagnostics). All laboratory analyses were performed blinded to clinical data, with daily calibration and external quality assessment.

Quality of life questionnaire and statistical analysis

Health-related quality of life was assessed using the SF-36 questionnaire (eight domains combined into physical and mental health summary categories, each scored 0–100, higher indicating better quality of life); the Lithuanian version has been formally validated [42]. Statistical analysis was performed using IBM SPSS version 20.0. Continuous variables not normally distributed (Shapiro-Wilk test) are presented as median (IQR) or mean $\pm$ SD; categorical variables as frequencies and percentages. Group

comparisons used the Wilcoxon signed-rank test, Mann-Whitney U test, McNemar's test, χ^2 , or Fisher's exact test, as appropriate; associations were assessed by multivariable linear or logistic regression. Symptom-immune associations in Group 2 were explored through unsupervised clustering (Gower distance, Ward's method), with cluster stability confirmed by 1,000 bootstrap resamples. In Group 3, clinical significance was evaluated using minimal clinically important differences (MCID) [43, 44], and 12-month SF-36 scores were compared with Lithuanian population norms [45]. A two-tailed $p < 0.05$ was considered statistically significant.

RESULTS

First study group results

This group included 100 subjects. Of these, 85 completed the 12-month follow-up period and were included in the final analysis: 40 (47.1%) were female, and 45 (52.9%) were male. The median age of the subjects was 59 years (IQR 51–64). In terms of disease severity, 53 (62.4%) subjects had recovered from critically severe COVID-19, and 32 (37.6%) had recovered from severe COVID-19.

The main reasons why some patients did not complete the study were logistical or personal constraints on attendance. There were no significant differences in baseline characteristics between those who completed the study and those who did not.

Pulmonary function tests

Pulmonary function tests were performed for all 85 participants during the follow-up period at all 3 scheduled visits. Significant improvement in pulmonary function was observed over time. Forced vital capacity (FVC), forced expiratory volume in the first second (FEV₁), and vital capacity (VC) improved when comparing 3, 6, and 12 months post-illness ($p < 0.05$). Lung diffusion capacity (DLCO) also improved but significantly more slowly compared to other parameters; after 12 months, when assessed according to individual normal ranges, it remained reduced in 14 patients (16.47%). The detailed dynamics of pulmonary function test results are presented in Table 1.

Table 1. Pulmonary function test results at 3, 6, and 12 months post-discharge, presented as median % of the predicted value (IQR)

Parameter	Month 3	Month 6	Month 12	p1	p2	p3
FVC, %	95 (85–106)	99.5 (89–111.75)	101 (88.5–112.5)	< 0.001	< 0.001	0.123
FEV ₁ , %	96 (85.5–106)	99.5 (90.3–108.75)	103.0 (88.5–110.5)	0.005	0.002	0.032
FEV ₁ /FVC	83 (80.5–86)	83 (78–85)	82 (79–85.5)	0.007	0.181	0.214
VC, %	96 (84–110)	102 (92–112.75)	103 (90.5–113)	< 0.001	0.001	0.431
DLCO, %	76 (64–84.5)	77 (68–86.75)	79 (71.5–84.5)	0.127	0.054	0.658

DLCO – lung diffusion capacity; FEV₁ – forced expiratory volume in the first second; FVC – forced vital capacity; VC – vital capacity.

The FEV₁/FVC ratio essentially did not change and remained within normal personal limits for most participants, thereby indicating that bronchial obstruction was not characteristic of this study group. However, restrictive respiratory function impairment was identified in 24.71% of participants at 3 months; its frequency decreased statistically significantly to 20.24% at 6 months and to 14.8% at 12 months.

Radiological lung changes

Lung CT scans were performed on 76 of the 85 subjects after 6 months and on 79 subjects after 12 months. Nine patients underwent the scan for other reasons before their 6-month visit, and, in the absence of clinical need, it was not repeated to avoid excessive radiation exposure. At the 12-month visit, 6 patients did not undergo a repeat CT scan: 4 patients refused the scan, and 2 patients underwent the scan in the interim period for other reasons.

After 6 months, inflammatory changes in the lungs were found in 77.63% of the subjects, most affecting the lower lobes (RLL 73.68%, LLL 69.74%) and, to a lesser extent, the upper lobes (~64%); the total CT score for inflammatory changes was 8 (IQR 1–14). After 12 months, inflammatory changes remained in 69.62% of the subjects (RLL 64.56%, RML 48.10%, RUL 53.16%, LLL 60.76%, LUL 54.43%), and the total score fell to 6 (IQR 0–12; $p < 0.001$ vs. 6 months). Fibrotic/reticular changes followed a similar pattern: present in 82.89% at 6 months (score 6, IQR 2–11, again predominating in the lower lobes) and 73.08% at 12 months (score 4.5, IQR 0–10; $p < 0.001$ vs. 6 months).

CT severity scores indicated that lobe lesions at 6 and 12 months were mostly mild (1–2 points), except for the RLL, where lesions were moderate (>25% of the lobe) in 46.05% of patients at 6 months and 21.52% at 12 months. Both inflammatory and fibrotic/reticular severity scores decreased significantly between 6 and 12 months for most lobes.

Immunological markers

White blood cell (WBC), lymphocyte, and lymphocyte subpopulation counts were performed for 84 patients at 3 months, 65 patients at 6 months, and 59 patients at 12 months. CD4+/CD28+/CD192+ counts were conducted for 81 patients at 3 months, 59 patients at 6 months, and 55 patients at 12 months, while CD8+/CD28+/CD192+ counts were performed for 81 patients at 3 months, 60 patients at 6 months, and 55 patients at 12 months. WBC, lymphocyte, and lymphocyte subpopulation counts were compared across the three time points.

The WBC count did not change significantly between months 3, 6, and 12 post-discharge. However, a statistically significant decrease in the lymphocyte

count, CD3+ cells, and CD8+ cells was observed at month 12 compared to month 3 post-COVID-19. Additionally, the number of CD3+HLA-DR+ cells decreased significantly in month 12 compared to both month 3 and month 6.

Association of pulmonary function tests, radiological findings, and immunological markers

Patients with a restrictive spirometry pattern had higher scores for CT inflammatory and fibrotic/reticular changes at acute COVID-19 and at 6 and 12 months post-discharge compared to those without a restrictive spirometry pattern, although the differences were not statistically significant. However, patients with a restrictive spirometry pattern at 3 and 6 months had higher CT inflammatory and fibrotic/reticular change severity scores at 12 months compared to those without restriction in spirometry.

At 6 months, patients with a restrictive spirometry pattern had a higher CD19+ cell count compared to those without restriction (259.90 cells/ μ L vs. 171.12 cells/ μ L, $p = 0.025$). Similarly, at 12 months, patients with a restrictive spirometry pattern had a higher CD19+ cell count compared to those without restriction (279.12 cells/ μ L vs. 173.74 cells/ μ L, $p = 0.042$).

Multivariable regression identified several significant associations between pulmonary function and immune cell subsets: higher CD4+/CD28+/CD192+ levels were associated with worse function (reduced TLC at 6 months; decreased FVC, FEV₁, VC at 12 months), whereas higher CD4+/CD28+/CD192+ levels were associated with better function at 12 months; higher CD3HLA-DR+ levels were negatively associated with FEV₁ and VC at 12 months; female sex was associated with lower DLCO at all time points; and older age was associated with higher CT inflammatory and fibrotic/reticular severity scores at 12 months.

A decreased lymphocyte count (0.99, 95% CI 0.98–1.00, $p = 0.017$), an increased CD19+ cell count (1.02, 95% CI 1.00–1.03), and an increased CD4+ cell count (OR 1.01, 95% CI 1.00–1.02) were associated with a restrictive spirometry pattern at 12 months.

Patients with residual inflammatory changes on CT had a lower count of CD3+HLA-DR+ cells compared to those without inflammatory changes at both 6 and 12 months. At 6 months, the count of CD3+HLA-DR+ cells was 367.54 vs. 606.06, $p = 0.048$, and the percentage was 17% vs. 24%, $p = 0.014$. At 12 months, the CD3+HLA-DR+ cell count was 261.14 vs. 539.15, $p = 0.021$, and the percentage was 14% vs. 19.5%, $p = 0.024$.

Second study group results

Study population and follow-up completion

Of the 100 enrolled patients, 93 completed all

follow-up visits and were included in the final analysis. The cohort comprised 50 women (53.8%) and 43 men (46.2%) with a median age of 59 years (IQR 51–64.5). Comorbidities were present in 59 patients (63.4%). Most participants were overweight or obese (91.4%), and all were unvaccinated at the time of infection and throughout the follow-up.

Regarding the disease severity levels, 17 patients (18.3%) had moderate, 32 (34.4%) severe, and 44 (47.3%) critical COVID-19. ICU admission was required for 43 patients (46.2%), with a median stay of 12 days (IQR 8–16); 7 patients (7.5%) underwent invasive mechanical ventilation. In-hospital complications occurred in 34 patients (36.6%). Laboratory data completeness varied across visits due to missed appointments and technical factors, with sample sizes ranging from 82 to 93 patients per parameter and time point.

No patient received long-term corticosteroids, immunomodulatory agents, or antivirals after discharge.

Symptom recovery over time

At 3 months, the majority reported fatigue (70.9%), dyspnea (81.7%), and reduced exercise tolerance (71.0%). These core symptoms declined substantially by 12 months: fatigue to 24.7%, dyspnea to 25.8%, and reduced exercise tolerance to 24.7% (all $p < 0.001$). This represents a two-thirds reduction in prevalence (Table 2).

Other symptoms such as musculoskeletal pain, cardiac complaints, insomnia/anxiety, and cognitive dysfunction and memory impairment were less frequent. Of these, only cardiac symptoms showed a significant early decline (11.8% at 3 months vs. 2.2% at 6 months, $p = 0.004$).

Symptom persistence was influenced by initial severity: at 12 months, dyspnea persisted in 36.4% of critically ill patients, compared to 17.6% of moderate cases ($p = 0.025$). Reduced exercise tolerance followed a similar pattern (34.1% vs. 5.9%).

Immune system recovery

Cellular Immunity

The total lymphocyte counts remained within the normal range throughout the follow-up. However, immune activation markers demonstrated dynamic changes: activated T cells (CD3+HLA-DR+) declined from 20% at 3 months to 13% at 12 months ($p < 0.001$); CD3+CD8+ T cells decreased significantly by 12 months (572 vs. 632 cells/ μ L at 3 months, $p = 0.020$); and the CD4/CD8 ratio showed a gradual upward trend, suggesting immune homeostasis restoration.

Table 2. Prevalence of post-COVID-19 symptoms at 3, 6, and 12 months post-discharge, N (%)

Symptom	Month 3, N (%)	Month 6, N (%)	Month 12, N (%)	p (3 vs. 12 mo.)
Fatigue	66 (70.97)	37 (39.78)	23 (24.73)	< 0.001
Dyspnea	76 (81.72)	49 (52.69)	24 (25.81)	< 0.001
Reduced exercise tolerance	66 (70.97)	47 (50.54)	23 (24.73)	< 0.001
Cardiac symptoms	11 (11.83)	2 (2.15)	3 (3.23)	0.057
Cognitive dysfunction/memory impairment	9 (9.68)	10 (10.75)	7 (7.53)	0.754

Table 3. Complement and immunoglobulins (C3c, C4, IgA, IgG, IgM) at 3, 6, and 12 months post-discharge

Parameter	Month 3	Month 6	Month 12
C4, g/L	0.25 (0.22–0.29)	0.26 (0.19–0.29)	0.24 (0.20–0.30)
C3c, g/L	1.23 (1.10–1.39)	1.30 (1.05–1.39)	1.35 (1.17–1.51)
IgA, g/L	2.06 (1.53–2.67)	2.42 (1.81–3.74)	2.72 (1.82–3.35)
IgG, g/L	11.14 (9.54–12.39)	11.16 (9.98–12.94)	11.72 (10.11–12.49)
IgM, g/L	0.92 (0.61–1.35)	0.77 (0.47–1.34)	0.69 (0.44–1.37)

C3c – complement 3c; C4 – complement 4; IgA – immunoglobulin A, IgM – immunoglobulin M, IgG – immunoglobulin G.

By contrast, NK cells and B cells remained stable at the group level. However, a subset (~20%) of patients demonstrated persistently low NK counts across all visits.

Complement Activation and Immunoglobulin Changes

The most striking finding was the progressive increase in the complement C3c levels throughout the 12-month follow-up period, occurring paradoxically as clinical symptoms improved. Complement C3c levels rose progressively from 1.23 g/L at 3 months to 1.35 g/L at 12 months (+10%, $p < 0.001$), even despite clinical improvement. C4 showed only minor transient fluctuations.

IgA levels demonstrated a significant and sustained increase throughout the follow-up, rising from 2.06 g/L (IQR 1.53–2.67) at month 3 to 2.42 g/L (IQR 1.81–3.74) at month 6 ($p < 0.001$), and remaining elevated at 2.72 g/L (IQR 1.82–3.35) at month 12 ($p = 0.003$ vs. month 3). In contrast, IgM declined modestly, while IgG and IgE remained stable (Table 3).

Clinical-immunological correlations

Several statistically significant associations were identified between the immune parameters and persistent post-COVID symptoms. Exploratory analyses linked fatigue (3 months) to lower NK counts and higher CD3+ T-cell percentages; dyspnea (6 months) to reduced NK counts and higher CD3+CD4+ T-cell percentages; myalgia/arthritis (12 months) to lower lymphocyte, CD3+, CD3+CD4+, and CD19+ counts; and cardiac symptoms (3 months) to higher C3c lev-

els (1.37 vs. 1.20 g/L, $p = 0.026$). Interestingly, at 12 months, patients with fatigue and a reduced exercise tolerance had lower – not higher – C3c levels than asymptomatic peers, suggesting a complex, phase-dependent role of complement in long COVID. Although the limited sample size precluded formal correlation analysis, these exploratory trends indicate that patients reporting persistent fatigue and dyspnea at 12 months exhibited higher activated T cells (CD3+HLA-DR+), slightly elevated C3c, and lower CD3+CD8+ counts than fully recovered individuals, suggesting that sustained immune activation may underlie lingering post-COVID symptoms.

Symptom clusters and immune endotypes

Unsupervised clustering of participants with complete symptom and immune data consistently resolved three clinically interpretable endotypes across bootstrap resamples, aligned with the pre-specified symptom domains: a respiratory endotype (“complement/NK-suppressed”) – dyspnea and reduced exercise tolerance, with lower NK-cell counts and higher CD3/CD4 levels at 6 months, and elevated C3c among those with early cardiopulmonary complaints; a neurocognitive endotype (“neuro-T-cell activation”) – cognitive dysfunction/memory impairment with elevated CD3+HLA-DR+% at month 3 ($\approx 30\%$ vs. $\sim 20\%$ in asymptomatic peers); and a musculoskeletal endotype (“lymphopenic/immune-insufficiency”) – myalgia/arthralgia at 12 months with lower total lymphocytes and reduced CD3+, CD3+CD4+, and CD19+ counts, suggesting a broader low-grade immune insufficiency rather than isolated activation.

The respiratory endotype was over-represented among survivors of critical illness, suggesting that the magnitude of the initial immune insult may shape endotype expression during recovery. Cluster membership and distinguishing features remained robust in sensitivity analyses using 6-month data alone and after adjustment for age, sex, BMI, and initial disease severity, indicating that the endotypes are not explained solely by obesity-related chronic inflammation. Nevertheless, they should be viewed as hypothesis-generating and warrant validation in larger, external cohorts.

Influence of disease severity

When immune recovery was analyzed based on the severity of the initial illness, distinct patterns emerged. Patients who had been critically ill showed a slower decline in activated T cells (CD3+HLA-DR+) and more prolonged suppression of both CD3+CD4+ and CD3+CD8+ T cells compared to those with moderate or severe illness.

When immune parameters were strati-

fied by the initial disease severity, patients recovering from critical COVID-19 maintained significantly higher IgM levels compared to those with severe disease across all time points: month 3 (1.01 vs. 0.75 g/L, $p = 0.033$), month 6 (0.96 vs. 0.60 g/L, $p = 0.040$), and month 12 (0.92 vs. 0.45 g/L, $p = 0.044$). IgG levels were also higher in the critical group at month 3 (11.67 vs. 10.27 g/L, $p = 0.031$). Complement C3c increased across all severity groups but was more pronounced in the severe group and among critical survivors.

Third study group results

This group included 122 subjects. Of these, 93 completed the entire 12-month follow-up period, i.e., these 93 research subjects attended all 3 scheduled visits, and were included in the final analysis. The main reasons for some patients not completing the study were logistical and/or personal barriers to attendance. There were no significant differences in the baseline characteristics between those who completed the study and those who did not.

The final analyzable group consisted of 93 subjects with a mean age of 58.2 ± 10.2 years; 53.8% were female. Fifty-six (60.2%) patients had experienced critical COVID-19 disease. Only 4 subjects (4.3%) had received at least one dose of the SARS-CoV-2 vaccine during the observation period, while the other study participants had not been vaccinated. Comorbidities were quite common: 35.5% of subjects had one, and 30.1% had two or more chronic diseases. The most common comorbidities were primary arterial hypertension (48.4%), diabetes mellitus (24.7%), and cardiovascular disease (20.4%); while one-third (34.4%) of the study participants had no chronic diseases before hospitalization. Detailed baseline characteristics of the study cohort are summarized above.

Changes in HRQoL over time

All eight SF-36 domains improved significantly from 3 to 12 months (Friedman test, $p < 0.001$). Seven of these domains demonstrated both statistically significant and clinically meaningful changes (see Table 4).

Domains with the largest improvements were Bodily Pain (+18.8 points, $r = 0.41$, surpassing its MCID of ≥ 10), General Health (+14.6, $r = 0.42$, MCID ≥ 5), and

Table 4. SF-36 domain scores over time and clinical significance (N = 93)

SF-36 domain	Month 3	Month 12	Change	Effect size r	MCID met
Physical Functioning	65.0 $\pm$ 22.1	75.2 $\pm$ 18.5	+10.2	0.37	Yes
Bodily Pain	63.2 $\pm$ 24.6	82.0 $\pm$ 20.3	+18.8	0.41	Yes
General Health	58.0 $\pm$ 18.9	72.6 $\pm$ 16.8	+14.6	0.42	Yes
Vitality	61.8 $\pm$ 20.4	72.9 $\pm$ 17.9	+11.1	0.30	Yes
Mental Health	68.0 $\pm$ 18.5	75.0 $\pm$ 16.9	+7.0	0.32	Yes
Role-Emotional	70.4 $\pm$ 29.2	74.0 $\pm$ 26.8	+3.6	0.16	No

Social Functioning (+10.4, $r = 0.38$, approaching its MCID of ≥ 12.5). Moderate improvements were seen for Physical Functioning (+10.2, meeting its MCID of ≥ 10), Vitality (+11.1, meeting its MCID of ≥ 10), Mental Health (+7.0, exceeding its MCID of ≥ 5), and Role-Physical (+8.1, below its MCID of ≥ 25). Role-Emotional showed the smallest improvement (+3.6, $r = 0.16$), remaining well below its MCID (≥ 25) and indicating limited recovery of emotional role functioning specifically.

Comparison with age-matched population norms

At 12 months, the patients had not fully returned to pre-pandemic age-matched population norms. The largest gaps were observed in Physical Functioning (75.2 vs. 82.1, gap = 6.9 points; $p = 0.003$), Role-Physical (73.6 vs. 78.3, gap = 4.7 points), and General Health (72.6 vs. 76.8, gap = 4.2 points; $p = 0.045$). In contrast, the Mental Health scores nearly reached the population norms (75.0 vs. 79.2, gap = 4.2 points) but remained slightly lower.

Predictors of recovery at 12 months

Multivariate linear regression models identified key predictors for better outcomes in key HRQoL domains. For Physical Functioning ($R^2 = 0.42$, $p < 0.001$): male sex ($\beta = 14.60$, 95% CI: 6.50–22.70, $p < 0.001$), fewer comorbidities ($\beta = -10.76$, 95% CI: -16.20 to -5.32, $p < 0.001$), and employment ($\beta = 8.45$, 95% CI: 2.10–14.80, $p = 0.010$). For Mental Health ($R^2 = 0.31$, $p = 0.002$): male sex ($\beta = 10.89$, 95% CI: 3.62–18.16, $p = 0.004$) and employment ($\beta = 6.73$, 95% CI: 0.95–12.51, $p = 0.023$). For General Health ($R^2 = 0.28$, $p = 0.006$): more comorbidity ($\beta = -7.46$, 95% CI: -13.82 to -1.10, $p = 0.021$) and older age ($\beta = -0.42$, 95% CI: -0.78 to -0.06, $p = 0.024$).

Sociodemographic disparities, healthcare utilization, and rehabilitation access

Significant 12-month outcome disparities were evident across sex, employment status, and comorbidity burden. Men and employed individuals scored consistently higher than women and unemployed individuals on most domains (e.g., Physical Functioning: 80.8 ± 16.2 vs. 66.1 ± 20.1 , $p < 0.001$; employed 78.2 ± 17.1 vs. unemployed 63.5 ± 21.3 , $p = 0.001$), and patients with two or more comorbidities scored markedly lower than those with none (Physical Functioning 60.6 ± 22.8 vs. 82.1 ± 14.6 , $p < 0.001$).

During the 12-month follow-up, a substantial proportion of patients continued to require medical care (47.3% pulmonology consultations, 22.6% cardiology follow-up, 6.5% home oxygen, 5.4% pulmonary embolism), yet rehabilitation utilization remained low: 58.1% received no rehabilitation at all, 29.0% underwent Stage I inpatient rehabilitation only, and just 12.9% accessed structured Stage II post-discharge rehabilitation. Patients receiving Stage II rehabilitation

showed numerically – though not statistically significantly – higher 12-month Physical Functioning and Mental Health scores than those without.

DISCUSSION

This 12-month prospective study demonstrates that recovery following COVID-19 pneumonia is a complex, heterogeneous, and multisystem process extending well beyond the acute phase of infection. The findings confirm that SARS-CoV-2 infection cannot be regarded solely as a transient respiratory disease, but rather as a condition with sustained effects on the pulmonary structure and function, immune system homeostasis, and health-related quality of life [13–17]. Pulmonary recovery was incomplete and non-uniform: although gradual improvement in spirometric parameters was observed, a clinically relevant proportion of patients continued to exhibit restrictive ventilatory patterns and reduced diffusion capacity at 12 months, particularly following severe and critical COVID-19 levels. Persistent inflammatory and fibrotic radiological changes on chest computed tomography showed only partial resolution and were closely associated with functional impairment, thereby underscoring the long-term interaction between structural lung damage and physiological recovery, consistent with international longitudinal studies [11, 18–20].

Beyond pulmonary sequelae, the study provides important insight into long-term immune system recovery. Immunological normalization did not follow a linear or uniform trajectory; persistent alterations in cellular immunity, including changes in activated T lymphocytes, CD8+ T-cell populations, and NK cells, were associated with ongoing respiratory symptoms, fatigue, and reduced exercise tolerance, suggesting that sustained immune dysregulation contributes to symptom persistence even after clinical stabilization [27–29]. A particularly novel finding is the paradoxical activation of innate and mucosal immune components during recovery: complement C3c and IgA concentrations increased progressively despite a parallel decline in overt clinical symptoms, while IgG and IgM remained relatively stable. This dissociation between clinical improvement and immune activation suggests that complement and IgA responses may reflect prolonged immune remodeling or altered immune homeostasis rather than ongoing tissue-damaging inflammation, consistent with the emerging concept of post-COVID immune endotypes [32–36]. Exploratory clinical-immunological associations further revealed that patients with persistent symptoms exhibited specific immune signatures – altered T-cell activation profiles and reduced NK cell counts – supporting the hypothesis that symptom clusters in post-COVID condition correspond to

biologically distinct immune endotypes involving differential contributions of cellular, humoral, and innate immune pathways.

Health-related quality of life improved gradually during follow-up but did not fully normalize in all patients, particularly among those with more severe acute disease and limited access to structured rehabilitation, mirroring findings from other national cohorts [23–26]. In summary, this study integrates pulmonary, radiological, immunological, and quality-of-life data to provide a comprehensive view of long-term recovery after COVID-19 pneumonia. The findings suggest that persistent post-COVID symptoms are more likely driven by heterogeneous immune recovery trajectories and incomplete structural lung repair than by ongoing systemic inflammation alone. Recognition of distinct post-COVID immune endotypes may help explain the marked clinical heterogeneity observed among COVID-19 survivors and supports the development of personalized, risk-adapted follow-up and rehabilitation strategies.

CONCLUSIONS

1. Following severe and critical COVID-19 pneumonia, a significant improvement in pulmonary function parameters (FVC, FEV₁, VC) was observed over the 12-month follow-up period, which indicates gradual recovery of respiratory function; however, pulmonary diffusing capacity (DLCO) recovered more slowly and remained clinically significantly reduced in a subset of patients after one year.
2. The dynamics of radiological lung abnormalities after COVID-19 pneumonia paralleled functional recovery trends: structural lung changes gradually regressed over time, yet residual radiological abnormalities persisted in a proportion of patients, reflecting incomplete recovery of lung parenchyma.
3. Analysis of immune system parameters revealed a heterogeneous recovery trajectory: lymphocyte counts and their subpopulations (CD4+, CD8+, NK, and B cells), as well as activated T lymphocytes, demonstrated non-uniform temporal changes, while humoral immunity was characterized by a paradoxical, progressive increase in IgA concentrations, a decrease in IgM levels, and stable IgG and IgE concentrations.
4. Evaluation of the associations between the pulmonary function parameters, radiological lung abnormalities, and immunological markers revealed selective and heterogeneous relationships: poorer functional and structural lung outcomes were associated with alterations in specific immunological markers; however, these associations

were not consistent across all immunological parameters assessed.

5. Assessment of the health-related quality of life demonstrated significant improvement in the physical and mental health domains over the 12 months; nevertheless, most SF-36 domain scores remained lower than the normative values of the general Lithuanian population. A slower recovery of quality of life was observed among women, unemployed individuals, and patients with a higher burden of chronic comorbidities.
6. A substantial gap was identified between the persistent healthcare needs of patients recovering from severe COVID-19 pneumonia and the rehabilitation services actually provided, highlighting the importance of comprehensive, individualized, and long-term patient monitoring and rehabilitation.

PRACTICAL IMPLICATIONS

The findings of this study have direct practical relevance for the clinical management of patients recovering from severe and critical COVID-19 pneumonia. The results support the need for long-term, structured monitoring of respiratory function, immune status, and health-related quality of life for at least 12 months following acute illness, particularly in patients with persistent functional or radiological lung impairment.

The identified selective associations between pulmonary function, radiological changes, and immunological parameters suggest that specific immune markers (activated T lymphocytes, NK cells, IgA, and components of the complement system) may serve as additional biological indicators to help identify patients at risk of delayed recovery and persistent post-COVID symptoms.

The identification of high-risk groups – notably, women, unemployed individuals, and patients with multiple chronic comorbidities – supports the implementation of a risk-based, personalized post-COVID care model, enabling an early referral to a multidisciplinary follow-up and rehabilitation.

Furthermore, the quality-of-life findings emphasize the necessity of integrating not only physical but also psycho-emotional and social rehabilitation components into post-COVID care. The observed mismatch between the patients' ongoing healthcare needs and the rehabilitation services provided underscores the need for structured post-COVID care programs and national rehabilitation guidelines.

The results may also inform healthcare service planning, optimization of resource allocation, and the development of future multicenter studies focused on the biological mechanisms of post-COVID syndrome and targeted therapeutic interventions.

ARTICLES PUBLISHING THE DISSERTATION RESULTS

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