

Original Article

Mitochondrial Dysfunction and Telomeric Shortening as Long-term Complications After COVID-19

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ABSTRACT

Objectives: To evaluate the potential role of telomere shortening and mitochondrial dysfunction in the development of long-term complications of COVID-19, including pulmonary fibrosis.

Methods: We analyzed 132 patients from the prospective COVID-FIBROTIC cohort 1 year after hospitalization for bilateral pneumonia. Leukocyte telomere length was measured and compared with that of 78 age- and sex-matched controls. Fibrosis biomarkers and radiological findings were assessed at 2 and 12 months. In a subgroup of 44 patients, mitochondrial protein expression was evaluated 2 years after infection using reverse-phase protein arrays. Associations among telomere length, mitochondrial proteins, inflammatory markers, and fibrotic sequelae were analyzed.

Results: Leukocyte telomere length was significantly shorter in patients than in controls (AUC, 0.84; $P < .0001$), independent of age or acute disease severity. At 12 months, 29% of patients showed fibrotic lung changes on HRCT. Elevated periostin and IL-6 levels correlated with persistent mitochondrial protein alterations at 2 years. Mitochondrial proteins such as ETF β and PKM2 differentiated patients with fibrotic sequelae and those with marked telomere attrition, suggesting their role as biomarkers. Moreover, in patients with fibrosis, telomere shortening correlated inversely with ACO1 levels, a protein involved in oxidative stress and iron metabolism.

Conclusions: SARS-CoV-2 infection induces sustained telomere shortening and long-term mitochondrial dysfunction, both of which are associated with fibrotic sequelae. These findings support a pathogenic link among mitochondrial dysregulation, telomere attrition, and pulmonary fibrosis, resembling mechanisms described in idiopathic pulmonary fibrosis. Monitoring these biomarkers may help identify patients at risk of chronic post-COVID complications.

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Introduction

The COVID-19 pandemic has affected more than 700 million people worldwide to date [1], and new hospital admissions continue to be reported. As the number of survivors grows, increasing attention has been directed toward the long-term consequences of

SARS-CoV-2 infection. Among these, long COVID has emerged as a major concern, with reported prevalence ranging widely from 10% to 77% of infected individuals.

During the pandemic, older individuals were disproportionately affected by severe COVID-19. This observation suggests that aging may represent a key risk factor for disease severity, as occurs in other chronic lung diseases such as idiopathic pulmonary fibrosis (IPF). Indeed, the incidence of severe COVID-19 and mortality increase with age [2], supporting the involvement of aging-related molecular pathways in the clinical course of the disease.

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Against this background, several studies have examined telomere length in patients with COVID-19 because of its close association with biological aging. These studies consistently report telomere shortening, particularly in severe cases, linking this alteration to clinical severity [3]. Survivors of SARS-CoV-2 infection have also been shown to exhibit signs of accelerated biological aging, including reduced telomere length [4], suggesting a potential role for these molecular changes as biomarkers of long-term sequelae. However, most available data derive from early postinfection phases, usually within weeks of hospital discharge [4], and it remains unclear whether telomere shortening is transient or persists long term.

Furthermore, mitochondrial dysfunction under conditions of oxidative stress, such as viral infections, is well established [5]. Accelerated telomere attrition and mitochondrial T-cell dysfunction have been described in viral infections, possibly reflecting increased cellular turnover driven by viral replication [6]. In COVID-19, mitochondrial alterations have been reported in bronchial epithelial cells, cell lines, and clinical samples, characterized by reduced oxidative phosphorylation and enhanced glycolysis, favoring viral replication [7]. Importantly, mitochondrial dysfunction appears to play a role not only during the acute phase but also in post-COVID syndrome, as these alterations may persist long after viral clearance [8].

Our objective was to evaluate the potential role of telomere shortening and mitochondrial dysfunction in the development of long-term complications of COVID-19, including pulmonary fibrosis.

Methods

Study design and participants

This study is based on a subcohort of the COVID-FIBROTIC study (Study of the Appearance of Lung Fibrotic Changes Associated with SARS-CoV-2 Infection; ClinicalTrials.gov identifier: NCT04409275; June 1, 2020), a prospective, observational, multicenter study aimed at evaluating pulmonary sequelae in patients admitted for bilateral COVID-19 pneumonia. The present cohort consisted of 132 patients from 5 hospitals in Spain who participated in the study.

Procedures

Patients were followed up after COVID-19 in outpatient clinics and were invited to participate in the study provided that they met no exclusion criteria. All included patients were scheduled for a first visit (V1) and a second visit (V2) at 2 and 12 months after hospital discharge, respectively. A third visit (V3) was conducted in 44 participants for mitochondrial analyses. During these visits, baseline data and current clinical status were collected.

At 2 months (V1), all 132 patients underwent blood sampling, pulmonary function testing, chest radiography, and high-resolution computed tomography (HRCT). At 12 months (V2), pulmonary function testing and blood analysis were repeated in all patients. Blood analysis included assessment of fibrosis biomarkers and extraction of DNA for telomere length evaluation. Only patients with persistent abnormalities on HRCT at 2 months underwent follow-up HRCT. At 24 months (V3), mitochondrial protein levels were evaluated in a subset of 44 patients from the original cohort as part of a dedicated mitochondrial study.

The use of different time points reflects both the distinct temporal dynamics of the biological processes studied and logistical constraints related to sample availability during the COVID-19 pandemic, with mitochondrial analyses incorporated as an exploratory extension of the original study protocol. The mitochondrial analy-

ses were conducted in a limited subgroup of patients with a small number of controls, which should be considered a methodological limitation of the study.

Patients were classified into two groups according to severity based on the World Health Organization (WHO) scale:

1. *Group 1*: hospitalized mild disease (WHO scale 4): acute respiratory failure requiring conventional supplemental oxygen.
2. *Group 2*: hospitalized severe and critical disease (WHO scales 5–7):
 - a. WHO scale 5: acute respiratory failure requiring noninvasive mechanical ventilation (NIV) or high-flow nasal oxygen.
 - b. WHO scale 6: intubation and invasive mechanical ventilation (IMV).
 - c. WHO scale 7: IMV and additional organ support.

Radiological assessment

HRCT images were evaluated by chest radiologists with extensive expertise in interstitial lung disease, following the Fleischner Society glossary of terms [9]. Fibrotic-like changes were defined as the presence of traction bronchiectasis, parenchymal bands, and/or reticular pattern. Readings were performed independently, and any discrepancies were resolved by consensus. Given the high level of expertise of both readers and the consensus-based approach, a formal interobserver agreement analysis was not performed.

Statistical analysis

Qualitative variables were described using frequencies and percentages, and quantitative variables were described using means and SD. Normality of continuous variables was assessed using the Shapiro–Wilk test. Mean comparisons were performed using the Student *t* test when normality assumptions were met; otherwise, the Mann–Whitney test was used. For qualitative variables, comparisons of percentages between groups were carried out using Fisher exact test for dichotomous variables or the χ^2 test for contingency tables with more than two categories. Correlation analysis was also performed to study the relationship between variables. All analyses were conducted using SPSS version 25. Statistical tests with $P < .05$ were considered significant.

Results

This study analyzed leukocyte samples from 132 patients in the COVID-FIBROTIC cohort [10], collected 1 year after acute SARS-CoV-2 infection. Patients were recruited between May 1 and July 31, 2020, a period characterized by circulation of early SARS-CoV-2 lineages in Spain. The baseline characteristics of the patients are shown in Table 1.

Leukocyte long-term telomere shortening after COVID-19

Telomere length analysis was performed in 131 leukocyte samples (1 sample was excluded because of quality issues). The mean age was 60 years, and 61.8% of patients were men.

Relative telomere length (RTL) was measured 1 year after hospitalization and compared with that of age- and sex-matched controls. Patients were stratified into three age groups (30–49, 50–69, and ≥ 70 years). RTL was significantly shorter in patients than in controls, confirming long-term telomere shortening after SARS-CoV-2 infection (Fig. 1).

To further assess the potential of RTL as a biomarker of long-term SARS-CoV-2 infection, we generated a receiver operating characteristic (ROC) curve, which demonstrated notable differences in

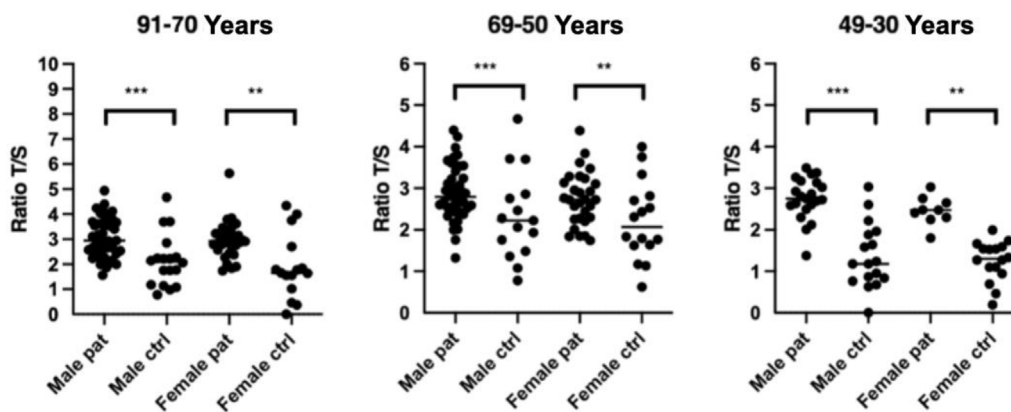


Fig. 1. Leukocyte telomere shortening in patients versus controls of the same age and sex 1 year after SARS-CoV-2 infection. Mean comparisons were performed using the Student *t* test. Telomere shortening was observed in all age groups in patients after COVID-19 compared with matched controls. Pat indicates patients; ctrl, controls.

Table 1
Patient characteristics.

Variable	Value
Age, years	60 (SD, 11.8)
Male sex	81 (61.8%)
Body mass index, kg/m ²	27.52 (SD, 4.01)
Never smokers	80 (61.1%)
Comorbidities	
Lung disease ^a	22 (16.8%)
Hypertension	47 (35.9%)
Diabetes	28 (21.4%)
Cardiovascular disease	16 (12.2%)
Chronic kidney disease	2 (1.5%)
Length of hospital stay, days	15.9 (SD, 14.46)
ICU stay, days	4.35 (SD, 9.97)
Severity groups^b	
Group 1 (milder disease, WHO scale 4)	91 (69.5%)
Group 2 (more severe disease, WHO scale 5-7)	40 (30.5%)
Lung function tests at 1 year after admission	
Forced vital capacity, %	104.17% (SD, 15.25)
Diffusing capacity of the lungs for carbon monoxide, %	83.84% (SD, 16.33)
Fibrotic changes on HRCT at 1 year after admission	38 (29%)

Data are presented as *n* (%) or mean (SD). BMI, body mass index; ICU, intensive care unit; FVC, forced vital capacity; DLCO, diffusing capacity of the lungs for carbon monoxide; HRCT, high-resolution computed tomography.

^a Lung disease includes asthma, obstructive sleep apnea, and other conditions.

^b WHO scale.

RTL levels between patients with COVID-19 and healthy controls. The optimal cutoff value for RTL was 2.230. Sensitivity and specificity were 84.7% and 76.0%, respectively, and the AUC was 0.84 ($P < .0001$) (Fig. 2A). When patients were divided into groups based on clinical characteristics and infection severity (group 1: patients who required, at most, respiratory support with nasal cannula; group 2: patients who required NIV and/or high-flow nasal oxygen, as well as patients who required intubation and IMV), no differences in telomere shortening at 1 year were found between the 2 groups (Fig. 2B).

Impact of COVID-19 on mitochondrial protein expression

Given the established role of mitochondrial dysfunction in premature pulmonary epithelial aging, particularly in angiotensin-converting enzyme 2 (ACE2)-expressing cells [11], we conducted a mitochondrial analysis in a subgroup of post-COVID patients.

Two years after infection, blood samples were collected from a subgroup of patients ($n=44$) from the previously analyzed series to obtain leukocytes, and proteins related to mitochondrial function were measured. Expression levels of proteins were

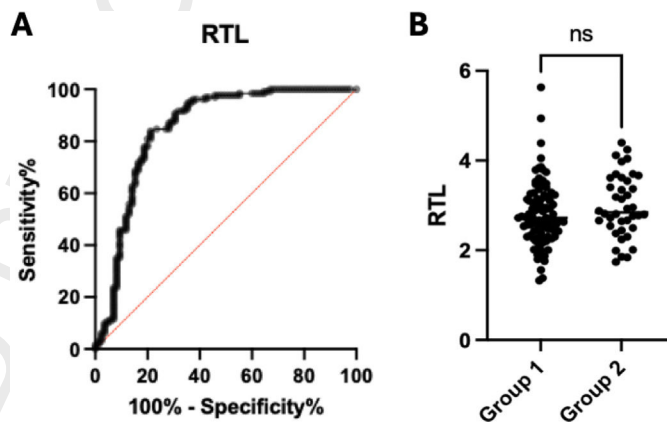


Fig. 2. (A) Receiver operating characteristic (ROC) curve and corresponding area under the curve (AUC) for RTL. (B) Telomere shortening according to severity groups. A similar RTL distribution was observed in both severity groups. Therefore, severity at admission does not determine greater telomere shortening.

compared with those in controls, revealing significant differences in glycolysis-related proteins, enolase 1 (ENO1); Krebs cycle proteins, succinate dehydrogenase subunit A and mitochondrial malate dehydrogenase (SDHA and MDH2); oxidative damage-related proteins, nitrotyrosine (NyTyr); reducing power generation-related proteins, glucose-6-phosphate dehydrogenase and isocitrate dehydrogenase 1 (G6PDH and IDH1); and oxidative phosphorylation-related proteins, the alpha regulatory subunit of mitochondrial F1-ATPase and cytochrome c oxidase subunit IV (ALFA-F1 and COX IV) (Fig. 3).

To assess how the degree of telomere shortening could affect long-term mitochondrial protein expression, patients were divided according to the degree of shortening, selecting those with shortening above the 90th percentile for age and sex. In the group with greater shortening, decreased levels of electron transfer flavoprotein subunit beta (ETFβ) and pyruvate kinase M2 isoform (PKM2) proteins were observed. ETFβ is a mitochondrial protein involved in fatty acid and amino acid oxidation, transferring electrons to the electron transport chain. Mitochondrial dysfunction, induced by oxidative stress and inefficient cellular respiration, increases DNA damage and accelerates telomere shortening. In aged cells, decreased ETFβ may contribute to reactive oxygen species accumulation, promoting telomere damage and cellular senescence [12].

On the other hand, PKM2 is an isoform of pyruvate kinase, a key enzyme in glycolysis that regulates energy metabolism and cell growth. In cancer and proliferative cells, PKM2 favors aerobic

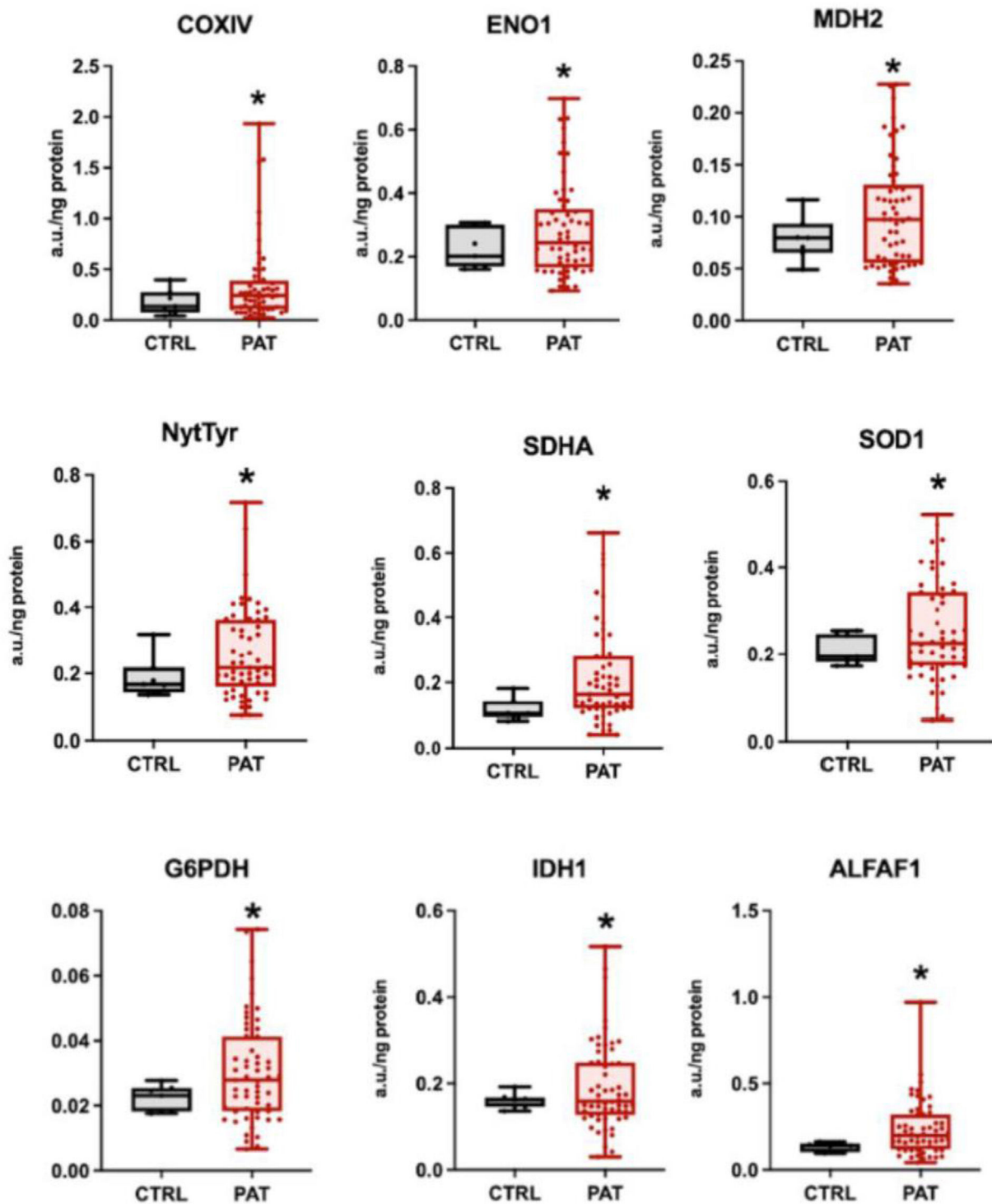


Fig. 3. Mitochondrial protein levels (expressed in arbitrary units [a.u.]) in patients versus controls. Normality was assessed before analysis; comparisons were performed using the Student *t* test or Mann–Whitney *U* test, as appropriate. Increased expression of several of these proteins was observed in patients compared with controls. COXIV indicates cytochrome c oxidase subunit IV; ENO1, enolase 1; MDH2, malate dehydrogenase 2; NyTyr, nitrotyrosine; G6PDH, glucose-6-phosphate dehydrogenase; IDH1, isocitrate dehydrogenase 1; ALFAF1, ATP synthase subunit alpha F1; SDHA, succinate dehydrogenase subunit A; and SOD1, superoxide dismutase.

206 metabolism/glycolysis over mitochondrial respiration, which can
207 alter redox homeostasis and affect DNA stability, including telomeres
208 [13]. PKM2 has been observed to regulate the expression of
209 genes involved in telomere maintenance by modulating the activity
210 of factors such as c-Myc and HIF-1 α . In certain contexts, PKM2
211 can translocate to the nucleus and affect transcription of genes
212 associated with telomere replication [14].

Inflammatory markers and persistent mitochondrial damage

213
214 As our group had previously identified an association between
215 blood periostin levels at 2 months after hospital discharge and pul-
216 monary fibrotic changes at 12 months [15], we investigated the
217 potential relationship between periostin levels and mitochondrial
218 function in long-term post-COVID-19 patients. We observed a pos-

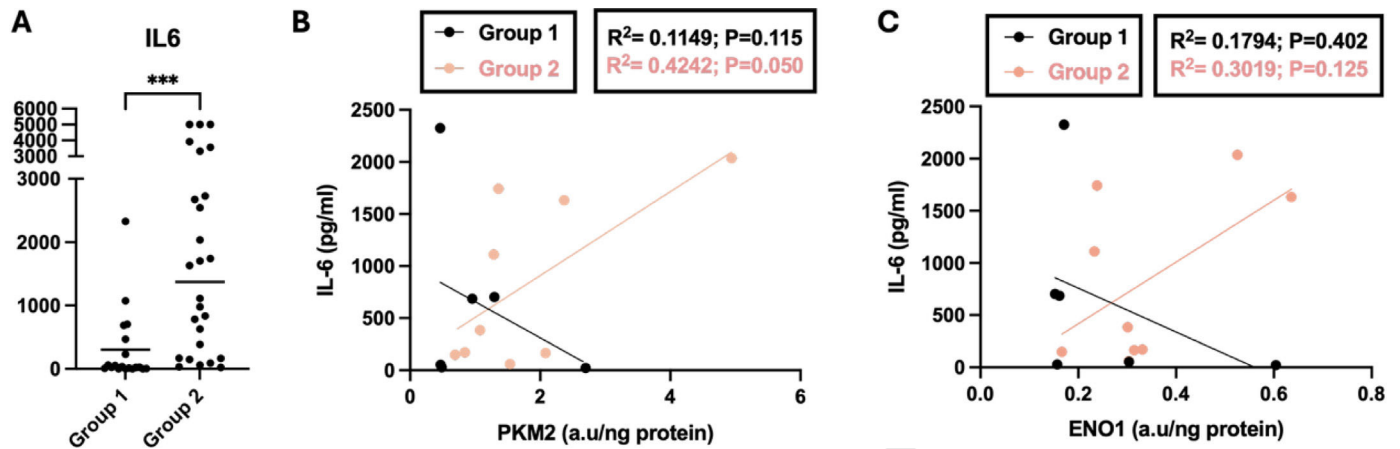


Fig. 4. (A) Comparison of peak IL-6 concentrations (pg/mL) during hospitalization between severity groups. Normality was assessed before analysis; comparisons were performed using the Student *t* test. Higher values were observed in more severely ill patients. (B and C) Correlation in leukocytes between IL-6 and PKM2 or ENO1 levels in COVID-19 patients classified according to maximum respiratory support required during hospitalization. Bivariate correlation was performed using Pearson coefficient. An inverse correlation between IL-6 and both PKM2 and ENO1 was observed across groups; however, only the association between PKM2 and IL-6 in group 2 approached statistical significance ($P=.05$).

219 itive correlation between periostin and leukocyte COX-IV levels
220 2 years after infection ($P=.012$; $r=0.38$). The COX-IV subunit of
221 Complex IV is a regulatory component, and its increase does not
222 necessarily imply improved mitochondrial respiratory capacity. It
223 has been reported that under conditions of oxidative stress, func-
224 tional hypoxia [16], and chronic inflammation [17], compensatory
225 transcriptional programs are activated, leading to increased expres-
226 sion of mitochondrial components.

227 Given the close interplay between inflammation and mitochon-
228 drial function, we evaluated another key inflammatory marker,
229 IL-6. This cytokine plays a central role in SARS-CoV-2 infection, with
230 markedly elevated levels during the acute phase of the disease [18].
231 Consistent with these findings, we also observed statistically signifi-
232 cant differences between groups according to disease severity
233 (Fig. 4A).

234 We then correlated IL-6 levels at admission with mitochondrial
235 protein levels at 2 years and found significant associations between
236 elevated IL-6 levels and increased ENO1 ($P=.022$; $r=0.52$) and
237 PKM2 ($P<.005$; $r=0.77$) levels 2 years after infection (Fig. 4B and
238 C). This relationship is biologically plausible, as IL-6 is a key proin-
239 flammatory cytokine involved in immune response and chronic
240 inflammation. Enolase, particularly neuron-specific enolase and
241 α -enolase, may act as an autoantigen and participate in inflamma-
242 tory diseases [19]. Under inflammatory conditions, IL-6 can induce
243 changes in the expression of metabolic enzymes, including enolase.
244 ENO1 has been shown to induce high levels of proinflammatory
245 cytokines. Choi et al. [20] reported that ENO1 induces high levels
246 of proinflammatory cytokines in concanavalin A-activated periph-
247 eral blood mononuclear cells and ENO1-expressing monocytes in
248 healthy individuals, as well as in macrophages from patients with
249 rheumatoid arthritis. Similarly, Bie et al. [21] demonstrated that
250 PKM2 forms aggregates that impair its enzymatic activity and gly-
251 colytic flux, driving cells into senescence. Because PKM2 is the
252 rate-limiting enzyme in the final step of glycolysis, it regulates
253 the Warburg effect, which provides energy for inflammatory cells;
254 PKM2 has been shown to promote dendritic cell activation [22].
255 Indeed, PKM2 has been proposed as a clinical marker of inflamma-
256 tion in vasculitis [23].

257 *Mitochondrial signature in COVID-related pulmonary fibrosis*

258 Our primary endpoint was to identify biomarkers capable of
259 predicting progression to pulmonary fibrosis following COVID-19.

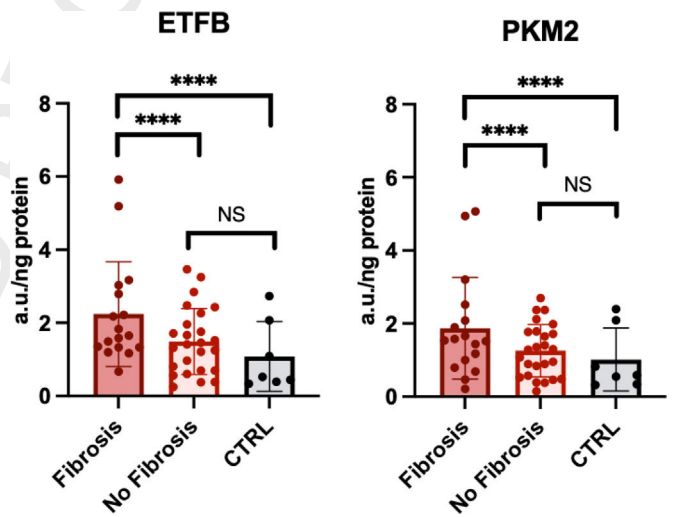


Fig. 5. Comparison of ETF β and PKM2 concentrations among patients who developed fibrotic changes at 1 year, those who did not, and controls. Comparisons were performed using the Student *t* test. Higher levels of both ETF β and PKM2 were observed in patients with fibrosis compared with those without fibrotic changes and with controls. ETF β indicates electron transfer flavoprotein β ; PKM2, pyruvate kinase M2.

260 Although no significant differences in telomere shortening were
261 observed between patients who developed fibrosis and those who
262 did not, we explored potential differences in mitochondrial pro-
263 tein expression. Accordingly, we investigated whether leukocyte
264 mitochondrial proteins altered in association with disease markers
265 were also linked to the development of fibrotic lung sequelae.

266 To differentiate patients with and without fibrotic sequelae,
267 mitochondrial protein levels were analyzed in both groups. Sig-
268 nificant differences were observed in ETF β and PKM2 expression:
269 patients without fibrotic sequelae showed no differences com-
270 pared with controls, whereas those with fibrotic sequelae exhib-
271 ited increased levels of both mitochondrial proteins (Fig. 5). This
272 finding indicates that elevations in ETF β and PKM2 are specific to
273 patients with fibrotic sequelae. Notably, these proteins were also
274 altered in patients with greater telomere shortening, reinforcing
275 the hypothesis that telomere attrition and pulmonary fibrosis are
276 closely linked and may share common underlying mechanisms.

To further investigate the relationship between leukocyte telomere shortening and pulmonary fibrosis, mitochondrial protein alterations were evaluated exclusively in patients with fibrotic sequelae. Patients were stratified according to whether telomere shortening exceeded the 90th percentile for age and sex.

ACO1 (cytosolic aconitase 1) levels differed significantly and showed an inverse correlation with relative telomere length, a finding not observed in nonfibrotic patients (Supplementary Fig. 1). Although ACO1 does not directly participate in telomere maintenance, its dysregulation may reflect an unfavorable cellular environment characterized by oxidative stress, mitochondrial dysfunction, and iron dysmetabolism, all of which contribute to telomere shortening. Therefore, our findings suggest that decreased ACO1 levels in this context may represent a cellular adaptation associated with the progression of pulmonary fibrosis.

Discussion

Severe SARS-CoV-2 infection and telomere attrition

The most common sequelae after COVID-19 include persistent radiological abnormalities [24], and in our cohort, 29% of patients exhibited fibrotic changes 1 year after infection. Age-related factors, particularly telomere shortening and oxidative stress, are increasingly recognized as key determinants of COVID-19 severity and potential biomarkers of long-term outcomes [35]. In parallel, mitochondrial dysfunction – closely linked to aging and telomere biology – also contributes to both acute and postacute COVID-19 [26].

We observed significant leukocyte telomere shortening in all patients 1 year after hospitalization, regardless of age, baseline characteristics, or disease severity. Unlike earlier reports [27], our findings indicate that telomere shortening persists over time rather than being limited to the acute phase or inflammatory response. Clinically, this may reflect accelerated biological aging, with implications including increased risk of chronic disease, immune dysfunction, and persistent post-COVID-19 symptoms. Therefore, telomere monitoring may provide prognostic value in post-COVID-19 recovery.

Relationship between telomere length alteration and fibrotic sequelae

Several studies have demonstrated that patients with COVID-19 may develop fibrotic pulmonary sequelae, which in some cases persist long term. Additionally, telomere shortening has been linked to fibrotic diseases, particularly idiopathic pulmonary fibrosis (IPF), the most extensively studied condition [28].

In this context, we evaluated telomere length evolution in patients hospitalized for COVID-19 and its relationship with radiological fibrotic lung sequelae at 12 months.

Our findings demonstrate that SARS-CoV-2 infection induces significant leukocyte telomere shortening 1 year after infection and suggest that this process may be associated with the development of long-term sequelae. Although our cohort consisted primarily of patients with severe disease, these results provide a strong basis for future studies in larger and more heterogeneous populations.

Studies assessing leukocyte telomere length could play a key role in long-term follow-up strategies for patients recovering from COVID-19, particularly those with severe disease. Telomere shortening in type II alveolar epithelial cells has been shown to correlate with telomere length in circulating monocytes. Several studies have demonstrated a strong correlation between these cell types, supporting the use of monocytes as a reliable surrogate for telomere assessment [29]. This approach facilitates longitudinal monitoring

in clinical practice and may serve as a prognostic biomarker for personalized follow-up.

Our findings support the concept that COVID-19 not only triggers an acute inflammatory response but may also leave a persistent molecular imprint that contributes to cellular aging and tissue dysfunction. We demonstrate that telomere length assessment using accessible methods such as peripheral blood analysis is valuable in both research and clinical settings. Although further validation in larger cohorts is required, our study provides a robust and reproducible methodological framework for characterizing the long-term molecular impact of SARS-CoV-2 infection.

Chronic mitochondrial dysfunction as a driver of post-COVID-19 pulmonary fibrosis

An increased inflammatory response, oxidative stress, and mitochondrial damage have been observed postmortem in the lungs of patients who died of COVID-19 [30]. In our study, we demonstrate similar findings in mitochondrial proteins derived from leukocytes 2 years after acute infection. This supports the use of peripheral blood as a practical tool for monitoring long-term mitochondrial effects. Notably, we observed increased expression of certain mitochondrial proteins, consistent with previous studies showing that oxidative stress and chronic inflammation can alter cellular transcriptional capacity [17]. It is important to note that increased levels of proteins such as COX-IV may occur without a corresponding increase in mitochondrial respiratory capacity. This increase likely reflects a compensatory response to persistent mitochondrial damage rather than a functional enhancement of oxidative phosphorylation (OXPHOS) [16].

Oxidative stress plays a key role in viral infections and specifically in COVID-19 [31]. We observed mitochondrial protein alterations associated with oxidative stress, disrupted fatty acid metabolism, and hyperglycolysis, a pattern described in post-COVID-19 syndrome [32]. Interestingly, this hyperglycolytic state has been linked to increased production of cytokines and reactive oxygen species (ROS) [33]. Furthermore, the coexistence of enhanced glycolysis and elevated mitochondrial protein expression has been previously reported in chronic inflammation, cellular senescence, and fibrosis, where it reflects uncoupled metabolic dysfunction rather than efficient metabolic adaptation [34].

Additionally, we observed increased levels of NADPH-generating enzymes, such as glucose-6-phosphate dehydrogenase (G6PDH). Indirect mitochondrial damage induced by SARS-CoV-2 has been linked to the angiotensin-converting enzyme 2 (ACE2) receptor. Viral infection reduces ACE2 expression, leading to upregulation of angiotensin II. Binding of angiotensin II to its receptor stimulates NADPH oxidase activity, resulting in increased ROS production [8].

Elevated plasma interleukin-6 (IL-6) levels are a hallmark of severe COVID-19 and were also observed in our cohort; these levels have been used to guide treatment [35]. High IL-6 levels may induce oxidative stress through ROS generation, contributing to mitochondrial dysfunction and sustained inflammation [36]. Consistent with this, we found that elevated IL-6 levels during hospitalization were associated with long-term alterations in mitochondrial proteins. Moreover, acute-phase inflammatory markers, including IL-6 and periostin, correlated with persistent mitochondrial dysfunction, suggesting a transition from acute inflammation to chronic oxidative stress that may contribute to fibrotic progression, as described in other chronic lung diseases [26].

Our results indicate that SARS-CoV-2-induced mitochondrial dysfunction, together with telomere shortening, underlies persistent fibrotic changes. Mitochondrial damage promotes the production of mitokines, cellular stress response molecules whose dysregulation has been linked to accelerated aging processes [38].

Altered proteins such as ETF β and PKM2 differentiated patients with fibrosis and severe telomere attrition (above the 90th percentile), and these same proteins also distinguished between patients with and without radiological fibrotic changes, suggesting their potential role as differential biomarkers.

Pulmonary fibrosis, telomere shortening, and mitochondrial dysfunction are interconnected within a pathological cycle that exacerbates the progression of lung disease [39]. Mitochondrial dysfunction leads to excessive ROS production, which contributes to chronic inflammation and tissue damage, thereby perpetuating fibrosis and pulmonary deterioration.

In this context, our findings suggest a shared pathophysiological model between post-COVID-19 pulmonary fibrosis and interstitial lung diseases such as idiopathic pulmonary fibrosis (IPF), as both entities share risk factors including advanced age, male sex, and comorbidities [40]. Additionally, we observed a correlation between low levels of ACO1 – a protein sensitive to oxidative stress and involved in iron metabolism – and increased telomere shortening. This observation is consistent with experimental studies demonstrating a significant role of ACO1 in the pathophysiology of IPF [41].

Mitochondrial dysfunction has been shown to persist after viral clearance and may contribute to prolonged symptoms in long COVID. Therefore, biomarkers of mitochondrial dysfunction could be useful for early identification and monitoring of chronic post-COVID-19 sequelae and for identifying patients at higher risk of developing long COVID.

Conclusions

SARS-CoV-2 infection is associated with persistent telomere shortening and mitochondrial dysfunction, independent of age, lasting for at least 1 year after infection. The association between inflammatory markers, mitochondrial impairment, and shorter telomere length – particularly in patients with fibrosis – suggests a shared pathogenic axis that may contribute to chronic post-COVID-19 lung damage.

Authors' contributions

All authors contributed to the literature search, study design, data interpretation, manuscript drafting, and critical revision of the work. All authors had full access to all data, contributed to writing and editing the article, and approved its submission. All study team members supported study implementation, sample collection, and data submission. All authors read and approved the final manuscript.

Declaration of generative AI and AI-assisted technologies in the writing process

The authors declare that artificial intelligence tools were used only for minor assistance in wording and language editing. No artificial intelligence tool was used to generate scientific content, data, or conclusions.

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Conflicts of interest

The authors declare no conflicts of interest.

Uncited references

[25,37].

Appendix A. Supplementary data

Supplementary data associated with this article can be found in the online version available at <https://doi.org/10.1016/j.arbres.2026.03.018>.

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