ORIGINAL ARTICLE

Short-Term Consequences of SARS-CoV-2-Related Pneumonia: A Follow Up Study

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Abstract

The aim of the study was to assess the short-term consequences of SARS-CoV-2-related pneumonia, also in relation to radiologic/laboratory/clinical indices of risk at baseline. This prospective follow-up cohort study included 94 patients with confirmed COVID-19 admitted to a medical ward at the Montichiari Hospital, Brescia, Italy from February 28th to April 30th, 2020. Patients had COVID-19 related pneumonia with respiratory failure. Ninety-four patients out of 193 survivors accepted to be re-evaluated after discharge, on average after 4 months. In ¼ of the patients an evidence of pulmonary fibrosis was detected, as indicated by an altered diffusing capacity of the lung for carbon monoxide (DLCO); in 6–7% of patients the alteration was classified as of moderate/severe degree. We also evaluated quality of life thorough a structured questionnaire: 52% of the patients still lamented fatigue, 36% effort dyspnea, 10% anorexia, 14% dysgeusia or anosmia, 31% insomnia and 21% anxiety. Finally, we evaluated three prognostic indices (the Brixia radiologic score, the Charlson Comorbidity Index and the 4C mortality score) in terms of prediction of the clinical consequences of the disease. All of them significantly predicted the extent of short-term lung involvement. In conclusion, our study demonstrated that SARS-CoV-2-related pneumonia is associated to relevant short-term clinical consequences, both in terms of persistence of symptoms and in terms of impairment of DLCO (indicator of a possible development of pulmonary fibrosis); some severity indices of the disease may predict short-term clinical outcome. Further studies are needed to ascertain whether such manifestations may persist long-term.

Keywords COVID-19 · SARS-CoV2 · Lung fibrosis · Interstitial lung disease · Prognostic factors · Sequelae

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1 Introduction

Coronavirus disease 2019 (COVID-19) pandemic represented, and still represents, a major clinical problem in Lombardy, one of the most affected Italian (and worldwide) regions; a high toll of victims was paid. In our clinical ward, a mortality rate of 25% was observed during the first pandemic outbreak (March–April 2020) [1].

However, a major issue is represented by the incidence of clinical sequelae of the disease, since it is not known which proportion of patients will develop pulmonary fibrosis (interstitial lung diseases, ILD). Available data are scarce [2, 3] or even anecdotal [4, 5].

Predicting factors determining outcome prognosis of patients that develop interstitial pneumonia with respiratory failure have been investigated; among them gender, hypertension, obesity, diabetes and other cardiovascular disorders

seems be substantially associated with SARS-CoV-2 infection and with poor outcome [1, 6–9]. In fact, the severity of the primary respiratory syndrome is increased in patients with pre-existing cardiovascular disease [1, 6, 7, 10, 11], as also documented by the association of the Charlson Comorbidity Index with the clinical outcome [7] and with the chance of healing [9].

Also, the severity of the lung involvement may be relevant from a prognostic point of view. The Brixia score is a radiologic score proposed by Borghesi and Maroldi [12] to assess severity of SARS-CoV-2 pneumonia, whose prognostic meaning was clearly demonstrated [1, 13, 14].

Also, the "4C mortality score" was suggested to be useful for risk stratification of patients with COVID-19 [15]. This index predicts in-hospital mortality in patients admitted with COVID-19, and considers age, comorbidities, respiratory rate, peripheral oxygen saturation, Glasgow coma scale and other laboratory and clinical parameters [15].

It was also postulated that some clinical symptoms [16] and psychological involvement [17, 18] may persist after the resolution of the acute phase of the disease.

For all these reasons we considered worthwhile to assess, in a prospective follow-up cohort study, the short-term clinical consequences of SARS-CoV-2-related pneumonia, also in relation to radiologic/laboratory/clinical indices of risk at baseline in our population of survivors to COVID-19.

2 Methods

2.1 Patients

We conducted a prospective cohort study at the Montichiari Hospital, a tertiary health-care center in Brescia, Italy, which was designated as a COVID-19 hub by the Italian health authorities.

Two hundred and fifty-eight patients admitted to General Medicine ward (COVID-19 M unit) of the Montichiari Hospital from February 28th to April 30th, 2020 were included in the study if they met the following inclusion criteria: (1) confirmed COVID-19 infection as determined by a positive reverse-transcriptase-polymerase-chain-reaction (RT-PCR) assay of a specimen collected on a nasopharyngeal swab; (2) bilateral pulmonary interstitial opacities on chest imaging that were not fully explained by congestive heart failure or other forms of volume overload; (3) an acute respiratory distress syndrome showing at least one of the following conditions: respiratory rate ≥ 30 breaths/min; peripheral capillary oxygen saturation (SpO_2) $\leq 93\%$ while breathing ambient air or ratio of the partial pressure of oxygen in arterial blood to the fractional concentration of oxygen in inspired air (PaO_2/FiO_2) ≤ 300 mmHg. Sixty-five of them died during or after

the admission to the hospital. All 193 surviving patients were invited to participate to a follow up program that included: a clinical assessment, standard laboratory testing, a chest X-ray, lung function tests with an evaluation of the diffusing capacity of the lung for carbon monoxide (DLCO), and, in case of the presence of alterations in such a test, a computed tomography (CT) scan of the chest. In addition, to assess the persistence/new onset of symptoms and/or psychological distress, a structured questionnaire was administered. The following items were investigated: presence/absence of fatigue, effort dyspnea, anorexia, dysgeusia, insomnia and anxiety.

Ninety-four patients out of 193 survivors accepted to be re-evaluated after discharge, on average after 4 months. The follow-up ended in August 2020.

The following laboratory parameters were evaluated at hospital admission, at the time of discharge and at the time of follow up: circulating white blood cells, granulocytes, monocytes, lymphocytes, and hemoglobin, c-reactive protein (CRP), procalcitonin, ferritin, D-dimer, international normalised ratio (INR) and activated partial thromboplastin time (aPTT), plasma creatinine and electrolytes, aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma glutamyl transferase (γGT) and urinalysis. This study has been conducted in accordance with the declaration of Helsinki and was approved by the Ethical Committee of the Spedali Civili of Brescia.

Drug treatment during admission Patients admitted to our Division of Medicine underwent standard therapy (hydroxychloroquine 400 mg daily, lopinavir 800 mg daily plus ritonavir 200 mg per day) [17–19], according to indications of our Institution at that time based on available information [19]. Some patients could not be treated with antiviral agents or antimalarial agents because such drugs were not always available due to the excessive requests from hospitals. In a subgroup of patients with severe respiratory distress intravenous corticosteroids (dexamethasone 20 mg intravenously per day for 5 days and then 10 mg i.v. per day for 5 days) were used, while another subgroup of patients received off-label a single low dose administration of the anti-interleukin-6 monoclonal antibody Tocilizumab (8 mg/kg i.v.- or 324 mg subcutaneous -s.c.- depending on the drug availability) in addition to standard therapy [20, 21]. During hospitalization, patients in both groups were assisted with non-invasive (i.e. low flow nasal cannula; high flow mask; Continuous Positive Airway Pressure –CPAP-) or invasive (i.e. mechanical ventilation) oxygen therapy, according to their needs. For further clinical information see reference [1].

Prognostic indices In 64 patients the Brixia radiologic score was evaluated at hospital admission and at follow up, according to Borghesi and Maroldi [12]. Briefly, a score (from 0 to 3) is assigned to each of previously defined

pulmonary zones based on the lung abnormalities detected on frontal chest projection as follows: score 0 (zero) no lung abnormalities; score 1 interstitial infiltrates, score 2 interstitial and alveolar infiltrates (interstitial predominance), score 3 interstitial and alveolar infiltrates (alveolar predominance). The scores of the six lung zones are then added to obtain an overall score ranging from 0 to 18.

For each patient, we calculated the Charlson Comorbidity Index (CCI) based on the available data [22]. This index takes into account age and coexisting conditions, in an algorithm used also to predict 10-year mortality. The percentage of COVID-19 related deaths increases with the Charlson Index [7]; this index was a logarithmic multiplier when the risk of death was assessed by increasing by one point the score, starting from the score of 2 [7, 22]. It was previously demonstrated, in a similar population, that such an index predicts mortality with an exponential increase in the odds ratio by each point. The Charlson index was calculated as absolute values and as predicted mortality at 10 years [22]. In addition, we calculated also the 4 C mortality score for COVID-19, according to Knight et al. [15].

2.2 Statistical Analyses

Data were analyzed with SPSS version 25.0 (Chicago, IL, USA). We report categorical variables as number (%) and continuous variables as mean (standard deviation) when data were normally distributed, and as median and interquartile range when data were not normally distributed (lymphocytes, procalcitonin, ferritin, D-dimer). Statistical significance between groups was assessed by means of Chi-square test for dichotomous variables, or by means of one-way analysis of variance (ANOVA) or by Mann–Whitney U test when appropriate. A multivariate Cox regression analysis was also performed considering the whole period of observation (from hospital admission to follow up) and the outcome in terms of normal or altered DLCO (% of predicted).

A P value < 0.05 was considered as statistically significant.

3 Results

A total of 94 patients were included in the current study. Baseline demographic and clinical characteristics of patients are similar to those observed in the general population of 258 patients admitted to our medical ward in that period and described elsewhere [1]. In particular, no major difference in risk factors or other clinical parameters was present between those who did or did not respond to our follow up call.

Lung function tests Parameter obtained through the evaluation of DLCO are detailed in reference [23] and criteria for definition of normalcy and/or extent of the impairment

are detailed in reference [24]. Briefly, a DLCO (% of predicted) $\geq 80\%$ was considered as normal; $< 80\%$ and $\geq 60\%$: mild impairment; $< 60\%$ and $\geq 40\%$: moderate impairment; $< 40\%$: severe impairment. Similar cutpoints were adopted for DLCO/VA (alveolar volume) = transfer coefficient of the lung for carbon monoxide (KCO) (% of predicted). Data are reported in Table 1.

In ¼ of the patients an evidence of pulmonary fibrosis was detected, as indicated by an altered diffusing capacity of the lung for carbon monoxide (DLCO); in 6–7% of the patients the alteration was classified as of moderate/severe degree. In all these cases the chest CT scan confirmed the presence of indices of pulmonary fibrosis. Those patients that were ventilated with CPAP or that have needed high oxygen flow (> than the median oxygen flow—FiO_2 value) had a worse DLCO pattern compared with those needing lower oxygen flows according to a Chi-square tests (Table 2). This is further confirmed by the observation of a significant inverse correlation between FiO_2 and DLCO (% of predicted): r = − 0.224, p = 0.003. There was also an association between days on oxygen supplementation during the acute phase of COVID-19 and DLCO (% predicted) r = − 0.186; p = 0.010. Laboratory parameters of the patients with normal or altered lung function tests as well as values of parameter measured with lung function test are reported in Tables 3, 4.

There were no differences between patients previously treated or not with antiviral agents, steroids, antimalaric agents or tocilizumab in terms of DLCO.

We observed some correlations between parameters derived from arterial blood sample and lung function test. In particular, a significant correlation was observed between PaO_2/FiO_2 (a reliable index of blood perfusion) and FVC (r = 0.30, p = 0.005), FEV1 (r = 0.33, p = 0.002), DLCO (r = 0.29, p = 0.006), % of predicted DLCO (r = 0.37, p < 0.001), probably due to the fact that patients with lower PaO_2/FiO_2 at the time of admission had a more severe COVID-19. In addition, a correlation was observed between duration of the hospitalization and % of predicted DLCO (r = − 0.31, p = 0.002).

Table 1 Lung function tests

Population: n = 94	DLCO (% of predicted)	DLCO/VA (KCO) (% of predicted)
Normal (n, %)	57 (60.6%)	71 (75.5%)
Altered (n, %) (any alteration)	37 (39.3%)	23 (24.5%)
Mild alteration (n, %)	30 (31.9%)	17 (18.1%)
Moderate alteration (n, %)	4 (4.26%)	5 (5.32%)
Severe alteration (n, %)	3 (3.19%)	1 (1.06%)
Moderate + severe alteration (n, %)	7 (7.45%)	6 (6.38%)

Table 2 Lung function tests in ventilated/high FiO$_2$ patients vs. not ventilated/low FiO$_2$ patients

	DLCO (% of predicted)	DLCO/VA (KCO) (% of predicted)
Ventilated or high FiO$_2$ (≥28%): n=47	81.2±18.3	89.5±20.5
Normal (n, %)	23 (48.9%)	35 (74.5%)
Altered (n, %) (any alteration)	24 (51.1%)	12 (25.5%)
Mild alteration (n, %)	19 (40.4%)	8 (17.0%)
Moderate alteration (n, %)	4 (8.51%)	4 (8.512%)
Severe alteration (n, %)	1 (2.13%)	0 (0%)
Moderate + severe alteration (n, %)	5 (10.6%)	4 (8.51%)
Not ventilated and low FiO$_2$ (<28%): n=47	87.3±18.3	93.1±2.5
Normal (n, %)	34 (72.3%)	36 (76.6%)
Altered (n,%) (any alteration)	13 (27.7%)	11 (23.4%)
Mild alteration (n, %)	11 (23.4%)	9 (19.1%)
Moderate alteration (n, %)	0 (0%)	1 (2.13%)
Severe alteration (n, %)	2 (4.25%)	1 (2.13%)
Moderate + severe alteration (n, %)	2 (4.25%)	2 (4.25%)

DLCO (% of predicted): Chi square test (Normal/altered − Ventilated or high FiO$_2$/Not ventilated and low FiO$_2$): p=0.003

DLCO/VA (KCO) (% of predicted): Chi square test (Normal/altered − Ventilated or high FiO$_2$/Not ventilated and low FiO$_2$): p=0.33 (NS)

Table 3 Laboratory parameters and lung function tests in the two groups of patients (normal or altered DLCO % of predicted)

	Normal lung function tests (n=57)	Abnormal lung function tests (n=37)	All patients (n=94)
Humoral parameters: White blood cells (#/mm^3)	6000±2600	6380±2920	6170±2730
Granulocytes (#/mm^3)	4400±2600	4860±2650	4590±2590
Monocytes (#/mm^3)	429±376	485±578	410±210
Lymphocytes (#/mm^3)	1940 (950)	2120 (1200)	2014 (980)
Hemoglobin (g/dL)	13.3±1.6	12.3±1.77 **	12.9±1.64
Platelets (# × 10^3/mm^3)	205±72	229±99	215±84
CRP (mg/L)	76.1±61.5	115.9±94.9 *	91.8±78.4
Ferritin (µg/L)	148 (115)	113 (161)	141 (142)
D-dimer (ng/mL)	220±80.4	398±485 *	297±332
Creatinine (mg/dL)	0.94±0.26	0.99±0.45	0.96±0.35
AST	52±52	44±29	49±40
ALT	43±46	32±25	39±39
INR	1.2±0.2	1.3±0.3	1.3±0.3
aPTT (s)	33.1±4.3	33.0±4.3	33.1±4.3
Lung function test			
FVC (L)	4.1±1.0	3.3±0.8***	3.8±1.0
FEV1 (L)	3.2±0.7	2.6±0.7***	3.0±0.8
DLCO (mL/min/mmHg)	23.5±5.7	15.5±2.8***	20.4±6.2
VA (mL/min)	5.5±1.0	4.4±0.9***	5.1±1.1
VA % predicted.	89.5%±10.9%	78.5%±15.9%***	84.8%±14.2%
DLCO % predicted	94.9±14.2	66.8±8.6***	84.2±18.4
DLCO/VA% predicted (=KCO)	97.0±20.1	82.2±19.3***	91.2±21.0
FEV1/FVC	78.7%±7.2%	78.5%±10.9%	78.6%±8.8%
DLCO/VA	4.3±0.6	3.6±0.8***	4.03±0.8

Table 4 Laboratory parameters and lung function tests in the two groups of patients (normal or altered DLCO/VA % of predicted)

	Normal Lung function tests (n=71)	Abnormal Lung function tests (n=23)	All patients (n=94)
Humoral parameters: White blood cells (#/mm^3)	6200±2600	6000±3100	6170±2730
Granulocytes (#/mm^3)	4700±2500	4400±2900	4590±2590
Monocytes (#/mm^3)	410±220	430±210	410±210
Lymphocytes (#/mm^3)	2010 (980)	2320 (1140)	2014 (980)
Hemoglobin (g/dl)	13.0±1.5	12.7±2.1	12.9±1.64
Platelets (# × 10^3/mm^3)	216±87	211±78	215±84
CRP (mg/L)	93.8±74.2	85.5±91.7	91.8±78.4
Ferritin (µg/L)	147 (140)	119 (125)	141 (142)
D-dimer (ng/ml)	270±325	384±350*	297±332
Creatinine (mg/dl)	0.96±0.27	0.97±0.53	0.96±0.35
AST	53±44	36±20*	49±40
ALT	42±43	29±22	39±39
INR	1.26±0.26	1.32±0.40	1.3±0.3
aPTT (s)	32.5±3.5	35.0±5.8	33.1±4.3
Lung function test			
FVC (L)	3.88±1.04	3.48±081	3.8±1.0
FEV1 (L)	3.04±0.76	2.71±0.72	3.0±0.8
DLCO (mL/min/mmHg)	21.3±6.4	17.8±4.3**	20.4±6.2
VA (ml/min)	5.1±1.2	5.1±0.9	5.1±1.1
VA % predicted	83.9%±14.0%	93.7%±14.8%	84.8%±14.2%
DLCO % predicted	87.2±18.2	74.7±13.6**	84.2±18.4
DLCO/VA% predicted (=KCO)	98.8±17.9	66.8±6.5***	91.2±21.0
FEV1/FVC	79.1%±9.1%	77.0%±7.94%	78.6%±8.8%
DLCO/VA	4.2±0.7	3.5±0.6***	4.03±0.8

CRP C-reactive protein, *AST* aspartate transaminase, *ALT* alanine aminotransferase, *INR* international normalized ratio, *aPTT* activated partial thromboplastin time, *FVC* forced vital capacity, *FEV1* forced expiratory volume in one second, *DLCO* diffusing capacity of lung for carbon monoxide, *VA* alveolar volume, *pred* predicted

One-way ANOVA: *p<0.05, **0<0.01, ***p<0.001 vs. normal
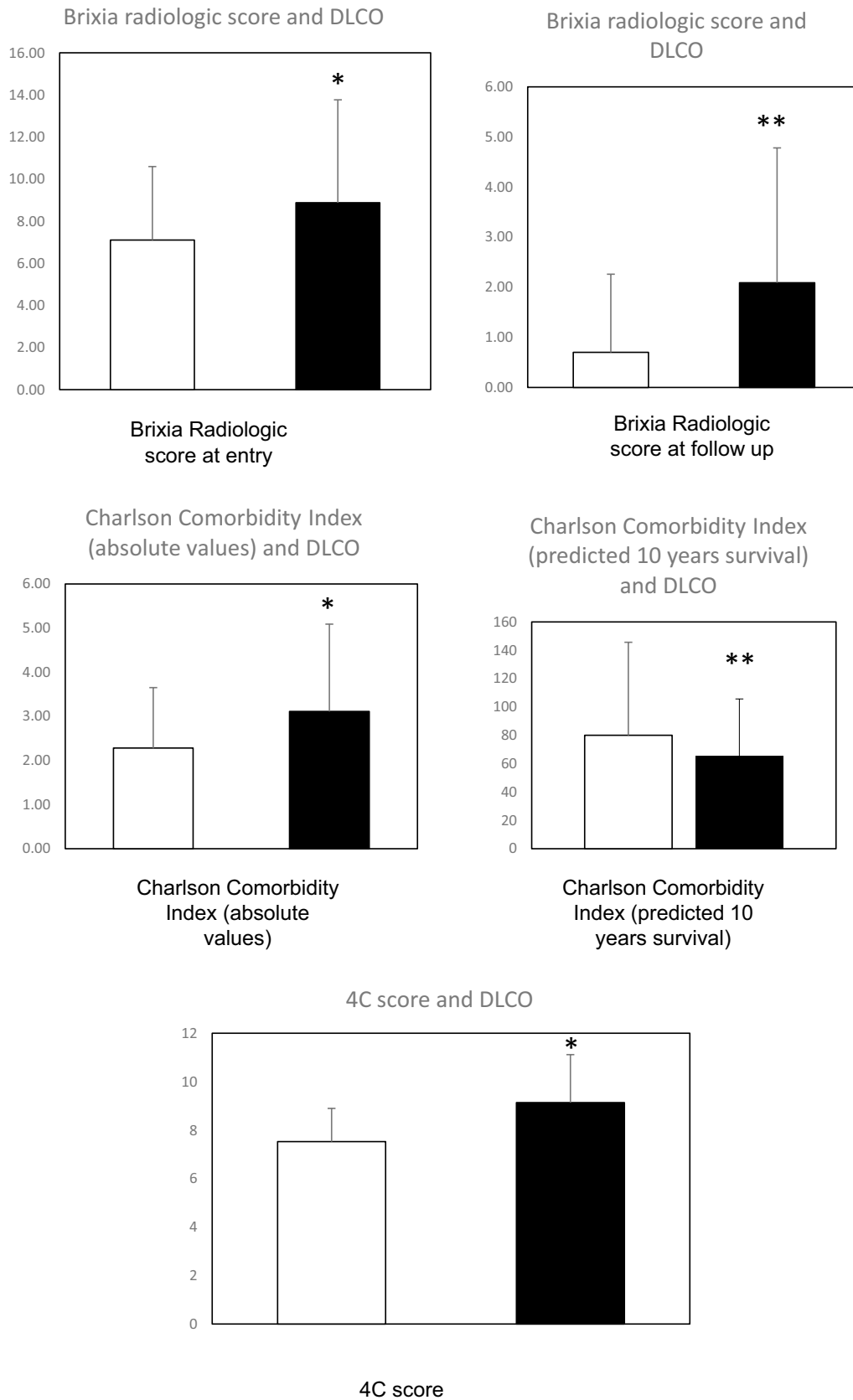
Table 5 Quality of life questionnaire

Population: n=91	Yes	No
Fever (n, %)	0 (0%)	91 (100%)
Fatigue (n, %)	47 (52%)	44 (485%)
Effort dyspnea (n, %)	33 (36%)	58 (64%)
Anorexia (n, %)	9 (10%)	82 (90%)
Insomnia (n, %)	28 (31%)	63 (61%)
Anxiety (n, %)	19 (21%)	71 (78%)
Dysgeusia or anosmia (n, %)	13 (14%)	78 (86%)

Quality of life questionnaire As mentioned, we also evaluated the quality of life thorough a structured questionnaire: 52% of the patients still lamented fatigue, 36% effort dyspnea, 10% anorexia, 14% dysgeusia, 31% insomnia and 21% anxiety. Data are reported in Table 5.

Prognostic indices The Brixia radiologic score both calculated at hospital admission and at follow up was

Table 6 Correlations between Brixia radiologic score, Charlson Comorbidity Index and 4C Mortality Score and lung function tests

	r	P
Brixia score at entry and predicted DLCO	− 0.245	0.05
Brixia score at entry and predicted DLCO/VA	0.045	NS
Brixia score at follow up and predicted DLCO	− 0.376	< 0.001
Brixia score at follow up and predicted DLCO/VA	− 0.095	NS
Charlson Comorbidity Index (absolute values) and		
Predicted DLCO	− 0.229	0.028
Predicted DLCO/VA	− 0.091	NS
Charlson Comorbidity Index (survival at 10 years) and		
Predicted DLCO	− 0.242	0.020
Predicted DLCO/VA	0.144	NS
4C Mortality Score and		
Predicted DLCO	− 0.213	0.042
Predicted DLCO/VA	0.147	NS

Brixia radiologic score and DLCO

Brixia Radiologic
score at entry

Brixia radiologic score and DLCO

Brixia Radiologic
score at follow up

Charlson Comorbidity Index (absolute values) and DLCO

Charlson Comorbidity
Index (absolute
values)

Charlson Comorbidity Index (predicted 10 years survival) and DLCO

Charlson Comorbidity
Index (predicted 10
years survival)

4C score and DLCO

4C score

Fig. 1 Brixia radiologic score (at hospital admission and at follow up, top panel), Charlson Comorbidity Index (absolute values and predicted 10 years survival: middle panel) and 4C score (bottom panel) in patients with normal (n = 57, empty bars) or abnormal (n = 37, full bars) DLCO (% of predicted). One-way ANOVA: * = p < 0.05, ** = p < 0.01

significantly correlated with predicted DLCO but not with predicted DLCO/VA (Table 6). When patients were subdivided according to the presence of a normal or altered predicted DLCO (any alteration), the Brixia radiologic score was significantly higher in patients with altered DLCO at follow up (Fig. 1).

Also Charlson Comorbidity Index significantly correlated with predicted DLCO in a direct way when absolute values were considered, while survival at 10 years was inversely correlated with DLCO (Table 6). Similarly, those patients with altered DLCO had significantly different Charlson Comorbidity Indices (Fig. 1). A similar result was obtained for 4C mortality score and predicted DLCO (Table 6, Fig. 1). No association with predicted DLCO/VA and risk score was observed.

A multivariate Cox regression analysis was also performed considering the outcome in terms of predicted DLCO (normal/altered: any alteration) and all the previously mentioned risk scores as prognostic factors; only the Brixia radiologic score evaluated at follow up remained in the model and were found to be significantly and independently associated with the occurrence of death (P = 0.027).

4 Discussion

COVID-19 has been associated with a very high mortality rate being interstitial pneumonia with respiratory failure the main cause of death [1, 6]. Among COVID-19 patients, about 25% present a severe complication of infection including acute respiratory distress syndrome (ARDS), with a rapid worsening of clinical conditions leading to the need of mechanical or invasive ventilation to support respiratory functions in intensive care units [25]. Although the direct cytopathic effect of the virus and viral invasion seems to be critical for a worsening of the clinical course, there is evidence that other factors may be implicated in the prognosis of the acute respiratory distress syndrome, including age and comorbidity [1, 7].

Some reports have suggested that a number of patients may have short-medium-term consequences of the disease, in terms of development of ILD/pulmonary fibrosis [4, 5]. However, the precise prevalence of potentially long-lasting lung consequences of the disease is uncertain.

In a retrospective study of 57 COVID-19 patients [3], abnormalities were detected in the pulmonary function tests in 43 (75.4%) of the patients, and 30 (52.6%) patients had DLCO values less than 80% of predicted values. Thirty-one patients (54.3%) had abnormal CT findings. However, the follow up period was restricted to the early convalescence phase (30 days after discharge from the hospital), therefore these findings may be regarded as short-term clinical sequelae of the disease.

Similarly, a study has enrolled 60 COVID-19 patients assessed 12 weeks after symptoms onset [2]. At least one pulmonary function variable was abnormal in 58% of patients and 88% had abnormal imaging on chest CT. An abnormal DLCO was present in 52% of patients. There was a strong association between days on oxygen supplementation during the acute phase of COVID-19 and both DLCO (% predicted) and total CT score [2]. A persistence of some symptoms, including dyspnea (20% of patients) was observed [2]. The persistence of symptoms and radiologic abnormalities was confirmed in a study enrolling 55 patients; SARS-CoV-2 infection related symptoms were detected after 3 months in 35 of them and different degrees of radiological abnormalities were detected in 39 patients [26]. However, a crucial point is represented by the medium/long term reversibility of lung alterations. A larger study investigated 384 COVID-19 patients followed for a median of 54 days post discharge: 53% reported persistent breathlessness, 34% cough and 69% fatigue while 14.6% had depression; 38% of chest radiographs remained abnormal with 9% deteriorating [16]. Wong et al. found ground-glass opacity with reticulation and irregular interlobular septal thickening in 64 out of 70 (91.4%) patients on CT examination within 48 days after discharge. In that study, follow-up at 3 and 6 months showed the findings were largely unchanged [27, 28].

A severe psychological impact of COVID-19 was also documented, with 46.6% showing alterations at the Impact of Event Scale-Revised [17] while in another study 52.4% showed persistent symptoms of anxiety and depression [18].

While in some reports it was suggested that the lung damage due to COVID-19 could be, in great part, reversible [29], there are obviously still no long-term studies in this regard.

Another interesting result of our study is the observation that the Radiologic Brixia score [12], both evaluated at hospital admission and at follow up was a predictor of impairment of lung function at follow up, in particular in terms of DLCO (% of predicted). Also, the Charlson Comorbidity Index, both as absolute values and as estimation of survival at 10 years as well as the 4C Mortality Score were predictors of residual short/term impairment of lung function. However, according to a multivariate Cox regression analysis, only Brixia radiologic score at follow up is an independent predictor of pulmonary outcome. We could not use in our study the QCOVID score [30] since we did not evaluate body mass index in our hospital records.

However, these scores have substantial limitations [31, 32] and care must also be taken when interpreting the predictions generated by these models since they are poorly reported, at high risk of bias, and their performance probably optimistic [29, 30]. It should be acknowledged that correlations between risk scores and DLCO observed in our study, although statistically significant, were not particularly close, and this may be ascribed to the inherent limitations of any risk score in this context.

Another caveat is related to the fact that decreased DLCO may not always reflect pulmonary fibrosis. Pulmonary fibrosis implies an irreversible structural change of the lung which does not seem to occur even after acute respiratory distress syndrome (ARDS) of other origin as suggested by the long term continuous improvement of different lung function parameters, including DLCO, after 5 years after discharge from intensive care units because of ARDS [33].

5 Conclusions

In conclusion, our study demonstrated that SARS-CoV-2-related pneumonia is associated to relevant short-term clinical consequences, both in terms of persistence of symptoms and in terms of impairment of DLCO (indicator of a possible development of pulmonary fibrosis); some severity indices of the disease may predict short-term clinical outcome. Therefore, discharge may not be the end of treatment, since attentions should be paid to short-medium term sequelae of COVID-19 [34]. Further studies are however needed to ascertain whether such manifestations may persist long-term or even indefinitely [35].

Declarations

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