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Short communication

Clinical status and lung function 10 weeks after severe SARS-CoV-2 infection

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A B S T R A C T

Introduction: Since studies about clinical status after COVID-19 are scarce, we conducted a cross sectional study with assessment of residual symptoms, lung function and chest CT.

Materials and Methods: During an outpatient follow-up visit, chest CT, pulmonary function and COVID-19 related symptoms were assessed approximately 10 weeks after diagnosis. Demographics, baseline (time of diagnosis) CT score and blood results were collected from patient files. Association between lung function and clinical characteristics (baseline), blood markers (baseline), chest CT (baseline and follow-up) and symptom score (followup) was analysed. Mann-Whitney U tests and Chi squared tests were used for statistical comparison between subgroups with and without restriction.

Results and discussion: Two hundred-twenty subjects were evaluated at a median follow-up of 74±12 (SD) days. Median symptom and median CT score at follow-up were 1(IQR=0- 2) and 2(IQR=0-6) respectively. Forty-six percent of patients had normal lung function, while TLC and TLCO below the lower limit of normal were observed in 38% and 22% of subjects respectively. This restrictive pulmonary impairment was associated with length of hospital stay (8 vs 6 days; p=0.003), admission to the intensive care unit (27% vs 13%;p=0.009), and invasive mechanical ventilation (10% vs 0.7%;p=0.001), but not with symptom score or CT score at baseline and follow-up.

Conclusions: Fifty-four percent of COVID-19 survivors had abnormal lung function 10 weeks after diagnosis. Restriction was the most prevalent pulmonary function, with the more critically ill patients being more prone to this condition. Yet, restriction could not be linked with abnormal imaging results or residual symptoms.

1. Introduction

The potential long-term sequelae of SARS-CoV-2 infection have raised concerns around the globe. Data about pulmonary function following COVID-19 are scarce. Mo et al. [1] described a correlation between COVID-19 related pneumonia severity and reduced diffusing capacity for carbon monoxide (TL_{CO}) at discharge. Frija-Masson et al. [2] reported that over half of patients had pulmonary restriction or low diffusing capacity 30 days after hospital discharge, correlating with more severe chest CT alterations at diagnosis. Similar lung function results were seen in a small cohort at 3 months follow-up [3].

2. Material and methods

After obtaining approval from the UZ Brussel ethics committee (B1432020000165), this cross-sectional study was conducted, evaluating patients in the outpatient clinic.

Approximately 10 weeks after COVID-19 pneumonia, clinical examination (including scoring COVID-19 related symptoms on a 0–6 scale), chest CT and pulmonary function testing were performed.

Demographics, imaging data and blood results at time of diagnosis (baseline) were collected from patient files.

All chest CT-scans received a 0–25 score, based on the percentage of affected lung as described by Pan et al. [4] in the specific context of COVID-19. For all patients with a CT score of 5 or more, predominant CT patterns (ground glass opacity, crazy paving, consolidation) were also

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recorded.

Mann-Whitney U tests (continuous variables) and Chi-squared tests (categorical variables) were used for statistical comparison between the restrictive and non-restrictive group.

3. Results

This study reports on 220 severe COVID-19 patients who were predominately middle aged (53 ± 13(SD) years), male (62%), Caucasian (76%), overweight (median BMI of 28.1) and non-smokers (<5 pack years) (78%). Prevalence of arterial hypertension (AHT) and diabetes mellitus (DM) was 35% and 18% respectively. Median haemoglobin levels in women and men were respectively, 13.0 g/dL (IQR:12.4–13.8) and 14.6 g/dL (IQR:13.7–15.4). Median CT score at baseline was 12 (IQR = 10–15). Of the patients with CT score ≥5 (n = 190), ground glass opacity was the predominant CT pattern at baseline, found in 86 (45%) patients. Sixty-two (33%) patients presented with consolidations and 19 (10%) patients with crazy paving. Twenty-three (12%) patients had a combination of the above three patterns.

At 74 ± 12 (SD) days follow-up, 137 patients (63%) reported at least one symptom with a median symptom score of 1 (IQR = 0–2). Fatigue (n = 90; 66%) and dyspnoea: (n = 65; 47%) were the most common symptoms. Median CT score was 2 (IQR = 0–6). Of the patients with CT score ≥5 (n = 58), ground glass opacity was still the predominant CT pattern at baseline, found in 48 (83%) patients. Only one patient presented with consolidations, two with crazy paving, and 7 (12%) patients had a combination of the three patterns.

One hundred and one (46%) patients had normal pulmonary function at follow-up, i.e., z-scores for indices of spirometry, diffusing capacity and lung volumes within ±1.64. Nevertheless, 84 (38%) had restrictive pulmonary function with a total lung capacity (TLC) z-score < -1.64, and diffusing capacity for carbon monoxide (TLco) was below the lower limit of normal (LLN) in 48 (22%) of the patients. Based on the difference in TLC, we divided the cohort into a restrictive and non-restrictive subgroup (Table 1). Demographic parameters (age, sex, BMI) and comorbidities (DM and AHT) did not significantly differ between both groups. The same was true for CT score (baseline and follow-up) and symptom score at follow-up. On the contrary, restrictive patients had gone through longer hospital stays (8 vs 6 days; p = 0.003), had been more frequently admitted to the intensive care unit (27% vs 13%; p = 0.009), and had needed more often invasive mechanical ventilation (10% vs 0.7%; p = 0.001). Some baseline laboratory measurements (LDH, troponin T and D-dimer) showed significantly higher levels in the restrictive group. The clinical characteristics of both subgroups are shown in Table 1. When excluding patients with possible confounding factors for lung function impairment (i.e. active smoking, obesity class ≥2 (BMI ≥35) or non-Caucasian patients), similar results were observed.

Table 1
Baseline and follow-up patient characteristics represented per subgroup (with and without restriction).

Total n = 220	Restriction ([a]) n = 84	No restrictionn = 136	p- value
	At baseline		
Age (years)	55 (47; 64)	55 (42; 61)	NS
Male	55 (65%)	80 (59%)	NS
BMI (kg m^2)	28.5 (25.5; 32.1)	27.7 (24.6; 31.3)	NS
Diabetes mellitus	19 (23%)	20 (15%)	NS
Arterial hypertension	33 (39%)	42 (31%)	NS
Smoking history (>5 pack years)	15 (18%)	37 (27%)	NS
ICU admission (n)	23 (27%)	18 (13%)	0.009
Invasive mechanical ventilation (n)	8 (10%)	1 (0.7%)	0.001
Days hospitalized (n)	8 (5; 14)	6 (4; 10)	0.003
Max CRP (mg/L)	115 (55; 230)	129 (41; 207)	NS
Max d-dimer (ng/mL)	1253 (624; 2275)	824 (506; 1388)	0.01
Max ferritin (μg/L)	1171 (584; 1783)	895 (442; 1622)	NS
Max LDH (U/L)	885 (707; 1305)	761 (600; 1038)	0.001
Max NT-proBNP (ng/L)	227 (89; 716)	102 (54; 413)	NS
Max Troponin T (μg/L)	0.011 (0.008; 0.015)	0.009 (0.007; 0.012)	0.02
CT score at diagnosis (0–25)	12 (10; 16)	12 (9; 15)	NS
Ten weeks after diagnosis at follow up			
CT score (0–25)	3 (0; 6)	1 (0; 5)	NS
Symptom score	1 (0; 2)	1 (0; 2)	NS
Patients with symptom score ≥1	36 (59%)	49 (36%)	NS
FEV_1 (z-score) ([b])	−0.9 (−1.5; −0.3)	0.1 (−0.5; 0.6)	<0.001
FVC (z-score) ([b])	−1.3 (-1.8; −0.8)	−0.1 (−0.5; 0.4)	<0.001
FEV_1/FVC (z-score) ([b])	0.8 (0.2; 1.2)	0.2 (−0.3; 0.7)	<0.001
TL_{CO} (z-score) ([c])	−1.2 (−2.2; −0.6)	−0.4 (−1.1; 0.4)	<0.001
K_{CO} (z-score) ([c])	0.5 (−0.5; 1.0)	−0.2 (−0.9; 0.6)	0.0005
TLC (z-score) ([c])	−2.5 (−3.1; −2.0)	−0.3 (−0.8; 0.3)	<0.001
MIP (z-score) ([d])	−0.2 (−1.2; 0.5)	0.0 (−0.6; 0.6)	0.02
MEP (z-score) ([d])	−0.8 (−1.4; 0.0)	−0.2 (−0.9; 0.4)	0.001

Continuous data are expressed as median (interquartile range). BMI: body mass index, ICU: intensive care unit, CT: computed tomography, CRP: *C*-reactive protein, LDH: lactate dehydrogenase, NT-proBNP: *N*-terminal pro-brain natriuretic peptide, TLC: total lung capacity, TL_{CO}: diffusing capacity for carbon monoxide, K_{CO}: transfer coefficient for carbon monoxide, FEV_1: forced expiratory volume in 1 s, MIP: maximum inspiratory pressure, MEP: maximum expiratory pressure.

[a] Included in restrictive groups are patients with z-score for TLC below −1.64.

[b] GLI 2012 [9]: reference values for Caucasians, African Americans and North and South East Asians.

[c] GLI 2019 [10]: reference values for Caucasians.

[d] Local reference values [11,12]: reference values for Caucasians.

4. Discussion

In this cross-sectional follow-up study of 220 COVID-19 patients, we observed that restriction was the most prevalent lung function impairment (38%). The probability of having TLC below the LLN at 10 weeks follow-up seems to be associated with a more severe acute COVID-19 infection, since these patients had experienced longer hospital stays, had more often been admitted to ICU and had more frequently needed invasive mechanical ventilation. By contrast, CT scores and symptom score, were not different between patients with or without restriction hence are not associated with long term sequalae.

The mechanisms behind persisting restriction are yet to be determined. Nusair et al. [5] recently suggested that low TL_{CO} in COVID-19 patients at hospital discharge is caused mainly by reduced alveolar volume and not residual interstitial lung abnormalities or pulmonary vascular abnormalities, a finding that is consistent with the observation of a preserved transfer coefficient (K_{CO}) in our cohort. Given that haemoglobin levels were normal in our patients, the observed TL_{CO} reductions cannot be attributed to anaemia.

Cardiovascular risk factors have been linked to more severe acute COVID-19 infection [6]. In our population DM and AHT were indeed more prevalent compared to the general population [7,8], but patients with these comorbidities were not overrepresented in the subgroup with restriction. This suggests that risk factors for contracting severe acute COVID-19 probably differ from those for long term lung function decline.

In comparison to the studies by Mo et al. and Frija-Masson et al., restriction appears to be more prevalent in our patients. Whether this is due to differences in regard to the different cut-offs used to define restriction in these studies, or due to inclusion of more severely ill patients in our cohort cannot be determined [1–3]. Indeed, age and the proportion of males were similar, but prevalence of comorbidities like DM and AHT was higher in our study population, indicating an unhealthier population at baseline. Moreover, although the ICU admission rate reported by Frija-Masson et al. [2] was comparable to our study, we observed an intubation rate twice as high, suggesting a greater amount of critically ill patients in our study population. Strengths of this study

are the large sample size, the systematic performance of chest CT at diagnosis and follow-up, as well as complete pulmonary function testing at 10 week follow-up and the inclusion of patients who had been admitted at the ICU. Limitations are the limited availability of prior pulmonary function results and the lack of Global Lung Function Initiative (GLI) reference values for lung volumes and diffusing capacity for non-Caucasians. Nevertheless, excluding non-Caucasian patients from our analysis did not alter the key findings.

5. Conclusion

This study reveals that restriction was the most prevalent pulmonary function impairment 10 weeks after COVID-19 pneumonia, with the more critically ill patients being more prone to this condition. Yet, pulmonary function impairment could not be linked with abnormal imaging results or residual symptoms. The latter indicates that structured follow-up including lung function testing should be offered to all patients. Undoubtedly, further research and longer term follow-up are necessary to evaluate long lasting effects of COVID-19 on pulmonary function.

CRediT authorship contribution statement

Jelle Smet: Conceptualization, Methodology, Investigation, Formal analysis, Writing - Original Draft. **Dimitri Stylemans:** Investigation, Formal analysis, Writing - Original Draft. **Shane Hanon:** Conceptualization, Methodology, Investigation, Formal analysis, Writing - Review & Editing. **Sylvia Verbanck:** Methodology, Investigation. **Eef Vanderhelst:** Validation, Formal analysis, Writing - Review & Editing. **Bart Ilsen:** Conceptualization, Methodology, Investigation, Formal analysis, Writing - Review & Editing.

Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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