Respiratory Medicine 182 (2021) 106421

Contents lists available at ScienceDirect

Respiratory Medicine

journal homepage: http://www.elsevier.com/locate/rmed

Short communication

Evolution of lung function and chest CT 6 months after COVID-19 pneumonia: Real-life data from a Belgian University Hospital

Dimitri Stylemans [a,*], Jelle Smet [a], Shane Hanon [a], Daniël Schuermans [a], Bart Ilsen [b], Jef Vandemeulebroucke [c], Eef Vanderhelst [a,1], Sylvia Verbanck [a,1]

[a] Vrije Universiteit Brussel, University Hospital UZ Brussel, Respiratory Division, Laarbeeklaan 101, 1090 Brussels, Belgium
[b] Vrije Universiteit Brussel, University Hospital UZ Brussel, Radiology Division, Laarbeeklaan 101, 1090 Brussels, Belgium
[c] Vrije Universiteit Brussel (VUB), Department of Electronics and Informatics (ETRO), Pleinlaan 2, 1050 Brussels, Belgium

ARTICLE INFO

Keywords:
Post COVID-19
Pulmonary function testing
Chest CT
LCI

ABSTRACT

Introduction: Most post COVID-19 follow-up studies are limited to a follow-up of 3 months. Whether a favorable evolution in lung function and/or radiological abnormalities is to be expected beyond 3 months is uncertain.
Materials and methods: We conducted a real-life follow-up study assessing the evolution in lung function, chest CT and ventilation distribution between 10 weeks and 6 months after diagnosis of COVID-19 pneumonia.
Results: Seventy-nine patients were assessed at 6 months of whom 63 had chest CT at both follow-up visits and 46 had multiple breath washout testing to obtain lung clearance index (LCI). The study group was divided into a restrictive (n = 39) and a non-restrictive subgroup (n = 40) based on TLC z-score. Restriction was associated with a history of intubation, neuromuscular blockade use and critical illness polyneuropathy. Restriction significantly improved over time, but was not resolved by 6 months (median TLC z-score of −2.2 [IQR: −2.7; −1.5] at 6 months *versus* −2.7 [IQR: −3.1; −2.1] at 10 weeks). LCI did not evolve between both follow-up visits. Symptoms and chest CT score improved irrespective of restriction.
Conclusion: We observed a disconnect between the improvement of COVID-19 related symptoms, chest CT lesions, and corresponding lung function. While CT imaging is almost normalized at 6 months, a further reduction of pulmonary restriction may be hoped for beyond 6 months in those patients showing restriction at their first follow-up visit.

1. Introduction

Long-term pulmonary consequences after COVID-19 pneumonia have yet to be elucidated. In our 10-week follow-up study of 220 patients with COVID-19 pneumonia, pulmonary restriction was found to be the most prevalent pulmonary function impairment [1]. Probably in part as a result of restriction, reductions in diffusing capacity (TL_{CO}) have been demonstrated in smaller cohorts [2–5]. These tended to be associated with disease severity [2,3] and residual CT abnormalities [4], but not with symptoms nor ICU admission [5]. Most post-COVID-19 follow-up studies are limited to three months, prompting the question whether a favorable evolution in lung function and/or radiological abnormalities is to be expected beyond 3 months. Based on data from SARS-CoV-1, we speculate that further reduction of pulmonary injury is possible after three months, but that irreversible fibrotic changes may persist [6]. Here, we study the evolution of lung function between 10 weeks and 6 months after COVID-19 pneumonia, against the backdrop of evolving CT scores since diagnosis. In addition, we assess ventilation distribution in order to rule out a COVID-19 related effect secondary to pulmonary restriction, in case restriction were heterogeneously distributed over the lungs.

2. Methods

A real-life follow-up study was conducted at the UZ Brussel outpatient respiratory clinic (Ethics committee; B1432020000165). From a previously reported cohort of 220 patients [1], assessed at a median follow up of 10 weeks (visit FU1), a subgroup of patients was invited for a second follow-up visit 6 months after diagnosis of COVID-19 pneumonia (visit FU2), based on clinical judgment of the treating chest

* Corresponding author. Respiratory Division, University Hospital UZ Brussel, Laarbeeklaan 101, 1090, Brussels, Belgium.
E-mail address: dimitri.stylemans@uzbrussel.be (D. Stylemans).
[1] contributed equally.

https://doi.org/10.1016/j.rmed.2021.106421
Received 8 January 2021; Received in revised form 22 March 2021; Accepted 15 April 2021
Available online 18 April 2021
0954-6111/© 2021 Elsevier Ltd. All rights reserved.

physician, who took into account lung function and visual inspection of CT images at FU1. At both FU1 and FU2, patients underwent complete pulmonary function testing (MasterScreen PFT,SentrySuite2.19,Mettawa,IL,USA). Where feasible, N2 multiple breath washouts (EasyPro; Wbreath3.55,NDDMedizintechnick, Switzerland) were performed to obtain lung clearance index (LCI). Chest CT was scored 0–25 based as described [1,7] and was also examined for predominant CT patterns (ground glass opacity, crazy paving, consolidation) using a deep learning algorithm specifically designed to quantify COVID-19 related lung lesions (https://icometrix.com/services/icolung).

3. Results

Of the initial cohort assessed at 10 weeks post-COVID-19 pneumonia, 92 patients were invited for a second follow-up at 6 months. Of these 92 patients, 79 (86%) presented at FU2 for lung function testing. Of the 79 patients, 63 (80%) had a CT at both follow-up visits (FU1 and FU2) which could be compared to their CT at diagnosis. Based on staff and equipment availability within the constraints of a COVID-19 safe environment, 46 (58%) of these patients also had LCI measurement.

The study group was divided into a restrictive (Restr; n = 39) and a non-restrictive subgroup (Non-Restr; n = 40), based on total lung capacity (TLC) z-score at FU1 below or above −1.64 (Online Data Supplement). The Restr subgroup differed from the Non-Restr subgroup in that it showed a higher number of non-Caucasians, as well as a higher number of intubated patients or with critical illness polyneuropathy, and a more frequent use of neuromuscular blockade (Table 1). There were no significant differences in BMI, hospitalization duration, or in self-reported >5% weight loss since hospitalization (P > 0.1); at FU2, >5% weight loss was present in only 6 patients.

In those patients with restriction at FU1 (median TLC z-score −2.7 [IQR: −3.1;-2.1]), restriction significantly improved over time but had not resolved by 6 months (median TLC z-score of −2.2 [IQR: −2.7;-1.5]). When expressed in terms of %predicted, median TLC at FU2 in the non-Restr and Restr subgroups were respectively, 95%pred and 74%pred. Because a sizable portion of the Restr group was of black ethnicity, we roughly estimated an ethnicity-adjusted median TLC, by applying the average 15% reduction in FVC in black vs Caucasian ethnicity based on [8,9], to TLC. As a result, ethnicity-adjusted median TLC was 77% instead of 74% predicted for the Restr group. Significant improvements in TL_{CO} were observed between FU1 and FU2, but not in transfer coefficient (K_{CO}), which remained normal throughout. At FU1, LCI was above the upper limit of normal in 6 (Restr) and 8 (Non-Restr) patients, who were all smokers. No significant changes in LCI were observed between FU1 and FU2 (p > 0.1).

Both symptoms and radiological abnormalities improved between FU1 and FU2 (Table 1), irrespective of restriction. In addition, the CT score, which had markedly improved from a median of 15 (IQR:12–16) at diagnosis to 7 (IQR:4–10) at FU1 for the group as a whole, continued to significantly decrease to 2 (IQR:0–5) at FU2 (Friedman; p < 0.001). In the 22 patients with a CT score ≥ 5 at FU2 (Restr:12; Non-Restr:10), ground glass was the most prevalent pattern (in 22 out of 22).

4. Discussion

This study in 79 patients documents the evolution of symptoms, chest CT and lung function including ventilation distribution between 10 weeks and 6 months after COVID-19 pneumonia. We extend previous reports of short-term improvements in chest CT abnormalities [1,10] by showing that the majority of CT score improvement occurs in the first 10 weeks, but that a further decrease is obtained when patients are reassessed at 6 months. Importantly, we observed a disconnect between the improvement of COVID-19-related CT lesions, and corresponding lung function abnormalities, in particular restriction.

Having ruled out ethnicity and BMI as determinants of those COVID-19 patients with persistent residual restriction, our data are suggestive of

Table 1
Clinical characteristics, symptoms scores, CT scores and lung function represented per subgroup (restrictive and non-restrictive patients).

Total n = 79	Restrictive (°) n = 39	Non-Restrictive n = 40	p-value
Anthropometrics			
Caucasian	28 (72%)	39 (98%)	**0.002**
Age (years)	56 [50; 64]	57 [50; 64]	NS
BMI (kg/m^2)	28.1 [25.3; 31.7]	27.1 [24.4; 30.5]	NS
Male	29 (74%)	29 (73%)	NS
Clinical History			
DM	7 (18%)	5 (13%)	NS
AHT	17 (44%)	11 (28%)	NS
Smoking	9 (23%)	14 (35%)	NS
ICU admission	15 (38%)	8 (20%)	0.07
Intubation	6 (15%)	1 (3%)	**0.045**
Neuromuscular blockade	4 (10%)	0 (0%)	**0.039**
Criticall ilness PNP	4 (10%)	0 (0%)	**0.039**
Hospitalization days	11 [6; 15]	8 [5; 10]	0.09

	Follow-up 1	**Follow-up 2**	**Follow-up 1**	**Follow-up 2**	**p-value**
Symptom score **(0–5)**	2 [0; 4]	1 [0; 2]*	2 [0; 4]	1 [0; 3]*	NS
CT- score **(0–25)** [b]	6.5 [4; 11]	3.5 [2; 7]*	7 [5; 10]	2 [0; 5]*	NS
FEV_1 **(z-score)** [c]	−1.2 [-1.5; −0.4]	−0.8 [-1.2; −0.2]*	0.1 [-0.7; 0.5]	0.0 [-0.5; 0.7]	**<0.001**
FVC **(z-score)** [c]	−1.4 [-2.0; −0.9]	−1.0 [-1.7; −0.6]*	−0.3 [-0.8; −0.5]	−0.2 [-0.8; 0.5]	**<0.001**
FEV_1/FVC **(z-score)** [c]	0.9 [0.2; 1.4]	0.6 [0.1; 1.3]	0.4 [-0.4; 0.9]	0.3 [-0.3; −0.8]	**0.009**
TL_{CO} **(z-score)** [d]	−1.4 [-2.1; −0.7]	−1.1 [-1.9; −0.4]*	−0.4 [-1.3; 0.5]	−0.5 [-1.2; 0.4]	**<0.001**
K_{CO} **(z-score)** [d]	0.1 [-0.7; 1.0]	0.4 [-0.7; 0.9]	0.0 [-1.1; 0.5]	−0.3 [-1.1; 0.4]	NS
MIP **(z-score)** [e]	−0.3 [-1.2; 0.5]	−0.3 [-0.9; 0.8]	0.1 [-0.9; 0.8]	−0.3 [-0.7; 0.5]	NS
MEP **(z-score)** [e]	−1.1 [-1.9; −0.1]	−1.0 [-1.6; −0.1]	−0.2 [-0.9; 0.7]	−0.3 [-1.1; 0.4]	**0.005**
LCI (°) **(z-score)** [e]	1.0 [0.0; 2.2]	0.3 [-0.9; 1.8]	0.7 [-0.1; 2.2]	1.1 [-0.7; 1.7]	NS
TLC **(z-score)** [e]	−2.7 [-3.1; −2.1]	−2.2 [-2.7; −1.5]*	−0.5 [-0.8; −0.2]	−0.5 [-0.8; 0.2]	**<0.001**

Continuous data are expressed as median [interquartile range]. P-values (between both subgroups at FU1): Chi-squared and MannWhitney test. NS: non-significant (p > 0.1).
*: significant difference (p < 0.05) in Wilcoxon test between FU1 and FU2 within each subgroup.
BMI: body mass index, DM: diabetes mellitus, AHT: arterial hypertension, smoking: actively or history of smoking (>5 pack years), ICU: intensive care unit, PNP: polyneuropathy, FU: follow up, FEV_1: forced expiratory volume in 1 second, FVC: forced vital capacity, TLC: total lung capacity, TLco: diffusing capacity for carbon monoxide, Kco = TLco/V_A: transfer coefficient for carbon monoxide, MEP: maximum expiratory pressure; LCI: lung clearance index.
(°) on n = 21 and 25 in respectively, restrictive and non-restrictive group.
[a] Included in restrictive groups are patients with z-score for TLC below −1.64.
[b] Based on COVID-19 specific CT scoring system [7]; on n = 30 and 33 in respectively, restrictive and non-restrictive group.
[c] Reference values based on GLI 2012 (http://gligastransfer.org.au/calcs/spiro.html): Caucasians, African Americans and North and South East Asians.
[d] Reference values for Caucasians based on GLI 2017: Caucasians only, taking into account GLI correction on September 25, 2020 (http://gligastransfer.org.au/calcs/tlco.html).
[e] Local reference values based on [13–15]: Caucasians only.

two mechanisms that could be further examined in these patients. The first one is expiratory muscle strength since MEP values were significantly lower in the Restr group, which could in turn be associated with history of intubation or neuromuscular blockade in this subgroup. To tease out whether this represents isolated respiratory as opposed to generalized muscle weakness requires a measurement of quadricipal and bicipal muscle strength. Second, we cannot exclude that some COVID-19 patients may have developed microthromboses and associated parenchymal damage [11], resulting in loss of alveolar volume. To explore this possibility, COVID-19 patients with long-term restriction could benefit from dual energy CT and lung compliance or impulse oscillometry measurements.

We also investigated whether ventilation distribution could be affected by the pulmonary restriction, and this was not the case. The slightly higher LCI values were related to smoking history, and did not show any change at all between 10 weeks and 6 months follow-up. This indicates that restriction inflicted by COVID-19 is homogeneously distributed over the lungs in contrast to for instance radiotherapy-induced localized restriction affecting both TLC and LCI [12].

Strengths of our study are the addition of a 6-month post-infection follow-up point, full lung function testing including plethysmography to obtain a direct measurement of restriction rather than surrogate measures such as FVC, verification of ventilation maldistribution where possible, and availability of chest CT at the different follow-up points. An inherent limitation to this kind of real-life study is that we cannot exclude that prior to contracting COVID-19, some patients might have had undiagnosed lung restriction.

In conclusion, this study reveals that both symptoms, lung function and chest CT scan continue to improve until 6 months after COVID-19 pneumonia. The potential mechanisms of persistent restriction at 6 months in those patients showing restriction at their first follow-up visit, could be interrogated with dedicated measurements of muscle weakness and lung compliance.

Declaration of funding sources

None.

CRediT authorship contribution statement

Dimitri Stylemans: Conceptualization, Methodology, Investigation, Formal analysis, Writing – original draft. **Jelle Smet:** Conceptualization, Methodology, Investigation, Formal analysis, Writing – original draft. **Shane Hanon:** Conceptualization, Methodology, Investigation, Formal analysis, Writing – review & editing. **Daniël Schuermans:** Methodology, Investigation. **Bart Ilsen:** Methodology, Investigation. **Jef Vandemeulebroucke:** Methodology, Investigation. **Eef Vanderhelst:** Conceptualization, Methodology, Investigation, Writing – review & editing, Supervision. **Sylvia Verbanck:** Validation, Conceptualization, Methodology, Investigation, Writing – review & editing, Supervision.

Declaration of competing interest

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.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.rmed.2021.106421.

References

[1] J. Smet, D. Stylemans, S. Hanon, B. Ilsen, E. Vanderhelst, Clinical status and lung function 10 weeks after severe SARS-CoV-2 infection, Respir. Med. 176 (2020) 106276, https://doi.org/10.1016/j.rmed.2020.106276.

[2] X. Mo, W. Jian, Z. Su, M. Chen, H. Peng, P. Peng, C. Lei, S. Li, R. Chen, N. Zhong, Abnormal pulmonary function in COVID-19 patients at time of hospital discharge, Eur. Respir. J. 55 (2020) 2001217, https://doi.org/10.1183/13993003.01217-2020.

[3] B. van den Borst, J.B. Peters, M. Brink, Y. Schoon, C.P. Bleeker-Rovers, H. Schers, H.W.H. van Hees, H. van Helvoort, M. van den Boogaard, H. van der Hoeven, M. H. Reijers, M. Prokop, J. Vercoulen, M. van den Heuvel, Comprehensive health assessment three months after recovery from acute COVID-19, Clin. Infect. Dis. (2020), https://doi.org/10.1093/cid/ciaa1750 ciaa1750.

[4] J. Frija-Masson, M.P. Debray, M. Gilbert, F.X. Lescure, F. Travert, R. Borie, A. Khalil, B. Crestani, M.P. d'Ortho, C. Bancal, Functional characteristics of patients with SARS-CoV-2 pneumonia at 30 days post-infection, Eur. Respir. J. 56 (2020) 2001754, https://doi.org/10.1183/13993003.01754-2020.

[5] T.V. Lerum, T.M. Aaløkken, E. Brønstad, B. Aarli, E. Ikdahl, K.M.A. Lund, M. T. Durheim, J.R. Rodriguez, C. Meltzer, K. Tonby, K. Stavem, O.H. Skjønsberg, H. Ashraf, G. Einvik, Dyspnoea, lung function and CT findings three months after hospital admission for COVID-19, Eur. Respir. J. (2020 Dec 10) 2003448, https://doi.org/10.1183/13993003.03448-2020.

[6] L. Xie, Y. Liu, Y. Xiao, Q. Tian, B. Fan, H. Zhao, W. Chen, Follow-up study on pulmonary function and lung radiographic changes in rehabilitating severe acute respiratory syndrome patients after discharge, Chest 127 (2005) 2119–2124, https://doi.org/10.1378/chest.127.6.2119.

[7] F. Pan, T. Ye, P. Sun, S. Gui, B. Liang, L. Li, D. Zheng, J. Wang, R.L. Hesketh, L. Yang, C. Zheng, Time course of lung changes at chest CT during recovery from coronavirus disease 2019 (COVID-19), Radiology 295 (2020) 715–721, https://doi.org/10.1148/radiol.2020200370.

[8] P.H. Quanjer, S. Stanojevic, T.J. Cole, X. Baur, G.L. Hall, B.H. Culver, P.L. Enright, J.L. Hankinson, M.S.M. Ip, J. Zheng, J. Stocks, ERS Global Lung Function Initiative. Multi-ethnic reference values for spirometry for the 3-95-yr age range: the global lung function 2012 equations, Eur. Respir. J. 40 (2012) 1324–1343.

[9] J.L. Hankinson, J.R. Odencrantz, K.B. Fedan, Spirometric reference values from a sample of the general U.S. population, Am. J. Respir. Crit. Care Med. 159 (1999) 179–187, https://doi.org/10.1164/ajrccm.159.1.9712108.

[10] S.M.H. Tabatabaei, H. Rajebi, F. Moghaddas, M. Ghasemiadl, H. Talari, Chest CT in COVID-19 pneumonia: what are the findings in mid-term follow-up? Emerg. Radiol. 27 (2020) 711–719, https://doi.org/10.1007/s10140-020-01869-z.

[11] S. Afat, A.E. Othman, K. Nikolaou, S. Gassenmaier, Dual-energy computed tomography of the lung in COVID-19 patients: mismatch of perfusion defects and pulmonary opacities, Diagnostics 10 (2020) 870, https://doi.org/10.3390/diagnostics10110870.

[12] S. Verbanck, S. Hanon, D. Schuermans, H. Van Parijs, V. Vinh-Hung, G. Miedema, D. Verellen, G. Storme, M. Vanhoeij, J. Lamote, M. De Ridder, W. Vincken, Small airways function in breast cancer patients before and after radiotherapy, Breast Canc. Res. Treat. 135 (2012) 857–865, https://doi.org/10.1007/s10549-012-2201-7.

[13] S. Verbanck, D. Schuermans, B.R. Thompson, E. Vanderhelst, Aligning lung function equipment and reference values in adults, Respiration 98 (2019) 246–252, https://doi.org/10.1159/000501283.

[14] S. Verbanck, A. Van Muylem, D. Schuermans, I. Bautmans, B. Thompson, W. Vincken, Transfer factor, lung volumes, resistance and ventilation distribution in healthy adults, Eur. Respir. J. 47 (2016) 166–176, https://doi.org/10.1183/13993003.00695-2015.

[15] S. Hanon, E. Vanderhelst, W. Vincken, D. Schuermans, S. Verbanck, Peak in- and expiratory flow revisited: reliability and reference values in adults, Respiration 100 (2021) 11–18, https://doi.org/10.1159/000511694.