# One-Year Outcomes of Mechanically Ventilated COVID-19 ICU Survivors: A Prospective Cohort Study

*To the Editor*:

Comprehensive data on long-term sequelae of coronavirus disease (COVID-19) are scarce, especially in mechanically ventilated COVID-19 survivors (1–3). Previously, we reported on persisting respiratory, physical, and mental impairments of these patients at 3 months after hospital discharge (4, 5). To assess long-term evolution of these sequelae, we repeated our multidomain assessment at 12 months after hospital discharge.

## Methods

All patients with COVID-19 treated at our ICU during the first European pandemic wave between March 2020 and June 2020 were consecutively included into the Maastricht Intensive Care COVID Cohort (MaastrICCht) (6). The institutional review board approved the study (METC azM/UM METC2020–1565, METC2020–2287), and informed consent was obtained. The cohort was registered in the Netherlands Trial Register (NL8613). Survivors, previously assessed at 3 months, were invited to our outpatient department 12 months after hospital discharge, where an identical multidomain assessment was performed (4, 5).

All participants underwent pulmonary function tests and high-resolution computed tomography scan (HRCT) in end-inspiration and end-expiration. These scans were independently assessed by two experienced chest radiologists for the presence of pulmonary abnormalities and their extent using a CT severity score, adapted from Wu and colleagues (7, 8). Physical performance was assessed by distance completed on 6-minute-walk distance test (6MWD) and by handgrip strength measured by a hand dynamometer (4). Health-related quality of life was assessed using the Euro-QoL-5D-5-level questionnaire and presented as a country-specific health utility score (HUS). In the Netherlands, HUS ranges from −0.446 (worse than death) through 0 (death or as bad as death) to 1 (perfect health). Dyspnea was measured by the Medical Research Council (MRC) dyspnea scale (range, 1 to 5, 1 indicating dyspnea during strenuous exercise and 5 indicating severe dyspnea when getting dressed and/or too breathless to leave the house) and fatigue using the multidimensional fatigue inventory (range, 20 to 100). The Hospital Anxiety and Depression Scale was used to assess anxiety and/or depressive symptoms (range, 0 to 21 for both the depression and anxiety subscales).

Temporal changes in continuous variables were analyzed using linear mixed effects models with subjects as random effects to account for the repeated measures design and presented as effect sizes for changes over time with 95% confidence intervals. Correlations were assessed with Pearson's correlation coefficient.

## Results

Between March 2020 and June 2020, 94 patients were admitted to the ICU and included in the MaastrICCht cohort. Fifty-two survivors (55%) were alive at 3 months after hospital discharge, and 48 of them (92%) participated at 3 months (4, 5). One patient refused additional follow-up, resulting in 47 survivors (90%) completing 1 year of follow-up. Baseline admission characteristics are presented in Table 1.

The results of the comprehensive assessment are shown in Table 2. Although the proportion of patients with ground glass opacities and other radiological abnormalities such as subpleural curvilinear and more intraparenchymal bands remained largely unchanged at 12 months, intensity and extent of these interstitial lung abnormalities were significantly less pronounced. Areas of reticulation were mostly stable. Mean CT severity score decreased

**Table 1.** Baseline Admission Characteristics

| | *N* = 48 |
|---|---|
| Age, yr | 63 (55–68) |
| Sex, male, *n* (%) | 33 (69) |
| BMI, kg/m$^2$ | 28 (25–30) |
| APACHE II score, points | 15 (13–17) |
| History of lung disease, yes, *n* (%) | 3 (6) |
| Smoking status | |
| Current smoker *n* (%) | 0 (0) |
| Former smoker *n* (%) | 23 (48) |
| Charlson Comorbidity Index, points | |
| 0 | 6 (13) |
| 1–2 | 24 (50) |
| 3–4 | 15 (31) |
| ⩾5 | 3 (6) |
| MV duration, d | 18 (9–28) |
| $P_{insp}$, cm $H_2O$ | 26 (24–28) |
| PEEP, cm $H_2O$ | 14 (12–14) |
| $V_T$/kg ideal bodyweight, ml/kg | 5.5 (5.0–6.0) |
| Dynamic compliance, ml/cm $H_2O$ | 37.3 (29.8–48.9) |
| Reintubation in ICU, yes, *n* (%) | 10 (21) |
| ICU length of stay, d | 20 (11–34) |
| Hospital length of stay, d | 32 (21–40) |
| Dialysis during admission, yes, *n* (%) | 3 (6) |
| ECMO during admission, yes, *n* (%) | 3 (6) |
| Corticosteroids*, yes, *n* (%) | 12 (25) |
| Hospital discharge location, *n* (%) | |
| Home | 8 (17) |
| Nursing home | 1 (2) |
| Rehabilitation center | 39 (81) |

*Definition of abbreviations*: APACHE = Acute Physiology and Chronic Health Evaluation; BMI = body mass index; ECMO = extracorporeal membrane oxygenation; MV = mechanical ventilation; PEEP = positive end expiratory pressure; $P_{insp}$ = inspiratory pressure.
Data are presented as median and interquartile range, or count and percentage, unless indicated otherwise.
*Defined as receiving steroid treatment for ⩾2 d.



Author Contributions: J.L.M.B., R.J.J.v.G., S.v.S., M.C.G.v.d.P., H.A.G., and R.P. conceived and designed the study. J.L.M.B., L.T., N.H.G.M.P., H.A.G., and R.P. contributed to data collection. J.L.M.B. and R.J.J.v.G. analyzed the data. J.L.M.B., R.J.J.v.G., H.A.G., and R.P. drafted the manuscript. L.T., B.H., M.C.G.v.d.P., N.H.H.G.M.P., M.A.S., and S.v.S. critically reviewed the manuscript. All authors approved the final manuscript. J.L.M.B., the corresponding author and guarantor, attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

Originally Published in Press as DOI: 10.1164/rccm.202112-2789LE on May 24, 2022

**Table 2.** Multidomain Outcomes at 3 and 12 Months after Hospital Discharge

| | 3 mo* (*n* = 48) | 12 mo (*n* = 47) | Effect size† (95% CI) | *P* Value |
|---|---|---|---|---|
| Days after intubation‡ | 120 (103 to 136) | 411 (393 to 419) | | |
| Days after hospital discharge‡ | 90 (80 to 98) | 377 (360 to 387) | | |
| Pulmonary function test§ | | | | |
| $FEV_1$, L | 2.94 (0.83) | 3.07 (0.86) | 0.22 (0.13 to 0.30) | <0.001 |
| $FEV_1$, % of predicted | 91 (20) | 101 (18) | 8 (6 to 11) | <0.001 |
| $FEV_1$:FVC ratio | 80 (7) | 80 (7) | 0 (−2 to 2) | 0.987 |
| FVC, L | 3.58 (1.04) | 3.87 (1.16) | 0.37 (0.25 to 0.48) | <0.001 |
| FVC, % of predicted | 86 (21) | 98 (19) | 10 (7 to 12) | <0.001 |
| TLC, L | 5.66 (1.53) | 5.61 (1.53) | 0.12 (−0.03 to 0.27) | 0.130 |
| TLC, % of predicted | 87 (19) | 88 (19) | 2 (0 to 4) | 0.088 |
| RV, L | 2.02 (0.58) | 1.75 (0.48) | −0.26 (−0.36 to 0.16) | <0.001 |
| RV, % of predicted | 88 (21) | 76 (20) | −11 (−16 to −7) | <0.001 |
| ITGV, L | 2.94 (0.99) | 3.30 (0.95) | 0.37 (0.23 to 0.51) | <0.001 |
| ITGV, % of predicted | 87 (25) | 99 (23) | 11 (7 to 15) | <0.001 |
| $D_{LCO}$, mmol/min/kPa | 5.60 (1.61) | 6.15 (1.49) | 0.88 (0.61 to 1.15) | <0.001 |
| $D_{LCO}$, % of predicted | 61 (14) | 76 (16) | 16 (12 to 19) | <0.001 |
| HRCT results‖ | | | | |
| Groundglass present, *n* (%) | 40 (87) | 40 (89) | | 1.000 |
| Subpleural bands present, *n* (%) | 31 (67) | 19 (42) | | 0.010 |
| Non subpleural bands present, *n* (%) | 41 (91) | 38 (84) | | 0.504 |
| Reticular opacities present, *n* (%) | 36 (78) | 28 (62) | | 0.070 |
| Bronchi(ol)ectasis present, *n* (%) | 31 (67) | 35 (78) | | 0.343 |
| Airtrapping, *n* (%) | | | | 0.293 |
| No adequate expiration | 7 (15) | 3 (7) | | |
| None | 19 (41) | 16 (36) | | |
| Significant | 20 (44) | 26 (58) | | |
| Physical performance¶ | | | | |
| 6MWD, m | 445 (133) | 512 (122) | 76 (52 to 100) | <0.001 |
| 6MWD, % of predicted | 80 (24) | 95 (23) | 15 (10 to 20) | <0.001 |
| Handgrip strength, kg | 29 (9) | 38 (12) | 8 (6 to 10) | <0.001 |
| Handgrip strength, % of predicted | 81 (18) | 104 (17) | 22 (18 to 27) | <0.001 |
| Patient-reported outcomes** | | | | |
| EQ5D Health Utility Score, points | 0.67 (0.19) | 0.84 (0.15) | 0.16 (0.12 to 0.22) | <0.001 |
| EQ5D Mobility score, points | 2.0 (1.2) | 1.6 (0.9) | −0.4 (−0.7 to −0.1) | 0.013 |
| EQ5D Self Care score, points | 1.6 (1.0) | 1.3 (0.6) | −0.3 (−0.5 to −0.1) | 0.018 |
| EQ5D Usual Activities, points | 2.6 (1.3) | 1.7 (1.0) | −0.9 (−1.3 to −0.5) | <0.001 |
| EQ5D Pain and Discomfort, points | 2.6 (1.0) | 1.9 (0.9) | −0.7 (−1.0 to −0.4) | <0.001 |
| EQ5D Anxiety and Depression, points | 1.5 (0.6) | 1.3 (0.6) | −0.2 (−0.4 to 0.0) | 0.047 |
| EQ5D VAS score, points | 59 (17) | 76 (13) | 16 (11 to 23) | <0.001 |
| HADS, points | 9.49 (8.03) | 7.12 (7.25) | −2.28 (−3.82 to −0.79) | 0.005 |
| HADS anxiety, points | 4.88 (4.16) | 3.84 (4.09) | −1.18 (−2.09 to −0.27) | 0.014 |
| HADS depression, points | 4.60 (4.30) | 3.28 (3.87) | −1.13 (−2.02 to −0.25) | 0.016 |
| Multidimensional fatigue inventory score, points | 61 (4) | 60 (6) | 0 (−3 to 1) | 0.482 |
| MRC Dyspnea scale, grade | 1.8 (1.1) | 1.5 (0.7) | −0.3 (−0.6 to 0.1) | 0.130 |

*Definition of abbreviations*: 6MWD = 6-minute-walk distance; CI = confidence interval; EQ5D = Euro-quality of life-5D; HADS = Hospital Anxiety and Depression Scale; HRCT = high-resolution computed tomography; ITGV = intrathoracic gas volume; MRC = Medical Research Council Dyspnea Scale; RV = residual volume; VAS = visual analogue scale.

Data are presented as mean (SD) or count (percentage), unless indicated otherwise. *P* values for difference between time points are tested using linear mixed-model analysis and paired categorical data using McNemar test.

*Data in this column were previously published (4, 5).

†Effect size for factor time derived from the mixed-effects models analysis containing all (repeated) measurements (i.e., the effect of 9 mo recovery on the outcome measure).

‡Median and interquartile range.

§Pulmonary function testing was not performed in four patients, and $D_{LCO}$ failed in two more patients at 3 mo. At 12 mo, pulmonary function testing was not done in five patients owing to logistical issues.

‖Randomized control trial was performed in 46 patients at 3 mo and 45 patients at 12 mo.

¶6MWD and handgrip strength were assessed in 45 patients at 3 mo. At 12 mo, seven patients were physically able yet declined physical assessment.

**Both at 3 and 12 mo, patient-reported outcomes were obtained for 44 patients.

from 10.9 (±6.3) to 8.8 (±2.6) (effect size, −2.2 points; 95% CI, −4.1 to −0.3; $P = 0.024$), mainly driven by reduction in extent of ground glass opacities, whereas contribution of subpleural bands to the CT severity score was limited.

No significant correlations between ICU length of stay and change in $D_{LCO}$ ($r = 0.190$; $P = 0.26$) and in EQ5D HUS ($r = 0.204$; $P = 0.21$) were detected, whereas ICU length of stay and increase in 6MWD were significantly correlated ($r = 0.446$; $P = 0.001$).

Furthermore, no significant correlations between change in $D_{LCO}$ and change in multidimensional fatigue inventory ($r = -0.054$; $P = 0.78$) and in MRC dyspnea scale ($r = -0.100$; $P = 0.593$) were found.

## Discussion

Diffusion capacity of the lungs and health-related quality of life in mechanically ventilated COVID-19 survivors were impaired at 3 months after hospital discharge, but significantly improved together with physical performance, in the following 9 months demonstrating at least partial reversibility of disease-related sequelae.

Lung diffusion impairment has been reported as the most pronounced abnormality in pulmonary function testing in COVID-19 survivors, being more frequent with increasing disease severity (3, 7). Our cohort demonstrated dynamic improvement but not full normalization in $D_{LCO}$. Whether diffusion capacity further improves remains to be investigated, as it could be a long-term sequela similar to persistent impairment reported in patients with severe acute respiratory syndrome (9). As we were not informed on baseline values, we were not able to assess to what extent residual impairment is directly related to COVID-19.

All participants underwent HRCT at 12 months, as it was unknown whether interstitial lung abnormalities at 3 months could progress to more severe interstitial fibrosis. At 12 months, the proportion of patients showing interstitial lung abnormalities remained largely unchanged, though extent and intensity were significantly reduced, whereas extent of air trapping was mostly limited. The decrease in extent of abnormalities is reflected in the reduction of CT severity score. However, the main observation was the evident reduction in density of abnormalities, which is not incorporated in the CT severity score but is in line with findings from other cohorts (10, 11). Following these results, we decided to no longer routinely perform HRCTs in ICU survivors. In addition, we found substantial recovery in muscle function and 6MWD, though all but three patients had concluded their stay at a rehabilitation clinic before the 3-month assessment.

Whereas respiratory and physical function as well as health-related quality of life improved, complaints of dyspnea (already mild at 3 months) and fatigue remained unaltered, although the MRC scale could be too crude to detect small differences. A study of the general population showed a mean multidimensional fatigue inventory of 48.5 in a comparable subset of patients (male, >60 yr) compared with slightly higher scores in our cohort (12). Fatigue is one of the most reported persistent symptoms after COVID-19 infection as well as survivors of severe acute respiratory syndrome, where it is described in more than 40% of patients up to 4 years after illness (2, 3, 9, 13–15).

By consecutively including all mechanically ventilated ICU patients, we studied the most critically affected patients, often excluded in other studies, or studied in mixed cohorts (1, 3, 7, 13, 14). The multidomain assessment at 3 and 12 months enabled us to characterize in detail the recovery of the critically ill after COVID-19. Response rate was high, optimizing internal validity. Main limitations are the single-center design, relatively limited sample size, lack of baseline assessment values, and inclusion during the first pandemic wave. These factors may limit generalizability owing to center-specific differences in age composition or use of extracorporeal membrane oxygenation (ECMO) and dialysis, as well as changes in treatment protocols over time. For example, only a quarter of patients received corticosteroids, which currently is standard of care and may affect long-term outcome. Lastly, the study was potentially underpowered for certain endpoints, as this was an observational study and sample size was determined by the number of admitted patients.

## Conclusions

Between 3 months and 1 year after hospital discharge, mechanically ventilated COVID-19 survivors showed significant recovery in respiratory and physical function, health-related quality of life, and radiological sequelae. However, no statistically significant improvement in complaints of fatigue and dyspnea could be detected. ■

**Author disclosures** are available with the text of this letter at www.atsjournals.org.

**Acknowledgment:** The authors thank Dr. Bas van Bussel for his valuable input during the drafting of the manuscript.

Julia L. M. Bels, M.D.*
Rob J. J. van Gassel, M.D.
*Maastricht University Medical Centre*
*Maastricht, the Netherlands*
and
*Maastricht University*
*Maastricht, the Netherlands*

Lieneke Timmerman, M.D.
*Maastricht University Medical Centre*
*Maastricht, the Netherlands*

Bena Hemmen, M.D.
*Maastricht University Medical Centre*
*Maastricht, the Netherlands*

*Maastricht University*
*Maastricht, the Netherlands*
and
*Adelante Zorggroep*
*Hoensbroek, the Netherlands*

Marcel C. G. van de Poll, M.D.
*Maastricht University Medical Centre*
*Maastricht, the Netherlands*
and
*Maastricht University*
*Maastricht, the Netherlands*

Nicky H. G. M. Peters, M.D.
*Maastricht University Medical Centre*
*Maastricht, the Netherlands*

Martijn A. Spruit, Ph.D.
*Maastricht University Medical Centre*
*Maastricht, the Netherlands*

*Maastricht University*
*Maastricht, the Netherlands*
and
*Ciro+*
*Horn, the Netherlands*

Susanne van Santen, M.D.
*Maastricht University Medical Centre*
*Maastricht, the Netherlands*

Hester A. Gietema, M.D.‡
*Maastricht University Medical Centre*
*Maastricht, the Netherlands*

and

*Maastricht University*
*Maastricht, the Netherlands*

Rein Posthuma, M.D.‡
*Maastricht University Medical Centre*
*Maastricht, the Netherlands*

*Maastricht University*
*Maastricht, the Netherlands*

and

*Ciro+*
*Horn, the Netherlands*

ORCID IDs: 0000-0001-9190-1661 (J.L.M.B.); 0000-0002-0780-2052 (R.J.J.v.G.); 0000-0003-3066-3254 (B.H.); 0000-0002-3302-4063 (M.C.G.v.d.P.); 0000-0003-3822-7430 (M.A.S.); 0000-0001-7036-3307 (H.A.G.); 0000-0003-0015-0116 (R.P.).

*Corresponding author (e-mail: julia.bels@mumc.nl).
‡Co–senior authors.

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## Allergen Immunotherapy Reverses Immune Response to SARS-CoV-2 Vaccine in Patients with Allergic Rhinitis: A Prospective Observational Trial

*To the Editor*:

Vaccines against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) have shown high efficacy in the prevention of coronavirus disease (COVID-19) (1). Allergic diseases, including allergic rhinitis (AR), asthma, and atopic dermatitis, are characterized by skewed type 2 immune responses and are estimated to affect 30–50% of the population globally (2). Recently, we have reported that after two doses, patients with AR displayed an enhanced humoral immune response to inactivated SARS-CoV-2 vaccines compared with healthy control samples, which was associated with an increase in type 2 follicular helper T ($T_{FH}2$) cells in patients with AR (3). Allergen immunotherapy (AIT) is an effective disease-modifying treatment for allergic diseases by inducing immune tolerance and correcting or antagonizing skewed type 2 responses (4). A significant reduction of $T_{FH}2$ cells and an increase of follicular regulatory T cells ($T_{FR}$) are noted in patients with AR after AIT (5, 6). Thus, it is critical and interesting to understand whether AIT will influence the efficacy of SARS-CoV-2 vaccination in allergic patients.

A prospective observational trial (ClinicalTrials: NCT05009134) was conducted to compare the immunological response to inactivated



Supported by the National Natural Science Foundation of China (NSFC) grants 82130030 and 8192010801 (Z.L.) and 82101198 (Y.Y.) and the Leader Fellowship from Australian National Health and Medical Research Council grant GNT2009554 (D.Y.).

Author Contributions: Y.Y. planned and performed most experiments with major support from A.H. and Y.-K.D. Z.-Z.W., N.W., Y.L., and H.-Y.Z. collected and processed blood samples. Z.-Z.W. and R.-F.Z. collected clinical data. Z.L., D.Y., and Y.Y. designed the study and supervised the project.

Originally Published in Press as DOI: 10.1164/rccm.202203-0608LE on June 1, 2022