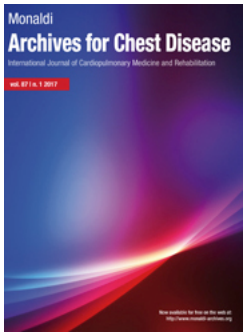

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Fibrotic outcomes from SARS-CoV-2 virus interstitial pneumonia

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Abstract

Following the onset of the new COVID-19 pandemic, particular attention is paid to the long-term outcomes, especially concerning patients affected by the SARS-CoV-2 virus leading to interstitial pneumonia. The aim of this research is to evaluate the possible evolution over time of interstitial pneumonia into post-inflammatory fibrosing interstitial disease.

This research included 42 patients admitted to the COVID ward for SARS-CoV-2 interstitial pneumonia, 10 patients with mild pneumonia and respiratory failure who were treated with O_2 only, 32 patients with severe pneumonia in which O_2 and non-invasive ventilation were used for respiratory assistance, and 4 patients treated with invasive mechanical ventilation. At 70±30 days, 6, 12, 24, and 36 months after discharge, the cohort of patients carried out the evaluation of inflammation indices, high-resolution computed tomography (CT) chest scans, and functional respiratory tests.

The comparative analysis showed that 83.3% of patients had residual parenchymal lung disease at 36-month follow-up, with a significantly higher rate in those with severe pneumonia and more extensive disease on initial CT. Regarding the pulmonary involvement model, patients presented ground-glass opacity or peripheral parenchymal bands, or a combination of them, peri- and intralobular interstitial thickening, which may be representative of fibrotic interstitial lung disease. There is a correlation between the severity of pneumonia, the inflammatory state, the need to increase respiratory support, and the quantity and persistence of CT-related lesions. Reductions in respiratory functions and exercise capacity were observed, the latter more pronounced in patients (24%) who had contracted severe pneumonia and required ventilatory support.Pulmonary outcomes from SARS-CoV-2 respiratory infections show a wide range of radiological findings, from complete recovery to stable outcomes of thickening and distortion of the interstitial architecture. From a functional point of view, there is an impairment of the alveolar-capillary diffusion capacity and, in cases who had contracted severe pneumonia, desaturation and reduced exercise tolerance in 24% of cases at a 36-month follow-up.

Key words: COVID-19 interstitial pneumonia, pulmonary fibrosis.

Introduction

COVID-19 infection may be asymptomatic or manifest itself as a mild respiratory tract disease while severe cases may present pneumonia, leading to acute respiratory distress syndrome (ARDS) in approximately 15% of hospitalised patients [1].

Studies have shown that in patients with this disease, once the acute phase had passed and they had recovered from the infection, changes in lung parenchyma and respiratory function were found, raising the question of whether these changes could evolve towards a condition of pulmonary fibrosis [2-4].

The hypothesis of a possible evolution of histopathological changes induced by SARS-CoV-2 infection into fibrosis has already been highlighted in previous coronavirus epidemics. Studies of autopsy findings during the epidemic in 2003 showed that the predominant lesion pattern was diffuse alveolar damage (DAD) with deposition of hyaline membranes, followed by a cellular proliferative phase including hyperplasia of type II pneumocytes, and a possible organisation of diffuse alveolar damage with fibroblast proliferation [5,6]. In the recent SARS-CoV-2 pandemic, a study conducted in northern Italy in patients who died of covid 19 interstitial pneumonia showed that the predominant pattern of lesions was diffuse alveolar damage, including hyaline membrane deposition, pneumocyte hyperplasia and the presence of platelet thrombi and fibrin in small arterial vessels [7,8].

Fibrotic pulmonary changes may result in functional impairment and reduced exercise tolerance. Follow-up studies were conducted for 15 years in healthcare staff who had contracted severe acute respiratory syndrome during the 2003 MERS in which it was shown that approximately 9% of patients had fibrotic lung lesions and that interstitial lung damage and functional decline recovered within the first two years [9], with a residual percentage showing stable lesions at follow-up until 2018. Also in a prospective study [10], in infected patients who survived the 2003 epidemic, impaired alveolar-capillary spread of cases and reduced exercise capacity were observed in 23.7% of patients.

Materials and Methods

Immediately after the first pandemic phase at our centre, follow-up was activated for patients with previous Covid and radiological demonstration of interstitial pneumonia.

Observational study. The inclusion criteria concerned patients who had been hospitalized for interstitial pneumonia and who had received respiratory support based on the severity of the clinical-radiological and functional respiratory grade. The inclusion into the study was based

on the collection of clinical, serological and radiological data performed during hospitalisation, with entry into the observational study which included the evaluation of the serological indices ESR and CRP, the D Dimer, the level of IL 6 in the blood, HR chest CT, respiratory functional tests with body plethysmography, DLCO, 6-meter walk test. The first check-up took place 70±30 days after discharge (T1). Follow-up then continued at 6(T2), 12(T3), 24(T4) and 36(T5) months.

Forty-two patients were selected. The average age was 54.8 ± 16.2 years, 35 men and 7 women who were hospitalised for sars-CoV2 interstitial pneumonia. Different levels of severity were considered in the selection criteria. Ten patients have contracted mild pneumonia and respiratory failure requiring only O_2 support (conventional oxygen therapy; high-flow oxygen), 32 had severe pneumonia, according to WHO classification [11], for whom CPAP also NIV and invasive ventilation with oro-tracheal intubation (4 patients) were required in addition to O_2 support.

Comorbidity was present in 34 patients (81% Tab. 1), of whom 6 had chronic respiratory diseases (17.6%): 2 with asthma, 3 with chronic bronchitis and 1 with bronchiectasis.

CT radiological lesions were identified on the basis of the radiological report and classified according to the following nomenclature into: ground-glass opacities (GGO), consolidations, interlobular and intralobular septa thickening, fibrotic striae, bronchiectasis.

The degree of dyspnea was assessed according to Borg's scale (m MRC).

The study of respiratory function included: Forced Expiratory Volume in the first second (FEV_1), Forced Vital Capacity (FVC), FEV_1 / FVC ratio, Total Lung Capacity (TLC), Vital Capacity (VC), Inspiratory Capacity (IC), Expiratory Reserve Volume (ERV), Airway Resistance (R_{aw}) and DL_{CO} using the single-breath technique [12]. All PFR measurements were expressed as absolute values and percentages of predicted normal values. Criteria for the classification of lung function changes were based on ATS Guidelines [13,14] and performed with Jagger Master Screen Body equipment.

The 6-MWT was performed according to the guidelines of the American Thoracic Society [15]. Dyspnea data, with a modified Medical Research Council (mMRC) scale, were collected before and after 6 MWT.

After the initial radiological and functional assessment (T1), according to the degree of extension of the lesions and functional deficit, the patients (except those with normal radiological pattern) underwent supplementary treatment with only prednisone at a low dose of 5 mg per day for a variable period of 50±10 days. Then they all underwent follow-up at

6(T2) and 12(T3), 24(T4) and 36(T5) months from the date of admission, with re-evaluation of the indices of inflammation, serum IL6, HR chest CT, assessment of the degree of dyspnea, respiratory function with global spirometry, DLCO, WT6m.

Statistical analysis

Statistical method. Data are described as mean±standard deviation or as absolute frequency and percentage. Inter-group averages were compared by means of Student's t-test for independent samples. Categorical variables were compared by Fisher's exact test. A $p<0.05$ was considered statistically significant.

Results

HRCT chest at 70±30 days after discharge showed a normal radiological pattern in only 7 patients (16.7%), all from the first group with O_2-only pneumonia. The radiological lesions still present in the remaining 35 patients (83.3%), of which only 3 were from the first group and all 32 patients were from the second group (Table 1), were represented by GGO combined with interlobular and intralobular septa thickening, fibrotic striae, consolidation, and traction bronchiectasis (Figure 1).

The evaluation of serum IL 6 still showed slightly elevated serum values (6.57±1.4pg/ml) in 10 patients, 2 of whom were in the first group with mild pneumonia (who had presented persistence of radiological lesions) and 8 were in the second group with severe pneumonia (Table 1).

The assessment of the degree of dyspnoea according to Borg's scale revealed a grade 1 (m MRC 1) in 20 patients and a grade 2 (m MRC 2) in 22 patients, all of whom had contracted severe pneumonia.

The DLCO values were 74±9% in the forms of interstitial pneumonia with O_2 support only, whereas the 32 patients with severe forms of pneumonia who received ventilatory support had a deficit of 60±6% of the theoretical value (Table 2).

Exercise tolerance, assessed by means of a 6-minute walking test, revealed a desaturation of less than 90% in 15 patients (40.5%), including 3 with mild pneumonia (17.6%) and 14 with severe interstitial pneumonia (82.3%). A higher number of comorbidities were found in patients with desaturation (Table 3).

Re-evaluation at 6, 12, 24 and 36 months

The radiological re-evaluation took place on 35 patients, including 3 from the first group and 32 from the second group who had persistent radiological lesions on T1.

HRCT chest (Figure 1) showed resolution of consolidations in all patients, a progressive reduction in the number and extent of the ground-glass opacities that persisted at 36 months (T5) in 4 patients (11.4%) with residual and tenuous subpleural areas, while fibrotic striae, distortion and interstitial reticular thickening persisted in combination in 35 patients (83.3%), traction bronchiectasis in 6 patients (17.1%) (Figure 1).

The serum IL-6 assay at 6 months (T2) detected slightly elevated values in only 2 of the initial 8 patients 5.8±05pg/ml. At 12 months (T3) and subsequently in T4 and T5 serum IL-6 values were in the normal range (0-5pg/ml)

Dyspnea was assessed as grade 1 (m MRC 1) in 15 patients and grade 2 (m MRC 2) in 20 patients.

After 24 and 36 months(T4,T5), re-evaluation of CO improved by about 5.4±06% in patients with mild pneumonia, and by 6±0.5% in patients with severe pneumonia (Table 2).

The walking test at 24 and 36 months (T4,T5) detected a desaturation <90% in 10 patients (23.8%), including only 1 patient in the first group with mild pneumonia (10%) and 9 patients (28%) in the second group with severe pneumonia (Table 3).

Discussion

Recent studies of post-covid radiological patterns, performed immediately after the first pandemic phase, confirm pulmonary fibrotic-type changes in patients who survived severe pneumonia. These changes were associated with advanced age, acute respiratory distress syndrome, longer hospital stay and non-invasive mechanical ventilation [16-19].

Among the fibrogenic mechanisms associated with viral infection, the following should be emphasised: the possible viral activation of profibrotic pathways with production of growth factors FGF, EGF, TGFbeta [20,21]; cytokine-induced damage [22]; direct cellular damage of the virus on alveolar type II cells on macrophages and endothelial cells [22,23]; lesions induced by mechanical ventilation; the patient's age.

Therefore, on the basis of these clinical-physiopathological premises, a functional respiratory and radiological follow-up was conducted in discharged patients diagnosed with SARS-CoV-2 interstitial pneumonia who presented interstitial pneumonia with respiratory failure and severe pneumonia according to the WHO classification.

The first assessment involved thoracic radiological imaging with HR chest CT scan and comparison with the radiological investigation performed on admission.

At 70±30 days after discharge, radiological abnormalities persisted in 35 patients (83.3%) with a prevalence in those who had developed severe pneumonia. Although pulmonary involvement continued with progressive resorption of lesions by resolution of oedema and cellular infiltration, after approximately 6, 12 and 24 and 36 months radiological abnormalities persisted with GGO, striae and subpleural parenchymal bands, thickening and distortion of the interstitial architecture. Laboratory results also showed at an early stage, and only in a portion of patients, higher levels of IL-6, D-dimer and PCR. Serum IL-6 assays then returned to normal in all patients, reflecting resolution of the acute inflammatory process.

Other baseline studies using generalized linear models have found that basal IL-6 levels could be proposed as predictors of medium/long-term radiological sequelae after COVID-related interstitial pneumonia [24,25]. Our results are consistent at least in the early T1 and T2 phases for a portion of patients.

Other studies evaluated the potential use of serum nucleocapsid antigen (NAg) and Krebs von den Lungen-6 (KL-6) glycoprotein as biomarkers of COVID-19 and their correlation with clinical, radiological and biochemical parameters [26-29]. Elevated levels of these biomarkers were coherent with increased inflammation, interstitial lung damage and more severe clinical manifestations, thus the hypothesis of their link to interstitial lung diseases, e.g. idiopathic pulmonary fibrosis (IPF), nonspecific interstitial pneumonia (NSIP).

We believe that in the persistence of long-term radiological sequelae, especially in patients with severe pneumonia who had required greater respiratory support, in addition to the action of interleukin 6, NAg and KL-6, other factors such as growth factors and injuries induced by mechanical ventilation may be decisive [30].

The degree of dyspnea, assessed through Borg's scale, persisting at grade 1 and 2 two years after the disease, as well as the severity of the disease, could also reflect the contribution of steroids to viral myopathy through various mechanisms such as the long period of inability and alterations in protein synthesis.

The evidence on pulmonary function tests after discharge and at 24 months shows a reduction in FVC, reduction TLC, D_{LCO}, 6 MWT, with prevalence in patients who had contracted severe pneumonia compared to patients with pneumonia (Table 2).

Focusing on DLCO, its stable deficit as shown by other shorter follow-up studies on covid19 [10], but also longer follow-ups during MERS and SARS [9], persists <80% in all patients (83.3%) who had contracted severe pneumonia.

The exercise tolerance assessment conducted in other studies [31,32], on a smaller number of patients and immediately at discharge, showed desaturation in 50% of the patients. In our work, after 36 months, 10 patients (23.9%) had desaturation <90% during WT, of whom 9 with severe pneumonia and use of ventilation, all with alveolus-capillary diffusion deficits, confirming a stable alteration in gas exchange due to damage at the level of the alveolus-capillary barrier. Our data therefore highlight that there is a correlation between the severity of pneumonia, the inflammatory state, the type of respiratory support received, the quantity and persistence of CT-related lesions, with a greater number of patients with functional deficit.

Conclusions

Our studies indicate that in a significant number of patients (83.3%) who contracted SARS-CoV-2 interstitial pneumonia, although there is a progressive resorption of the lesions expressed as inhomogeneities and/or consolidations, there is persistence, even after 36 months, of thickening and distortion of the interstitial architecture. The persistence of lesions is prevalent in relation to the initial severity of pneumonia, with greater infiltration, and to the type of respiratory support received. Alterations in gas exchange and reduced exercise tolerance are present in approximately 24% of patients, expecially those with severe pneumonia, outlining a picture of Covid-related post-inflammatory lung interstitial disease.

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Abbreviations:
ARDS: Acute Respiratory Distress Syndrome
SARS-CoV-2: Severe Acute Respiratory Syndrome Coronavirus 2
COVID-19: Coronavirus Disease of 2019
MERS-CoV: Middle East Respiratory Syndrome Coronavirus Infection
IL-6: Interleukin 6
KL-6: Krebs von den Lungen-6
Nag: serum nucleocapsid antigen
CT HR: Computed Tomography High Resolution
DLCO: Diffusion Capacity Lung Carbon Monoxide
m MRC: Modified British Research Council Questionnaire
WT6m: Walking Test 6 Minute
CPAP: Continuous Positive Airway pressure
NIV: Non Invasive Ventilation
FGF: Fibroblast Growth Factors
EGF: Epidermal Growth Factors
TGF: Transforming Growth Factors beta
IPF: idiopathic pulmonary fibrosis
NSIP: nonspecific interstitial pneumonia

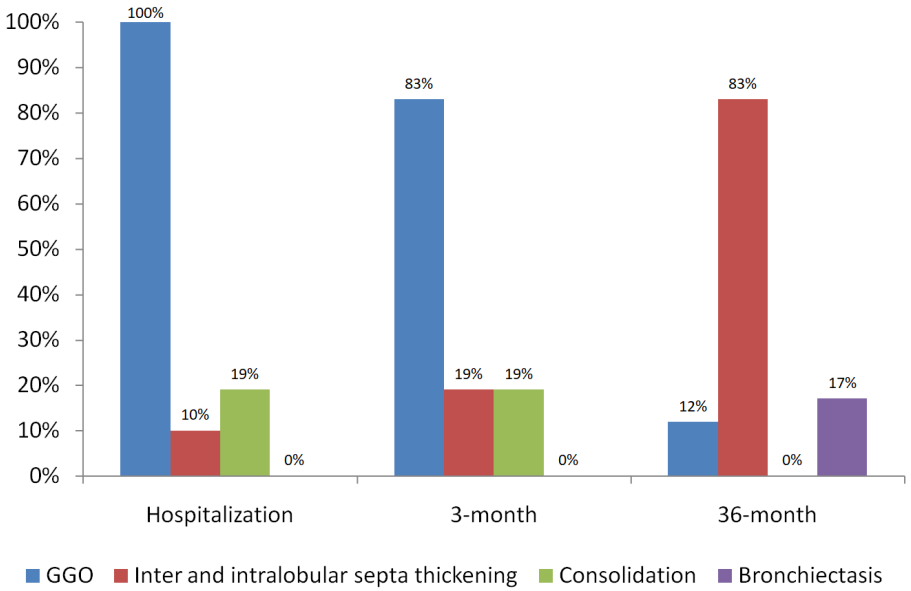

Figure 1. Predominant lesions HRCT chest. After hospitalization at 3 months, the radiological lesions were still present in the remaining 35 patients (83.3%), of which only 3 from the first group (mild pneumonia) and all 32 patients from the second group (severe pneumoniae), were represented by GGO combined with interlobular and intralobular septa thickening, fibrotic striae, consolidation and traction bronchiectasis. At 36 months HRCT chest showed resolution of consolidations in all patients, a progressive reduction in the number and extent of the ground-glass opacities that persisted in 4 patients (11.4%) with residual and tenuous subpleural areas, while fibrotic striae, distortion and interstitial reticular thickening persisted in combination in 35 patients (83.3%), traction bronchiectasis in 6 patients (17.1%).

Table 1. Basic characteristics and co-morbidities of patients.

Gender
Male 35 (83.3%)
Female 7 (16.7%)
Age 54.8 ± 16.2 years
Mild Pneumonia 10 patients (23.8%)
Severe pneumonia 32 patients (76.2%)
Comorbidity 34 (80.9%)
Hypertension 15 (44.1%)
Diabetes 5 (14.7%)
Obesity 4 (11.8%)
Respiratory diseases 6 (17.6%)
Coronary heart disease 4/(11.8%)
Laboratory examinations
D Dimer 489±200 ng/mL
PCR 4.5±2 mg/L
IL6 0-5 pg/mL (32 pat.)
IL6 6.57±1.4 pg/mL (10 pat.)

Table 2. DLCO functional data.

	Total	**MILD PNEUMONIA**	**SEVERE PNEUMONIA**	**p-value**
	42	10	32	
DLCO% pred				
70± 30 days after discharge		74±9%	60±6%	<0.001
After 24 months		+5.4±0.6 %	+6±0.5%	0.003
KCO%pred		76-82%	65-75%	

Table 3. Functional data WalkTest (WT6m).

	Total	**MILD PNEUMONIA**	**SEVERE PNEUMONIA**	**p-value**
	42	10	32	
6mwt Sat<90%				
70±30 days after discharge	17 (40%)	3 (30%)	14 (44%)	0.490
After 24 and 36 months (23.8%)	10 (24%)	1 (10%)	9 (28%)	0.404
Comorbidity		1-3	1-4	