COVID-19 and its continuing burden after 12 months: a longitudinal observational prospective multicenter trial

Figures and Tables

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# Tables

Table 1: Baseline characteristics, post-acute steroid therapy and rehabilitation status of the study cohort and the COVID-19 severity groups.

| **Variable** | **CovILD cohort** | **Ambulatory COVID-19** | **Moderate COVID-19** | **Severe COVID-19** | **Significancea** | **Effect sizea** |
| --- | --- | --- | --- | --- | --- | --- |
| N number | 108 | 27 | 55 | 26 |  |  |
| Sex | female: 41% (n = 44) male: 59% (n = 64) | female: 67% (n = 18) male: 33% (n = 9) | female: 35% (n = 19) male: 65% (n = 36) | female: 27% (n = 7) male: 73% (n = 19) | p = 0.039 | V = 0.31 |
| Age, years | median: 56 [IQR: 49 - 68] range: 19 - 87 | median: 47 [IQR: 38 - 55] range: 19 - 70 | median: 62 [IQR: 53 - 72] range: 27 - 87 | median: 56 [IQR: 52 - 64] range: 44 - 79 | p < 0.001 | η² = 0.19 |
| Weight classb | normal: 39% (n = 42) overweight: 43% (n = 46) obesity: 19% (n = 20) | normal: 56% (n = 15) overweight: 33% (n = 9) obesity: 11% (n = 3) | normal: 29% (n = 16) overweight: 51% (n = 28) obesity: 20% (n = 11) | normal: 42% (n = 11) overweight: 35% (n = 9) obesity: 23% (n = 6) | ns (p = 0.31) | V = 0.17 |
| Smoking | never: 63% (n = 68) ex: 34% (n = 37) active: 2.8% (n = 3) | never: 81% (n = 22) ex: 15% (n = 4) active: 3.7% (n = 1) | never: 53% (n = 29) ex: 44% (n = 24) active: 3.6% (n = 2) | never: 65% (n = 17) ex: 35% (n = 9) active: 0% (n = 0) | ns (p = 0.23) | V = 0.19 |
| Comorbidity present | 75% (n = 81) | 41% (n = 11) | 85% (n = 47) | 88% (n = 23) | p < 0.001 | V = 0.46 |
| Metabolic disease | 42% (n = 45) | 19% (n = 5) | 49% (n = 27) | 50% (n = 13) | ns (p = 0.087) | V = 0.27 |
| Diabetes | 15% (n = 16) | 3.7% (n = 1) | 15% (n = 8) | 27% (n = 7) | ns (p = 0.18) | V = 0.23 |
| Hypercholesterolemia | 21% (n = 23) | 3.7% (n = 1) | 31% (n = 17) | 19% (n = 5) | ns (p = 0.084) | V = 0.27 |
| Cardiovascular disease | 40% (n = 43) | 7.4% (n = 2) | 47% (n = 26) | 58% (n = 15) | p = 0.0025 | V = 0.39 |
| Pulmonary disease | 19% (n = 20) | 11% (n = 3) | 22% (n = 12) | 19% (n = 5) | ns (p = 0.62) | V = 0.11 |
| Malignancy | 9.3% (n = 10) | 3.7% (n = 1) | 15% (n = 8) | 3.8% (n = 1) | ns (p = 0.31) | V = 0.19 |
| Immune deficiency | 5.6% (n = 6) | 0% (n = 0) | 3.6% (n = 2) | 15% (n = 4) | ns (p = 0.13) | V = 0.25 |
| Chronic kidney disease | 6.5% (n = 7) | 0% (n = 0) | 5.5% (n = 3) | 15% (n = 4) | ns (p = 0.18) | V = 0.22 |
| Gastrointestinal disease | 13% (n = 14) | 0% (n = 0) | 20% (n = 11) | 12% (n = 3) | ns (p = 0.14) | V = 0.24 |
| Steroid therapyc | 19% (n = 20) | 3.7% (n = 1) | 16% (n = 9) | 38% (n = 10) | p = 0.033 | V = 0.32 |
| Rehabilitation | none: 68% (n = 71) inpatient: 25% (n = 26) outpatient: 6.7% (n = 7) n = 104 | none: 89% (n = 24) inpatient: 0% (n = 0) outpatient: 11% (n = 3) n = 27 | none: 81% (n = 43) inpatient: 13% (n = 7) outpatient: 5.7% (n = 3) n = 53 | none: 17% (n = 4) inpatient: 79% (n = 19) outpatient: 4.2% (n = 1) n = 24 | p < 0.001 | V = 0.5 |
| aComparison between the COVID-19 severity strata. Categorical variables: χ² test with Cramer V effect size statistic; numeric variables: Kruskal-Wallis test with η² effect size statistic. P values corrected for multiple testing with Benjamini-Hochberg method. | | | | | | |
| bBody mass index (BMI); overweight > 25 kg/m², obesity > 30 kg/m² | | | | | | |
| cSteroid therapy in cases of non-resolving pneumonia beginning from week four post diagnosis at the discretion of the physician. | | | | | | |

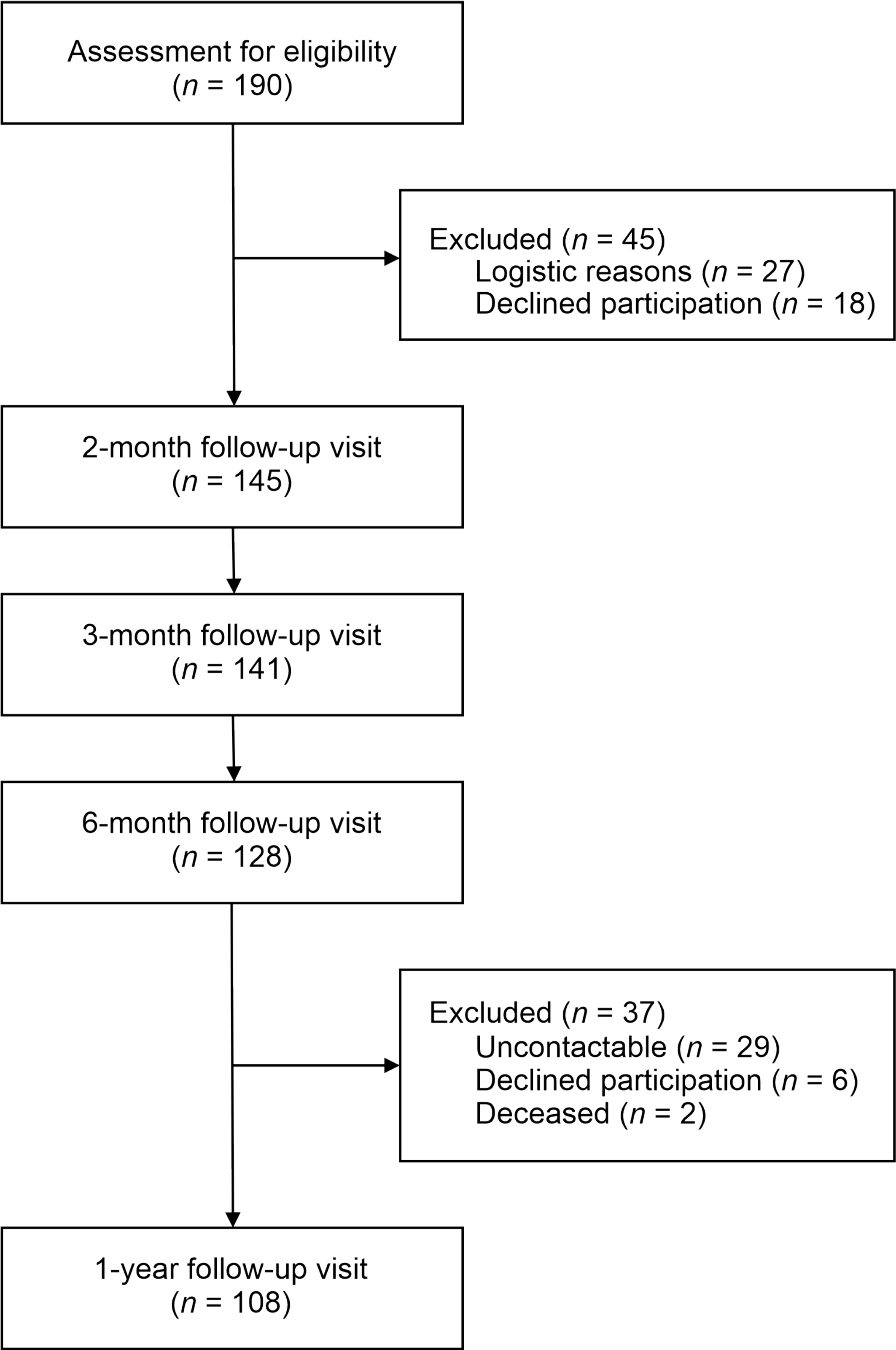
Table 2: Key outcome measures at the one-year follow-up in the study cohort and the COVID-19 severity groups.

| **Variable** | **CovILD cohort** | **Ambulatory COVID-19** | **Moderate COVID-19** | **Severe COVID-19** | **Significancea** | **Effect sizea** |
| --- | --- | --- | --- | --- | --- | --- |
| Symptoms present | 65% (n = 68) n = 105 | 59% (n = 16) n = 27 | 67% (n = 36) n = 54 | 67% (n = 16) n = 24 | ns (p = 0.85) | V = 0.068 |
| LFT abnormalityb | 33% (n = 35) n = 106 | 22% (n = 6) n = 27 | 32% (n = 17) n = 53 | 46% (n = 12) n = 26 | ns (p = 0.31) | V = 0.18 |
| CT abnormality (CT score ≥1)c | 51% (n = 52) n = 101 | 13% (n = 3) n = 23 | 52% (n = 27) n = 52 | 85% (n = 22) n = 26 | p < 0.001 | V = 0.5 |
| Diastolic dysfunction | 63% (n = 67) n = 107 | 30% (n = 8) n = 27 | 69% (n = 37) n = 54 | 85% (n = 22) n = 26 | p < 0.001 | V = 0.42 |
| aCOVID-19 severity groups compared with χ² test with Cramer V effect size statistic. P values corrected for multiple testing with Benjamini-Hochberg method. | | | | | | |
| bLFT abnormality: abnormality in lung function testing, <80% predicted value (FEV1: forced expiratory volume in 1 second; FVC: forced vital capacity; DLCO: diffusion lung capacity for carbon monoxide; TLC: total lung capacity) or <70% predicted value cutoffs (FEV1:FVC: FEV1 to FVC ratio.) | | | | | | |
| cCT abnormality: any abnormality in chest computed tomography, CT severity score ≥ 1. | | | | | | |

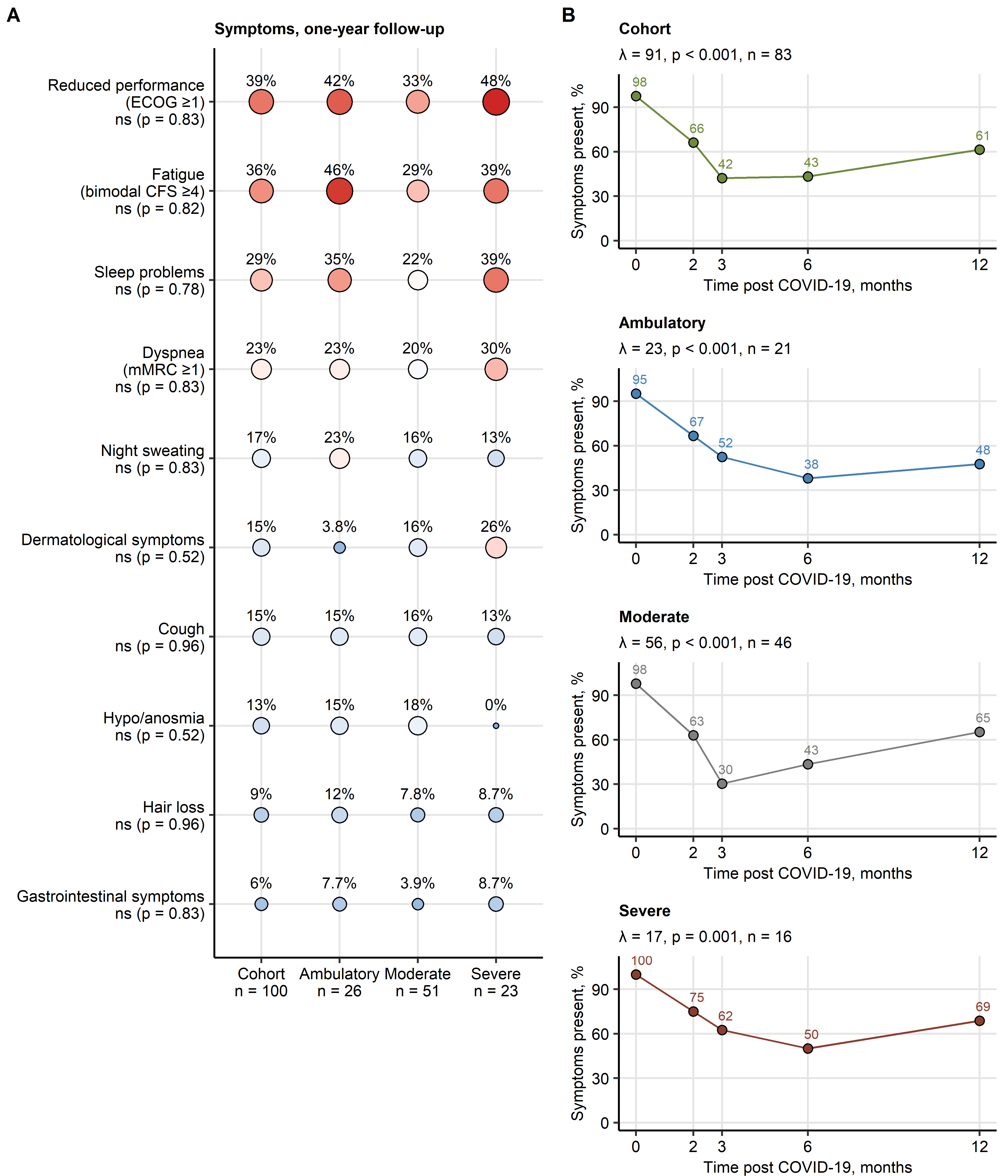
Table 3: Physical performance, fatigue, self-perceived general health, quality of life and mental health readouts at the one-year follow-up in the study cohort and the COVID-19 severity groups.

| **Variable** | **CovILD cohort** | **Ambulatory** | **Moderate** | **Severe** | **Significancea** | **Effect sizea** |
| --- | --- | --- | --- | --- | --- | --- |
| 6MWD, mb | median: 550 [IQR: 490 - 630] range: 270 - 760 n = 102 | median: 580 [IQR: 540 - 640] range: 400 - 740 n = 26 | median: 540 [IQR: 460 - 620] range: 270 - 760 n = 51 | median: 520 [IQR: 480 - 620] range: 310 - 700 n = 25 | ns (p = 0.18) | η² = 0.034 |
| 6MWD vs ref., mc | median: -13 [IQR: -75 - 42] range: -230 - 140 n = 102 | median: -27 [IQR: -83 - 25] range: -230 - 120 n = 26 | median: -3.6 [IQR: -63 - 47] range: -230 - 130 n = 51 | median: -25 [IQR: -67 - 39] range: -210 - 140 n = 25 | ns (p = 0.49) | η² = 0.0013 |
| 6MWD < ref.d | 56% (n = 57) n = 102 | 62% (n = 16) n = 26 | 51% (n = 26) n = 51 | 60% (n = 15) n = 25 | ns (p = 0.73) | V = 0.099 |
| Fatigue score (likert CFS)e | median: 12 [IQR: 11 - 16] range: 0 - 32 n = 101 | median: 11 [IQR: 11 - 17] range: 0 - 26 n = 27 | median: 12 [IQR: 11 - 15] range: 1 - 24 n = 51 | median: 13 [IQR: 11 - 23] range: 1 - 32 n = 23 | ns (p = 0.52) | η² = -3.5e-05 |
| Fatigue (bimodal CFS ≥4)e | 37% (n = 38) n = 103 | 44% (n = 12) n = 27 | 31% (n = 16) n = 52 | 42% (n = 10) n = 24 | ns (p = 0.54) | V = 0.13 |
| General health score (EQ5D5L VAS)f | median: 85 [IQR: 75 - 90] range: 40 - 100 n = 102 | median: 85 [IQR: 75 - 94] range: 40 - 100 n = 27 | median: 85 [IQR: 80 - 90] range: 50 - 100 n = 51 | median: 80 [IQR: 70 - 90] range: 40 - 100 n = 24 | ns (p = 0.66) | η² = -0.0071 |
| Imp. general health (VAS <73, EQ5D5L)f | 19% (n = 19) n = 102 | 19% (n = 5) n = 27 | 14% (n = 7) n = 51 | 29% (n = 7) n = 24 | ns (p = 0.42) | V = 0.16 |
| Mobility impairment score (EQ5D5L)g | median: 1 [IQR: 1 - 1] range: 1 - 3 n = 103 | median: 1 [IQR: 1 - 1] range: 1 - 2 n = 27 | median: 1 [IQR: 1 - 1] range: 1 - 3 n = 52 | median: 1 [IQR: 1 - 1.2] range: 1 - 3 n = 24 | ns (p = 0.32) | η² = 0.013 |
| Imp. mobility (score >1, EQ5D5L)g | 14% (n = 14) n = 103 | 11% (n = 3) n = 27 | 9.6% (n = 5) n = 52 | 25% (n = 6) n = 24 | ns (p = 0.31) | V = 0.18 |
| Self-care impairment score (EQ5D5L)g | median: 1 [IQR: 1 - 1] range: 1 - 2 n = 103 | median: 1 [IQR: 1 - 1] range: 1 - 1 n = 27 | median: 1 [IQR: 1 - 1] range: 1 - 2 n = 52 | median: 1 [IQR: 1 - 1] range: 1 - 2 n = 24 | ns (p = 0.31) | η² = 0.014 |
| Imp. self-care (score >1, EQ5D5L)g | 2.9% (n = 3) n = 103 | 0% (n = 0) n = 27 | 1.9% (n = 1) n = 52 | 8.3% (n = 2) n = 24 | ns (p = 0.31) | V = 0.18 |
| Activity impairment score (EQ5D5L)g | median: 1 [IQR: 1 - 1] range: 1 - 3 n = 103 | median: 1 [IQR: 1 - 1.5] range: 1 - 3 n = 27 | median: 1 [IQR: 1 - 1] range: 1 - 3 n = 52 | median: 1 [IQR: 1 - 2] range: 1 - 3 n = 24 | ns (p = 0.18) | η² = 0.033 |
| Imp. usual activity (score >1, EQ5D5L)g | 18% (n = 19) n = 103 | 26% (n = 7) n = 27 | 9.6% (n = 5) n = 52 | 29% (n = 7) n = 24 | ns (p = 0.18) | V = 0.23 |
| Pain/discomfort score (EQ5D5L)g | median: 1 [IQR: 1 - 2] range: 1 - 4 n = 103 | median: 1 [IQR: 1 - 2] range: 1 - 3 n = 27 | median: 1 [IQR: 1 - 2] range: 1 - 4 n = 52 | median: 1.5 [IQR: 1 - 2] range: 1 - 4 n = 24 | ns (p = 0.27) | η² = 0.019 |
| Pain/discomfort (score >1, EQ5D5L)g | 36% (n = 37) n = 103 | 41% (n = 11) n = 27 | 27% (n = 14) n = 52 | 50% (n = 12) n = 24 | ns (p = 0.26) | V = 0.2 |
| Anxiety/depression score (EQ5D5L)g | median: 1 [IQR: 1 - 2] range: 1 - 5 n = 103 | median: 1 [IQR: 1 - 2] range: 1 - 4 n = 27 | median: 1 [IQR: 1 - 1] range: 1 - 3 n = 52 | median: 1 [IQR: 1 - 2] range: 1 - 5 n = 24 | ns (p = 0.22) | η² = 0.027 |
| Anxiety/depression (score >1, EQ5D5L)g | 28% (n = 29) n = 103 | 30% (n = 8) n = 27 | 21% (n = 11) n = 52 | 42% (n = 10) n = 24 | ns (p = 0.31) | V = 0.18 |
| Stress score (PSS)h | median: 5 [IQR: 3 - 8] range: 0 - 11 n = 102 | median: 4 [IQR: 1 - 6.5] range: 0 - 11 n = 27 | median: 5 [IQR: 2.8 - 8] range: 0 - 11 n = 52 | median: 8 [IQR: 5 - 9.5] range: 0 - 11 n = 23 | ns (p = 0.061) | η² = 0.068 |
| Elevated stress (PSS >5)h | 49% (n = 50) n = 102 | 33% (n = 9) n = 27 | 48% (n = 25) n = 52 | 70% (n = 16) n = 23 | ns (p = 0.14) | V = 0.25 |
| Somatic symptom disorder score (SSD-12)i | median: 7 [IQR: 3 - 13] range: 0 - 30 n = 101 | median: 5 [IQR: 2 - 10] range: 0 - 25 n = 27 | median: 5 [IQR: 2 - 9.8] range: 0 - 30 n = 50 | median: 16 [IQR: 6.8 - 22] range: 0 - 30 n = 24 | p = 0.031 | η² = 0.087 |
| Resilience score (BRCS)j | median: 16 [IQR: 13 - 18] range: 4 - 20 n = 100 | median: 18 [IQR: 14 - 19] range: 4 - 20 n = 27 | median: 16 [IQR: 12 - 18] range: 4 - 20 n = 49 | median: 16 [IQR: 14 - 17] range: 4 - 20 n = 24 | ns (p = 0.22) | η² = 0.026 |
| Resilience (BRCS)k | low: 29% (n = 29) medium: 26% (n = 26) high: 45% (n = 45) n = 100 | low: 22% (n = 6) medium: 19% (n = 5) high: 59% (n = 16) n = 27 | low: 35% (n = 17) medium: 27% (n = 13) high: 39% (n = 19) n = 49 | low: 25% (n = 6) medium: 33% (n = 8) high: 42% (n = 10) n = 24 | ns (p = 0.54) | V = 0.14 |
| aComparison between the COVID-19 severity strata. Categorical variables: χ² test with Cramer V effect size statistic; numeric variables: Kruskal-Wallis test with η² effect size statistic. P values corrected for multiple testing with Benjamini-Hochberg method. | | | | | | |
| b6MWD: six-minute walking distance, meters. | | | | | | |
| c6MWD vs ref.: difference between the reference and observed 6MWD value, meters | | | | | | |
| d6MWD < ref.: 6MWD below the reference value. | | | | | | |
| eCFS: 11-item Chalder fatigue score, incr.: increased. | | | | | | |
| fEQ5D5L: European quality of life 5 dimensions, 5 levels, VAS: visual analogue scale, imp.: impaired. | | | | | | |
| gEQ5D5L: European quality of life 5 dimensions, 5 levels, imp.: impaired | | | | | | |
| hPSS: 4-item perceived stress scale. | | | | | | |
| iSSD-12: 12-item somatic syndrome disorder – B criteria scale. | | | | | | |
| jBRCS: brief resilient coping score. | | | | | | |
| kResilient coping class: low: 4 - 13 points, medium: 14 - 16 points, high: 17 - 21 points of the BRCS scale. | | | | | | |

# Figures



**Figure 1. Flow diagram of the study analysis inclusion.**

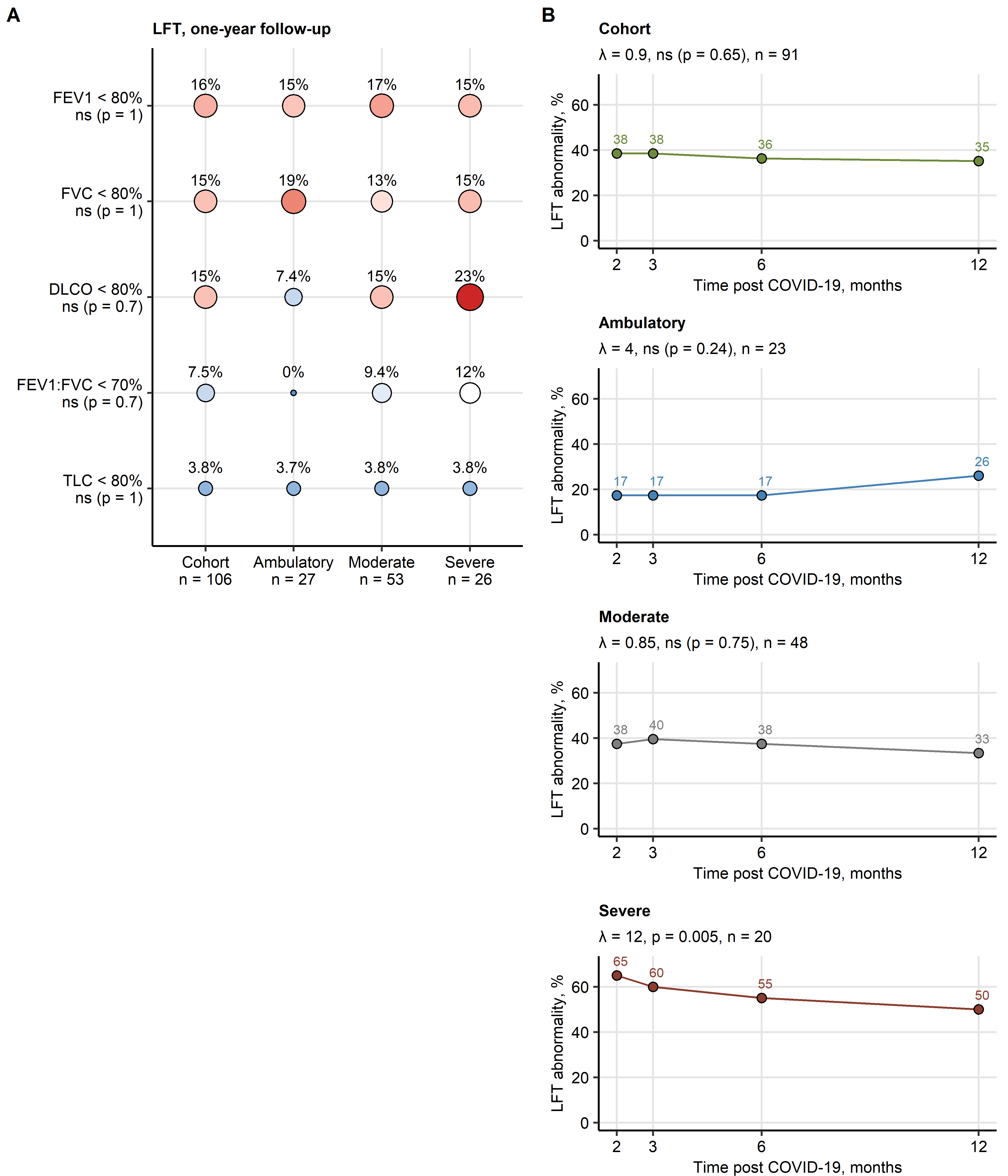


**Figure 2. COVID-19 symptom recovery.**

*Presence of COVID-19 symptoms (reduced performance: Eastern Cooperative Oncology group score [ECOG] 1, fatigue: bimodal Chalder fatigue score [CFS] 4, dyspnea: modified Medical Research Council score [mMRC] 1, self reported: sleep problems, night sweating, cough, hair loss, hyposmia/anosmia, dermatological and gastrointestinal symptoms) was analyzed in the entire study collective and in ambulatory, moderate and severe COVID-19 survivors.*

*(A) Percentages of individuals with particular symptoms at the one-year follow-up. Differences between the COVID-19 severity strata were investigated by test corrected for multiple testing with Benjamini-Hochberg method. Point size and color code for the percentage. P values are displayed in the Y axis. Numbers of complete observations are indicated in the X axis.*

*(B) Percentages of individuals with any symptoms during acute COVID-19 and at the 2-, 3-, 6-month and one-year follow-up. Participants with the complete longitudinal data set were included in the analysis. The symptom kinetic was analyzed by second-order mixed-effect logistic modeling and likelihood ratio test (full vs null model). P values were corrected for multiple testing with the Benjamini-Hochberg method. Likelihood ratio (), p values and numbers of participants with the complete longitudinal data set are presented in the plot captions.*

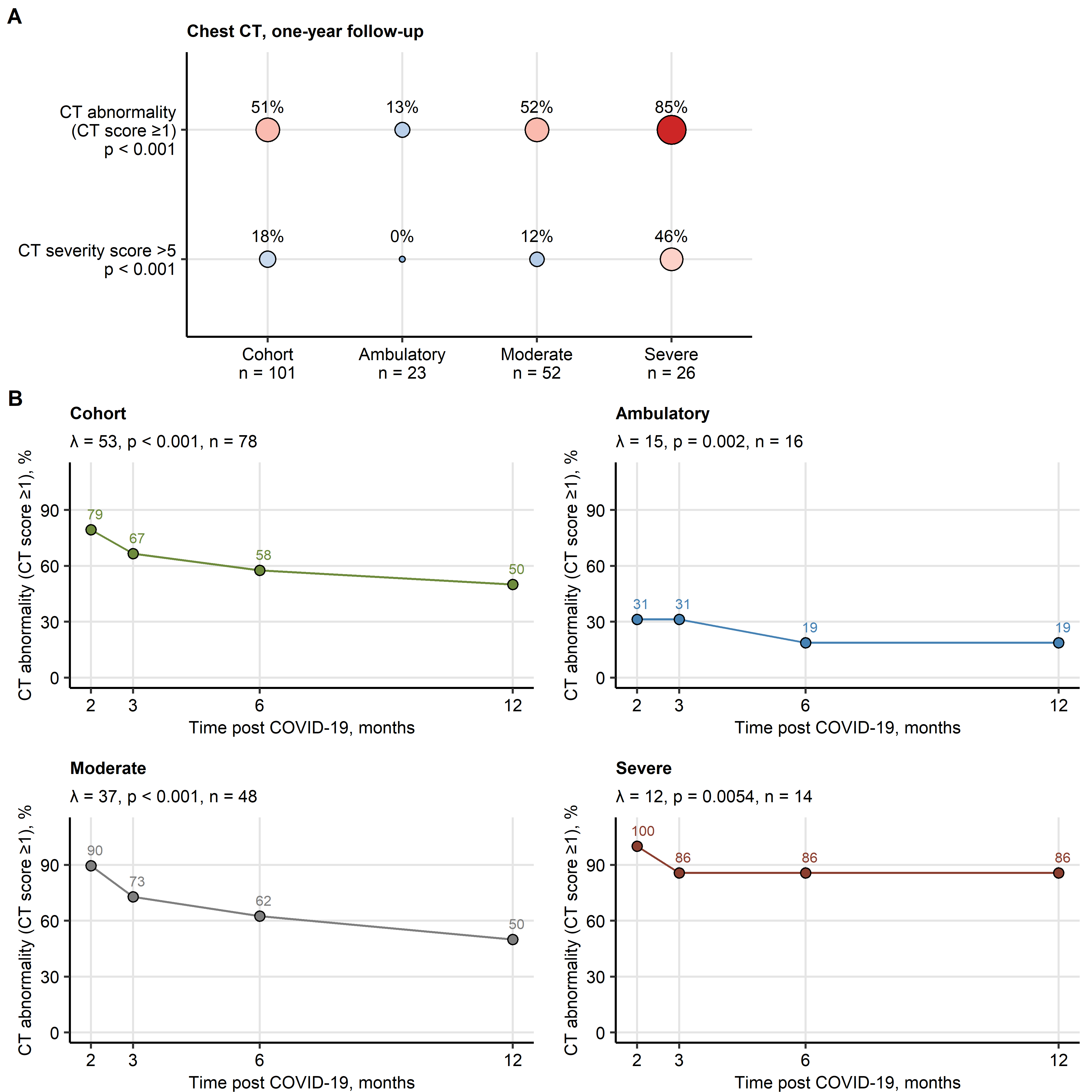


**Figure 3. Functional lung recovery.**

*Lung function testing (LFT) was analyzed in the entire study collective and in ambulatory, moderate and severe COVID-19 survivors.*

*(A) Percentages of individuals with particular LFT abnormalities at the one-year follow-up. Differences between the COVID-19 severity strata were investigated by test corrected for multiple testing with Benjamini-Hochberg method. Point size and color code for the percentage. P values are displayed in the Y axis. Numbers of complete observations are indicated in the X axis. FEV1: forced expiratory volume in 1 second; FVC: forced vital capacity; DLCO: diffusion lung capacity for carbon monoxide; RV: residual volume, FEV1:FVC: FEV1 to FVC ratio, TLC: total lung capacity.*

*(B) Percentages of individuals with any LFT abnormality (FEV1, FVC, DLCO or TLC: <80% predicted value or FEV1:FVC <70% predicted value) at the 2-, 3-, 6-month and one-year follow-up. Participants with the complete longitudinal data set were included in the analysis. The LFT finding kinetic was analyzed by second-order mixed-effect logistic modeling and likelihood ratio test (full vs null model). P values were corrected for multiple testing with the Benjamini-Hochberg method. Likelihood ratio (), p values and numbers of participants with the complete longitudinal data set are presented in the plot captions.*

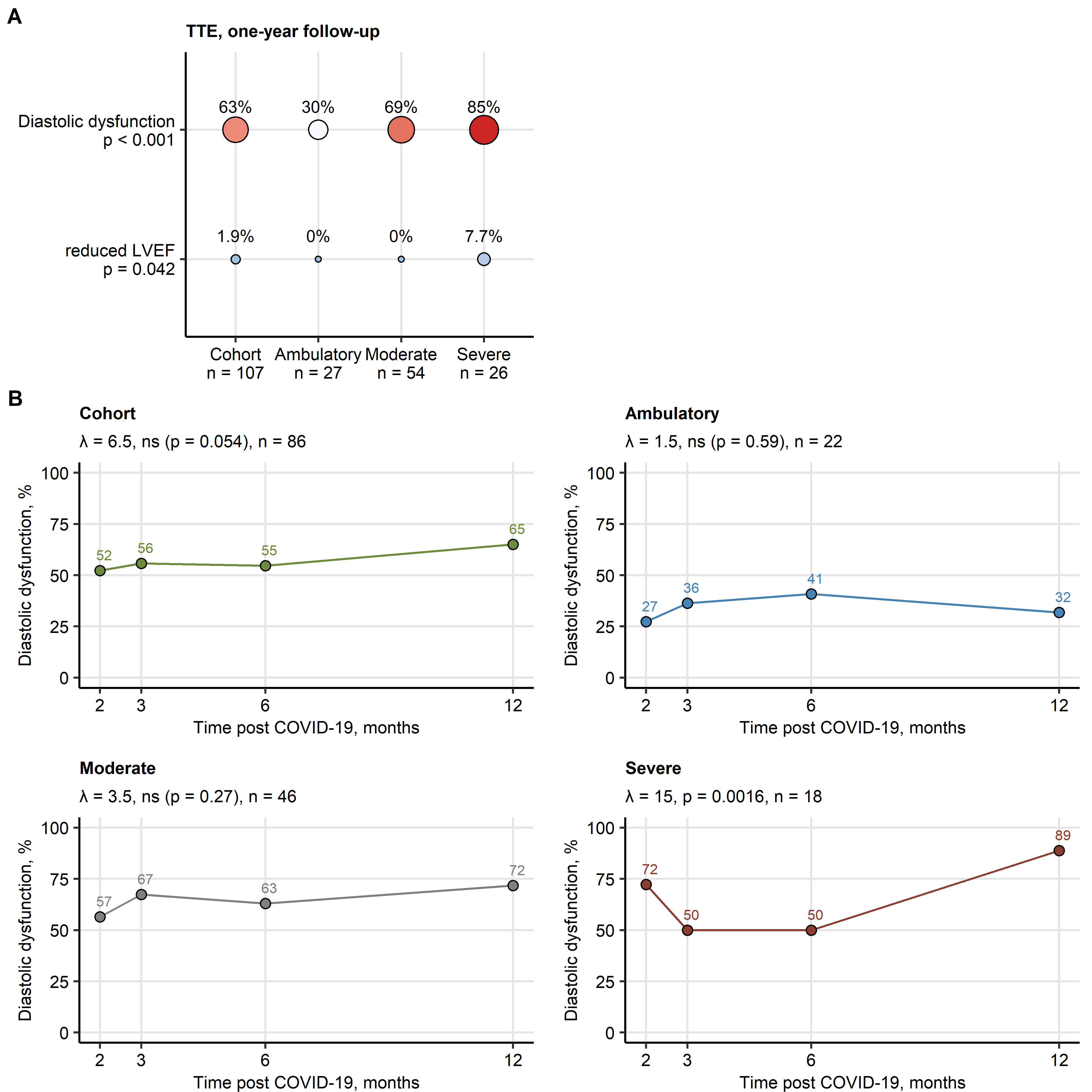


**Figure 4. Radiological lung recovery.**

*Chest computed tomography (CT) was analyzed in the entire study collective and in ambulatory, moderate and severe COVID-19 survivors.*

*(A) Percentages of individuals with any chest CT abnormality (CT severity score 1) and abnormalities scored >5 CT severity score points at the one-year follow-up. Differences between the COVID-19 severity strata were investigated by test corrected for multiple testing with Benjamini-Hochberg method. Point size and color code for the percentage. P values are displayed in the Y axis. Numbers of complete observations are indicated in the X axis.*

*(B) Percentages of individuals with any chest CT abnormality at the 2-, 3-, 6-month and one-year follow-up. Participants with the complete longitudinal data set were included in the analysis. The CT finding kinetic was analyzed by second-order mixed-effect logistic modeling and likelihood ratio test (full vs null model). P values were corrected for multiple testing with the Benjamini-Hochberg method. Likelihood ratio (), p values and numbers of participants with the complete longitudinal data set are presented in the plot captions.*

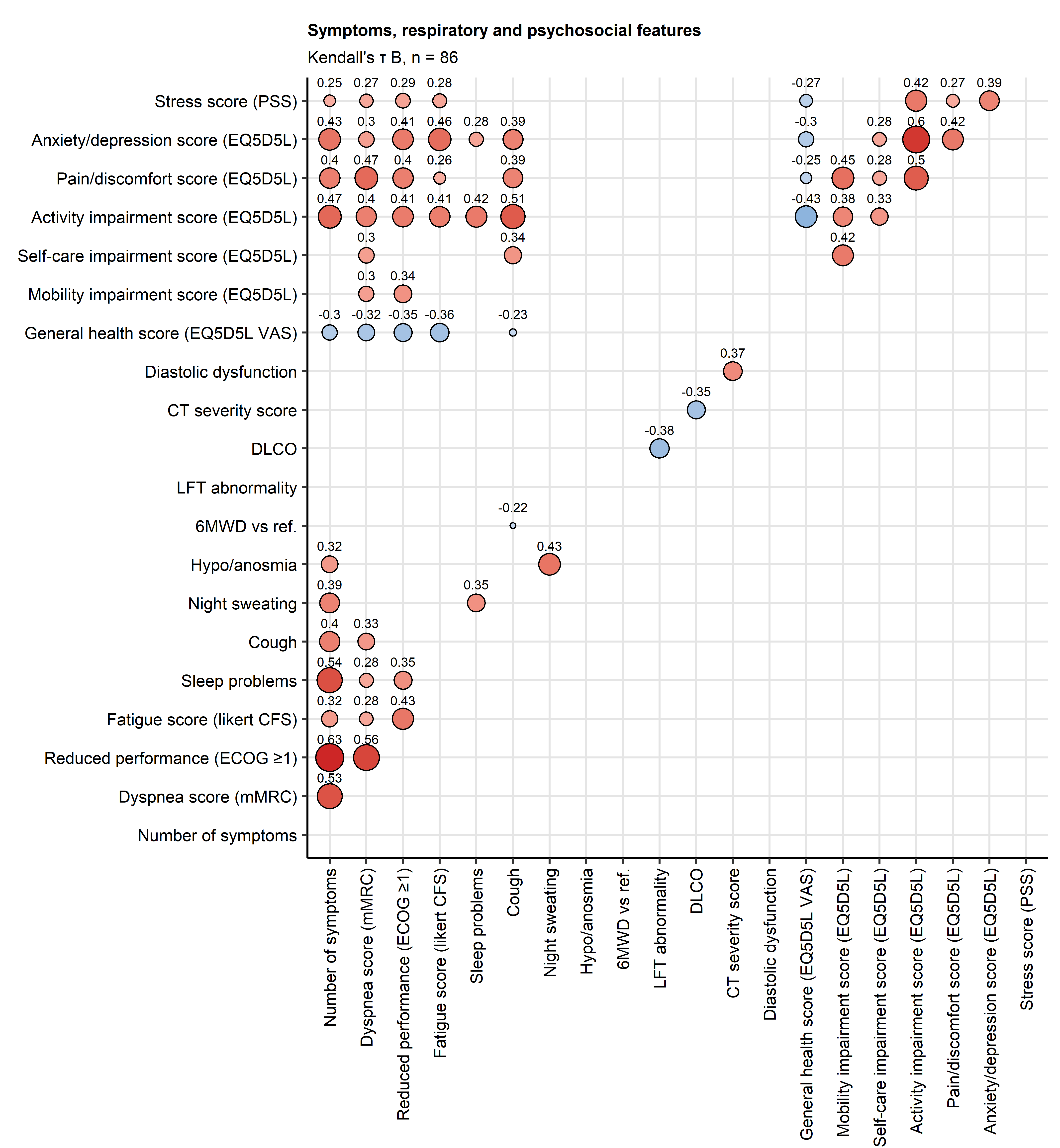


**Figure 5. Cardiological recovery.**

*Transthoracic echocardiography (TTE) was performed in the entire study collective and in ambulatory, moderate and severe COVID-19 survivors.*

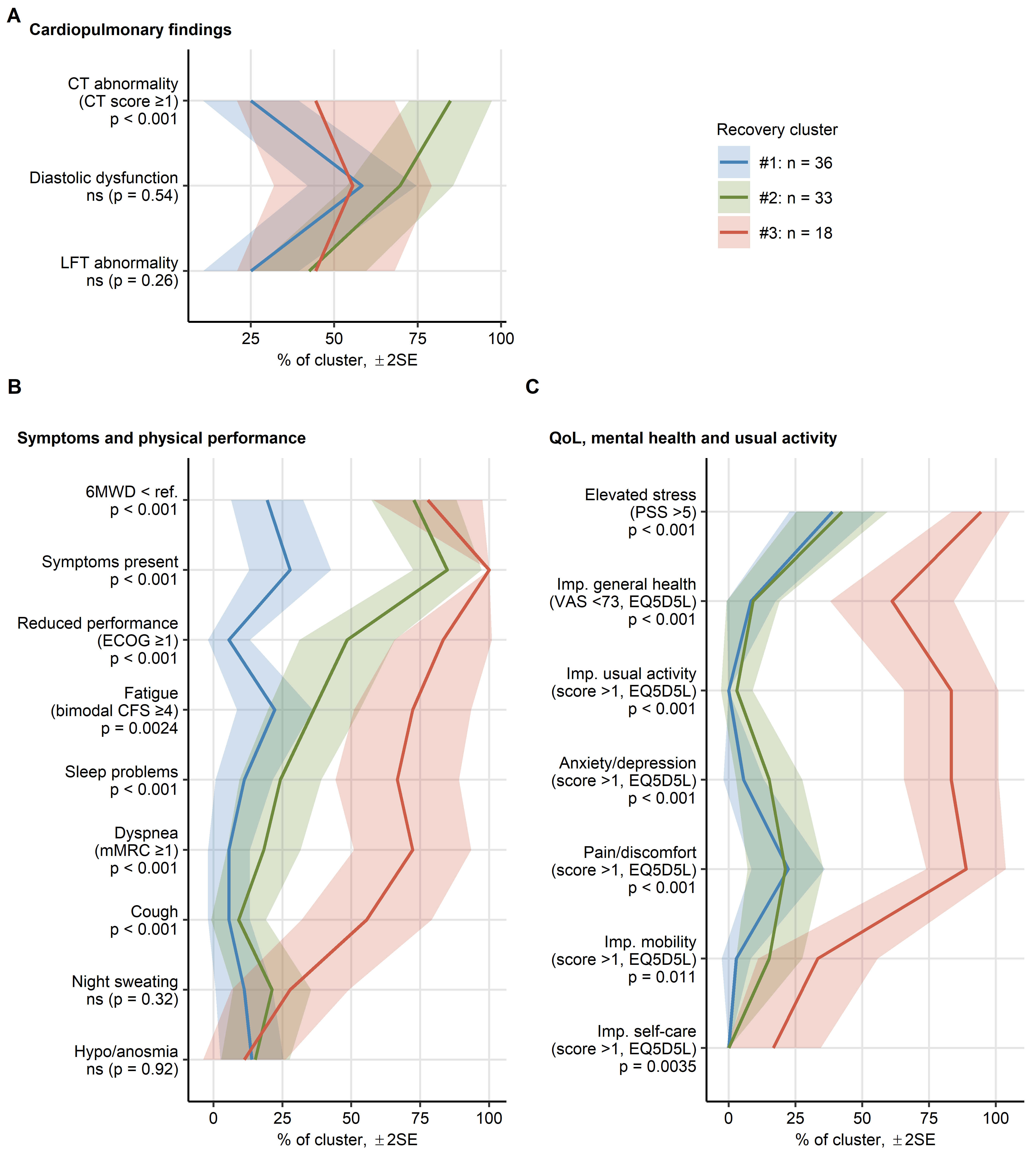
*(A) Percentages of individuals diagnosed diastolic dysfunction of any severity and reduced left ventricular ejection fraction (LVEF) at the one-year follow-up. Differences between the COVID-19 severity strata were investigated by test corrected for multiple testing with Benjamini-Hochberg method. Point size and color code for the percentage. P values are displayed in the Y axis. Numbers of complete observations are indicated in the X axis.*

*(B) Percentages of individuals diagnosed diastolic dysfunction at the 2-, 3-, 6-month and one-year follow-up. Participants with the complete longitudinal data set were included in the analysis. The diastolic dysfunction kinetic was analyzed by second-order mixed-effect logistic modeling and likelihood ratio test (full vs null model). P values were corrected for multiple testing with the Benjamini-Hochberg method. Likelihood ratio (), p values and numbers of participants with the complete longitudinal data set are presented in the plot captions.*



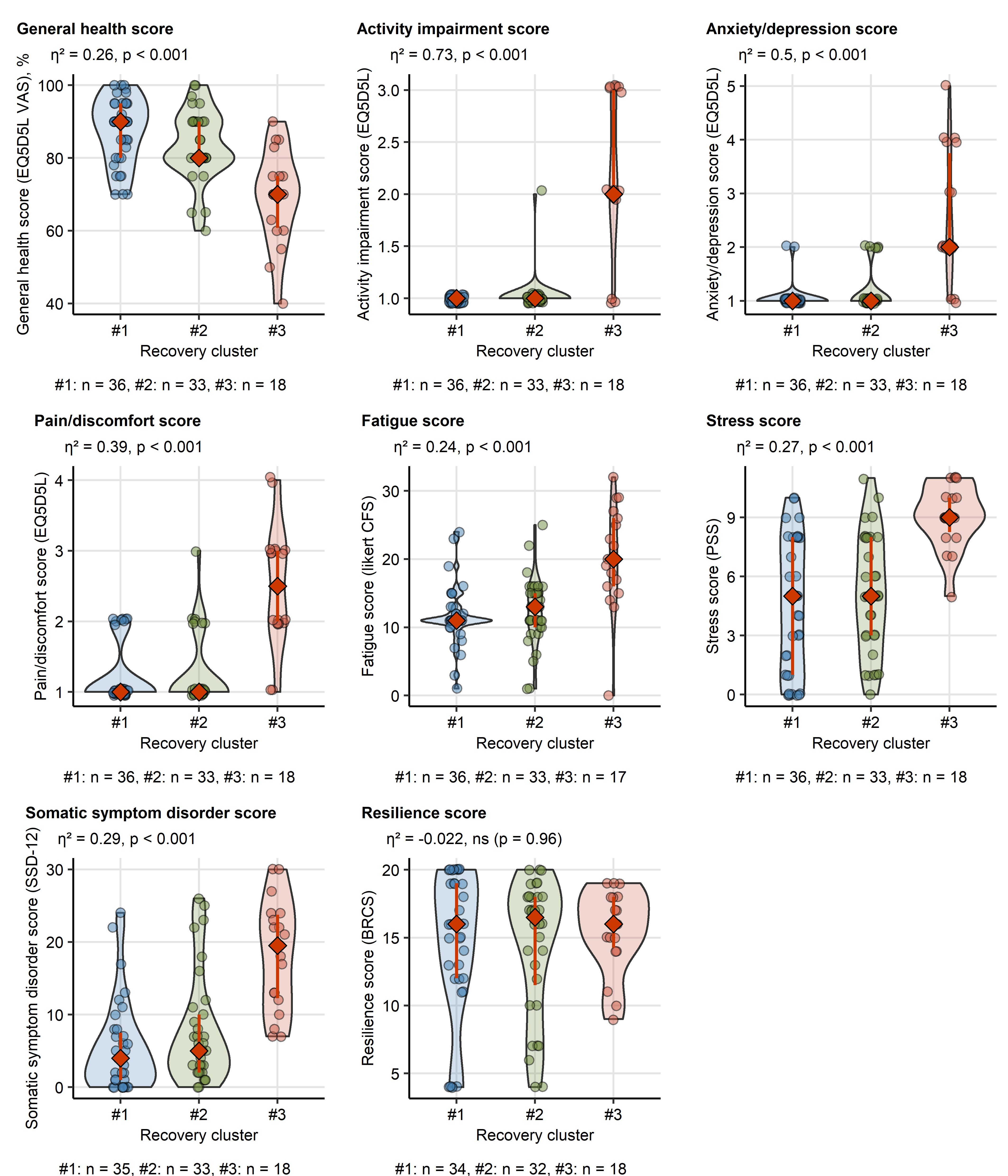
**Figure 6. Correlation of symptoms, physical performance, cardiopulmonary findings, mental health and quality of life at the one-year follow-up.**

*Association of COVID-19 symptoms (number of symptoms: # symptoms, dyspnea score: modified Medical Research Council score [mMRC], reduced performance: Eastern Cooperative Oncology Group score [ECOG] 1, fatigue: likert Chalder fatigue score [CFS], self-reported: sleep problems, cough, night sweating and hyposmia/anosmia), mobility (6MWD < ref.: six minute walking distance, difference versus the reference value), lung function (LFT: any lung function testing abnormality, DLCO: diffusion lung capacity for carbon monoxide), chest computed tomography (CT) severity score, diastolic dysfunction, self-perceived general health (EQ5D5L VAS: European quality of life 5 dimensions, 5 levels, visual analogue scale), quality of life and mental health scoring (EQ5D5L: European quality of life 5 dimensions, 5 levels) and stress (PSS: 4-item perceived stress scale) at the one-year follow-up. Pairwise correlations were investigated by Kendall’s B test. P values were corrected for multiple testing with the Benjamini-Hochberg method. coefficients for significant correlations are presented. Point size and color code for the value. The number of complete observations is indicated in the plot caption.*



**Figure 7. COVID-19 recovery clusters.**

*Clustering of the study participants in respect to symptoms (any symptom present, dyspnea: modified Medical Research Council score [mMRC] 1, reduced performance: Eastern Cooperative Oncology Group score [ECOG] 1, fatigue: bimodal Chalder fatigue score [CFS] 4, self-reported: sleep problems, cough, night sweating and hyposmia/anosmia), mobility (6MWD < ref.: six minute walking distance, difference versus the reference value), cardiopulmonary abnormalities (any chest computed tomography [CT] abnormality: CT severity score 1, any lung function testing [LFT] abnormality, diastolic dysfunction), significant stress (4-item perceived stress scale [PSS] >5), impaired self-perceived general health (European quality of life 5 dimensions, 5 levels, visual analogue scale [EQ5D5L VAS] <73, imp.: impaired) as well as features of quality of life and mental health (European quality of life 5 dimensions, 5 levels [EQ5D5L], cutoff: score >1) at the one-year follow-up. Clustering analysis was done with the PAM algorithm (PAM: partitioning around medoids, simple matching distance). Differences in frequency of the cardiopulmonary (A), symptom and mobility (B) as well as self-perceived general health, quality of life and mental health (C) clustering variables between the recovery clusters were analyzed by test. P values were corrected for multiple testing with the Benjamini-Hochberg method. Lines represent the estimated percentages of the feature in the cluster, tinted regions represent 2SEM intervals. P values are indicated in the Y axis. Numbers of participants assigned to the clusters are displayed in A.*



**Figure 8. Quality of life, fatigue and mental health rating in the COVID-19 recovery clusters.**

*Quality of life, general health and rating of fatigue, stress, somatic symptom disorder and resilience were assessed at the one-year follow-up were compared between the COVID-19 recovery clusters. Statistical significance was determined by Kruskal-Wallis test with effect size statistic. P values were corrected for multiple testing with Benjamini-Hochberg method. Effect size statistic and p values are presented in plot captions. Numbers of participants assigned to the clusters are presented under the plots.*

*EQ5D5L: European quality of life 5 dimensions, 5 levels; VAS: visual analogue scale; CFS: Chalder fatigue score; SSD-12: somatic syndrome disorder - B criteria scale; PSS: 4-item perceived stress scale; BRCS: brief resilient coping scale.*