CovILD, one-year follow-up

Figures and Tables

CovILD study team

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Tables

Table 1: Baseline characteristics of the study cohort and the COVID-19 severity groups.

Variable	CovILD cohort	Ambulatory COVID-19	Moderate COVID-19	Severe COVID-19	Significance[a]	Effect size[a]
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 = 0.04	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	η^2 = 0.19
Weight class[2]	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 = 0.32)	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 = 0.24)	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 = 0.086)	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
CVD[b]	40% (n = 43)	7.4% (n = 2)	47% (n = 26)	58% (n = 15)	p = 0.0027	V = 0.39
Pulmonary disease	19% (n = 20)	11% (n = 3)	22% (n = 12)	19% (n = 5)	ns (p = 0.63)	V = 0.11
Malignancy	9.3% (n = 10)	3.7% (n = 1)	15% (n = 8)	3.8% (n = 1)	ns (p = 0.32)	V = 0.19

Variable	CovILD cohort	Ambulatory COVID-19	Moderate COVID-19	Severe COVID-19	Significance[a]	Effect size[a]
Immune deficiency	5.6% (n = 6)	0% (n = 0)	3.6% (n = 2)	15% (n = 4)	ns (p = 0.14)	V = 0.25
CKD[c]	6.5% (n = 7)	0% (n = 0)	5.5% (n = 3)	15% (n = 4)	ns (p = 0.19)	V = 0.22
GID[d]	13% (n = 14)	0% (n = 0)	20% (n = 11)	12% (n = 3)	ns (p = 0.15)	V = 0.24
Rehabilitation	no: 68% (n = 71) inpatient: 25% (n = 26) outpatient: 6.7% (n = 7) n = 104	no: 89% (n = 24) inpatient: 0% (n = 0) outpatient: 11% (n = 3) n = 27	no: 81% (n = 43) inpatient: 13% (n = 7) outpatient: 5.7% (n = 3) n = 53	no: 17% (n = 4) inpatient: 79% (n = 19) outpatient: 4.2% (n = 1) n = 24	p < 0.001	V = 0.5

[a]Comparison between the COVID-19 severity strata. Categorical variables: χ^2 test with Cramer V effect size statistic; numeric variables: Kruskal-Vallis test with η^2 effect size statistic. P values corrected for multiple testing with Benjamini-Hochberg method.

[2]Body mass index (BMI); overweight > 25 kg/m^2, obesity > 30 kg/m^2

[b]CVD: Cardiovascular disease

[c]CKD: Chronic kidney disease

[d]GID: Gastrointestinal disease

Table 2: Key outcome measures of participants according to COVID-19 severity groups.

Variable	CovILD cohort	Ambulatory COVID-19	Moderate COVID-19	Severe COVID-19	Significance[a]	Effect size[a]
Symptoms present	65% (n = 68) n = 105	59% (n = 16) n = 27	67% (n = 36) n = 54	67% (n = 16) n = 24	ns (p = 0.86)	V = 0.068
LFT abnormality[b]	33% (n = 35) n = 106	22% (n = 6) n = 27	32% (n = 17) n = 53	46% (n = 12) n = 26	ns (p = 0.32)	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

[a]COVID-19 severity groups compared with χ^2 test with Cramer V effect size statistic. P values corrected for multiple testing with Benjamini-Hochberg method.

[b]LFT 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.)

[c]CT abnormality: any abnormality in chest computed tomography, CT severity score ≥ 1.

Table 3: 12-month sub-maximal exercise performance and mental health across COVID-19 severity groups.

Variable	CovILD cohort	Ambulatory	Moderate	Severe	Significance[a]	Effect size[a]
SMWD, m[b]	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)	η^2 = 0.034
SMWD vs ref., m[c]	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 = 0.5)	η^2 = 0.0013
SMWD < ref.[d]	56% (n = 57) n = 102	62% (n = 16) n = 26	51% (n = 26) n = 51	60% (n = 15) n = 25	ns (p = 0.74)	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)	η^2 = -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 = 0.55)	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)	η^2 = -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 = 0.43)	V = 0.16
Mobility impairment score (EQ5D5L)	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 = 0.33)	η^2 = 0.013
Imp. mobility (score > 1, EQ5D5L)	14% (n = 14) n = 103	11% (n = 3) n = 27	9.6% (n = 5) n = 52	25% (n = 6) n = 24	ns (p = 0.32)	V = 0.18

Variable	CovILD cohort	Ambulatory	Moderate	Severe	Significance[a]	Effect size[a]
Self-care impairment score (EQ5D5L)	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 = 0.32)	$\eta^2 = 0.014$
Imp. self-care (score > 1, EQ5D5L)	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 = 0.32)	V = 0.18
Activity impairment score (EQ5D5L)	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)	$\eta^2 = 0.033$
Imp. usual activity (score > 1, EQ5D5L)	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)	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 = 0.28)	$\eta^2 = 0.019$
Pain/discomfort (score > 1, EQ5D5L)	36% (n = 37) n = 103	41% (n = 11) n = 27	27% (n = 14) n = 52	50% (n = 12) n = 24	ns (p = 0.27)	V = 0.2
Anxiety/ depression score (EQ5D5L)	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 = 0.23)	$\eta^2 = 0.027$
Anxiety/ depression (score > 1, EQ5D5L)	28% (n = 29) n = 103	30% (n = 8) n = 27	21% (n = 11) n = 52	42% (n = 10) n = 24	ns (p = 0.32)	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)	$\eta^2 = 0.068$
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 = 0.15)	V = 0.25

Variable	CovILD cohort	Ambulatory	Moderate	Severe	Significance[a]	Effect size[a]
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 = 0.03	η^2 = 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 = 0.23)	η^2 = 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 = 0.55)	V = 0.14

[a]Comparison between the COVID-19 severity strata. Categorical variables: χ^2 test with Cramer V effect size statistic; numeric variables: Kruskal-Vallis test with η^2 effect size statistic. P values corrected for multiple testing with Benjamini-Hochberg method.

[b]SMWD: six-minute walking distance, meters.

[c]SMWD vs ref.: difference between the reference and observed SMWD value, meters

[d]SMWD < ref.: SMWD below the reference value.

[e]CFS: 11-item Chalder fatigue score, incr.: increased.

[f]VAS: visual analogue scale, imp.: impaired.

[h]PSS: 4-item perceived stress scale.

[i]SSD-12: 12-item somatic syndrome disorder – B criteria scale.

[j]BRCS: brief resilient coping score.

[k]low: 4 - 13 points, medium: 14 - 16 points, high: 17 - 21 points in the BRCS scale.
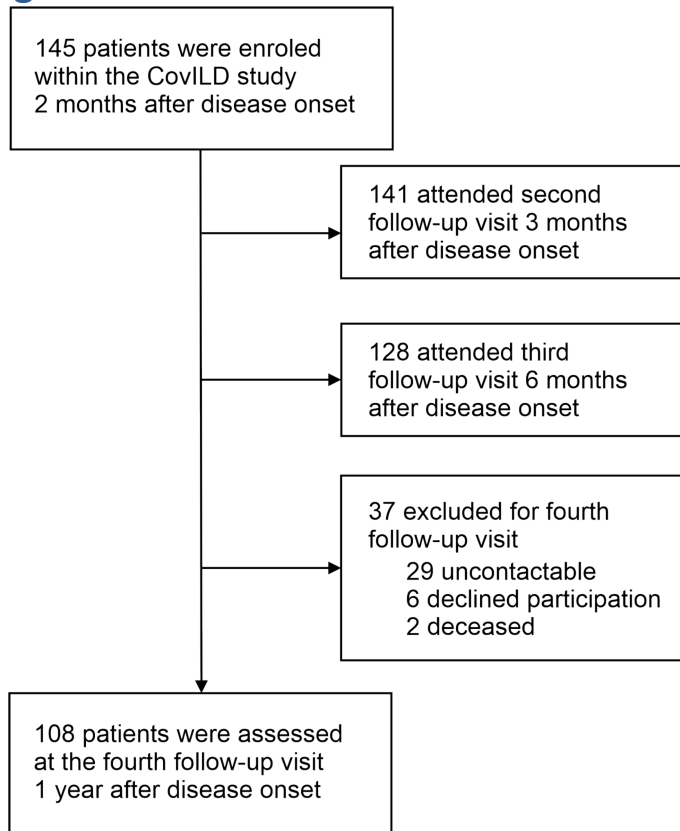
Figures

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┌─────────────────────────────┐
│ 145 patients were enroled   │
│ within the CovILD study     │
│ 2 months after disease onset│
└─────────────────────────────┘
             │
             │        ┌─────────────────────────┐
             ├───────▶│ 141 attended second     │
             │        │ follow-up visit 3 months│
             │        │ after disease onset     │
             │        └─────────────────────────┘
             │
             │        ┌─────────────────────────┐
             ├───────▶│ 128 attended third      │
             │        │ follow-up visit 6 months│
             │        │ after disease onset     │
             │        └─────────────────────────┘
             │
             │        ┌───────────────────────────────┐
             ├───────▶│ 37 excluded for fourth        │
             │        │ follow-up visit               │
             │        │     29 uncontactable          │
             │        │     6 declined participation  │
             │        │     2 deceased                │
             │        └───────────────────────────────┘
             │
             ▼
┌─────────────────────────────┐
│ 108 patients were assessed  │
│ at the fourth follow-up visit│
│ 1 year after disease onset  │
└─────────────────────────────┘
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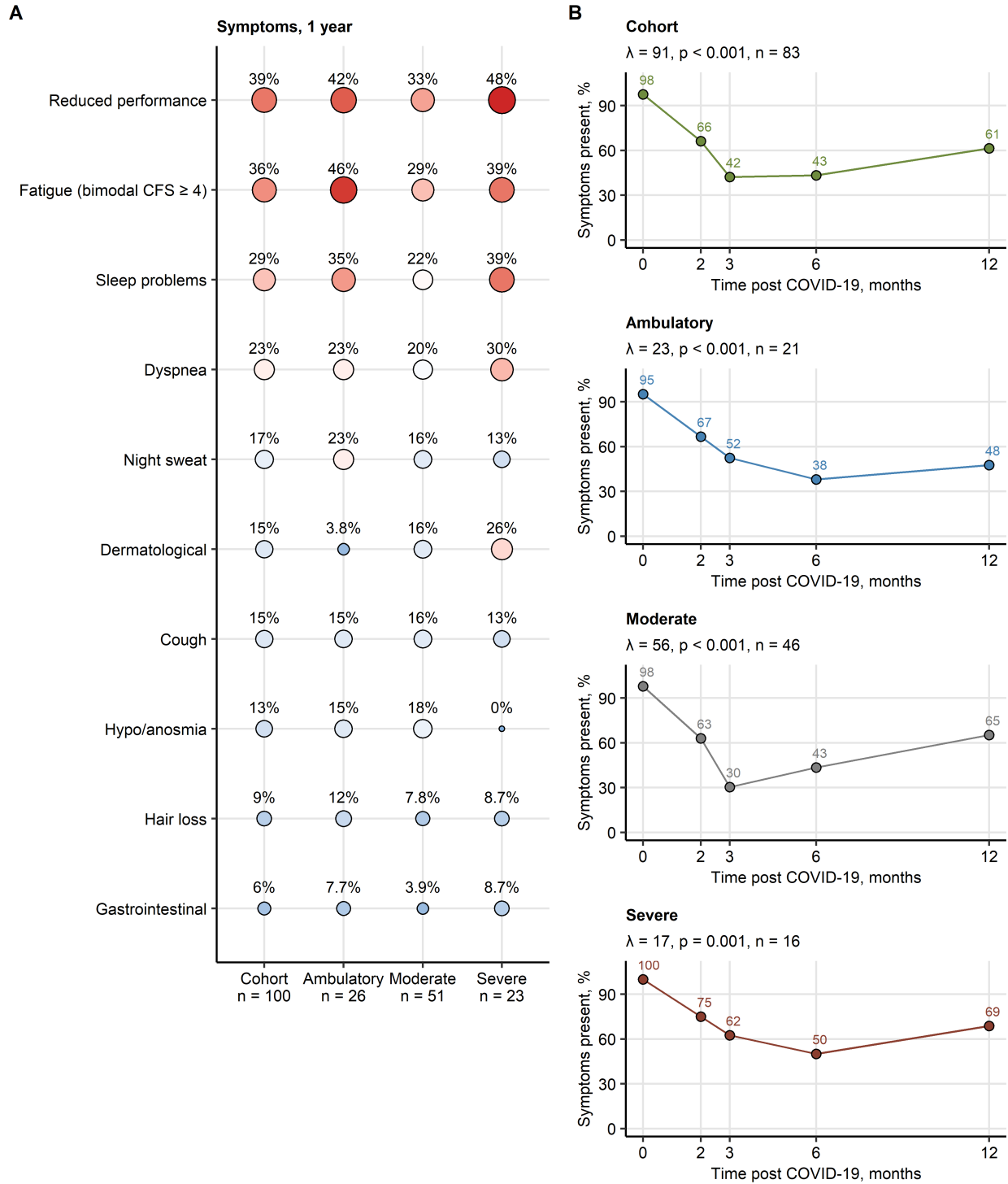**Figure 1. CONSORT flow diagram of the study analysis inclusion.**

Figure 2. COVID-19 symptom recovery.

Presence of COVID-19 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 1-year follow-up. Numbers of complete observations are indicated on the plot axis. Point size and color codes for the symptom percentage.

(B) Percentages of individuals with any symptoms during acute COVID-19 and at the 2-, 3-, 6-month and 1-year follow-up. Participants with the complete longitudinal data set were included in the analysis. The recovery was modeled 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 (λ), p values and numbers of participants with the complete longitudinal data set are presented in the plot captions.

Chalder FS: Chalder fatigue score.
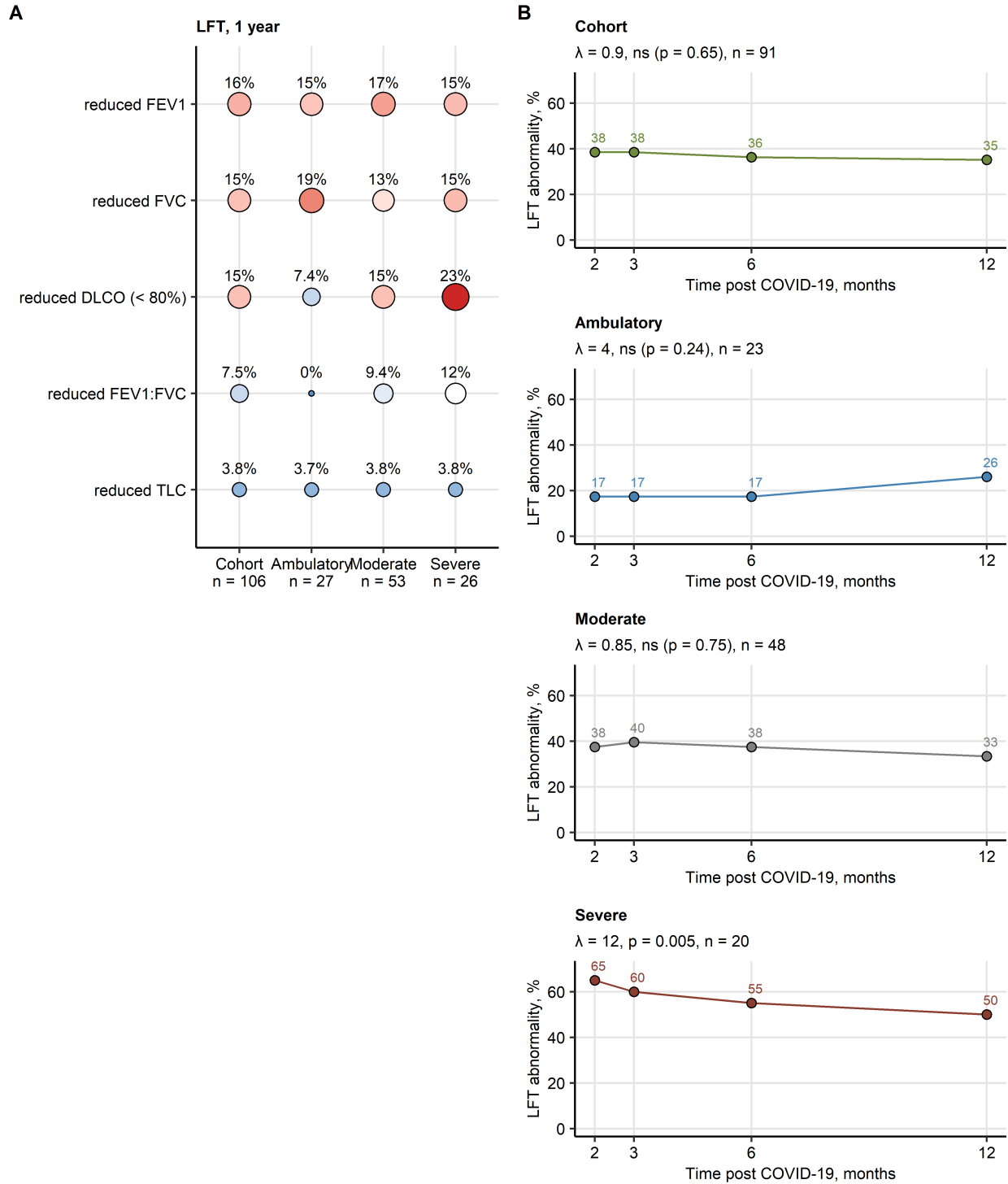
Figure 3. Functional lung recovery.

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 1-year follow-up. Numbers of complete observations are indicated on the plot axis. Point size and color codes for the abnormality percentage. 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 at the 2-, 3-, 6-month and 1-year follow-up. Participants with the complete longitudinal data set were included in the analysis. The recovery was modeled 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 (λ), p values and numbers of participants with the complete longitudinal data set are presented in the plot captions.
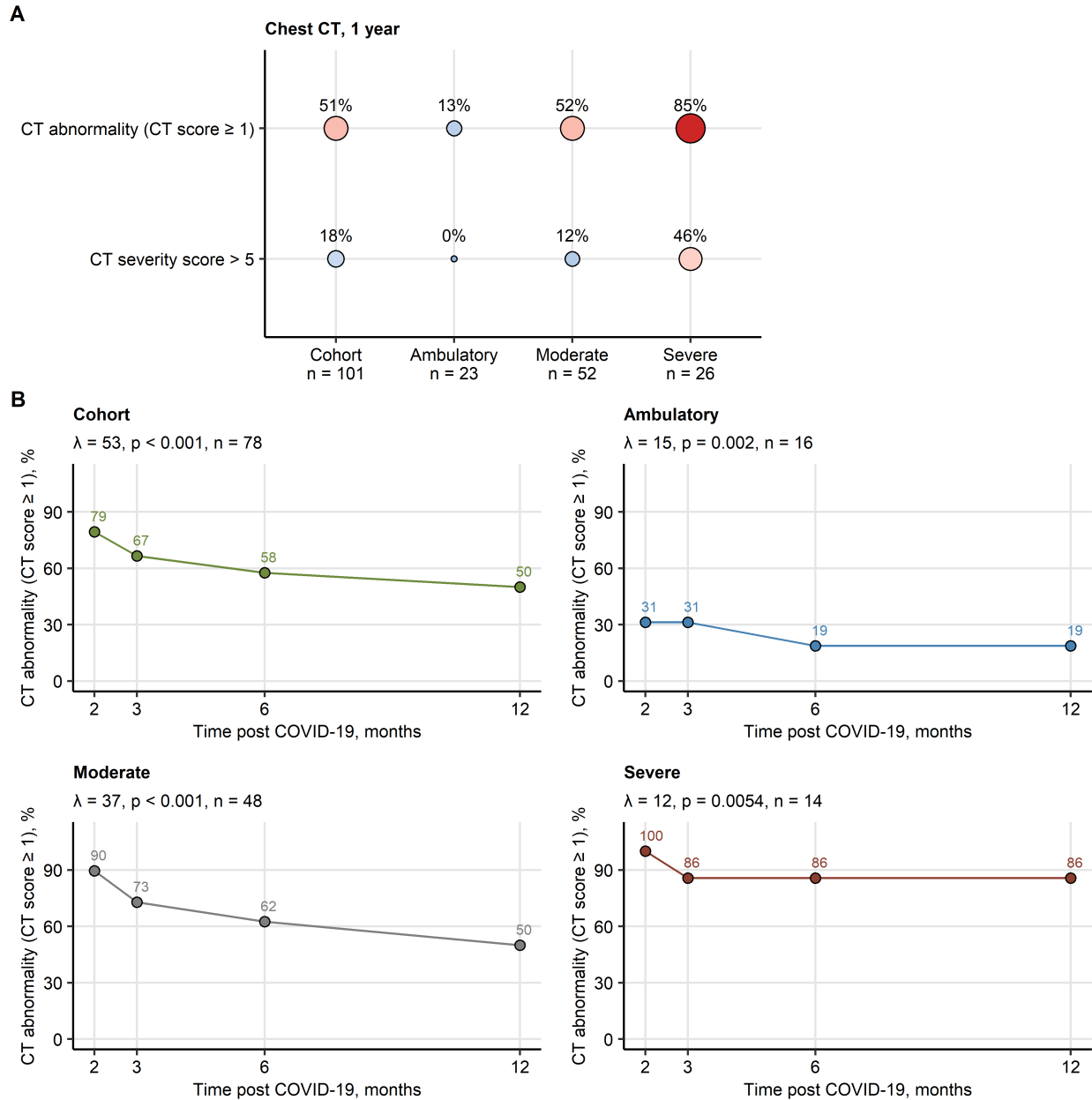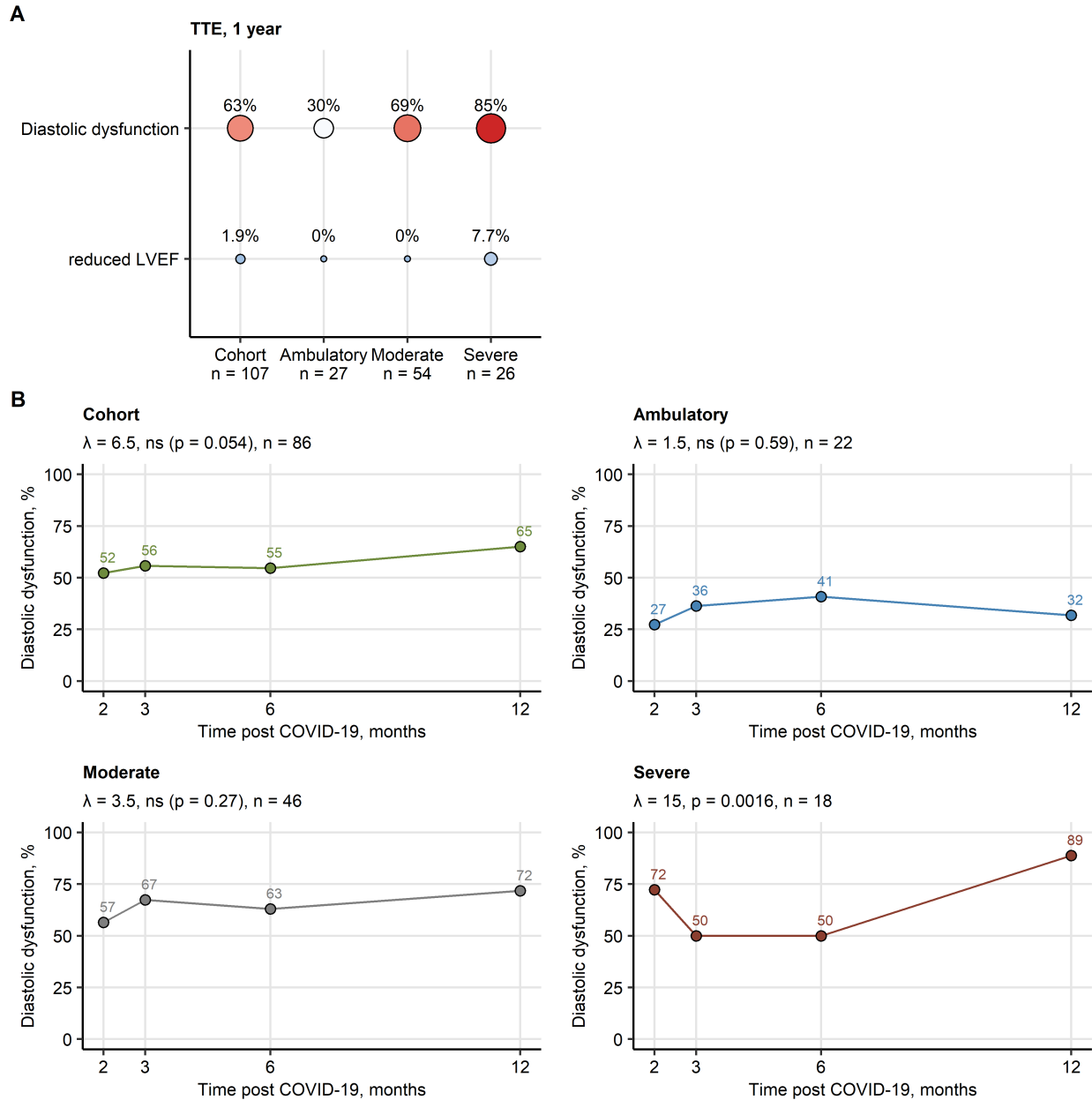
Figure 4. Radiological lung recovery.

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 and abnormalities scored > 5 CT severity score points at the 1-year follow-up. Numbers of complete observations are indicated on the plot axis. Point size and color codes for the abnormality percentage.

13

(B) Percentages of individuals with any chest CT abnormality at the 2-, 3-, 6-month and 1-year follow-up. Participants with the complete longitudinal data set were included in the analysis. The recovery was modeled 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 (λ), p values and numbers of participants with the complete longitudinal data set are presented in the plot captions.

A

TTE, 1 year

Diastolic dysfunction — 63% · 30% ○ 69% · 85% ●

reduced LVEF — 1.9% · 0% · 0% · 7.7% ·

Cohort n = 107 · Ambulatory n = 27 · Moderate n = 54 · Severe n = 26

B

Cohort
λ = 6.5, ns (p = 0.054), n = 86

Diastolic dysfunction, % — 52, 56, 55, 65 — Time post COVID-19, months

Ambulatory
λ = 1.5, ns (p = 0.59), n = 22

Diastolic dysfunction, % — 27, 36, 41, 32 — Time post COVID-19, months

Moderate
λ = 3.5, ns (p = 0.27), n = 46

Diastolic dysfunction, % — 57, 67, 63, 72 — Time post COVID-19, months

Severe
λ = 15, p = 0.0016, n = 18

Diastolic dysfunction, % — 72, 50, 50, 89 — Time post COVID-19, months

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 1-year follow-up. Numbers of complete observations are indicated on the plot axis. Point size and color codes for the abnormality percentage.

15

(B) Percentages of individuals diagnosed diastolic dysfunction at the 2-, 3-, 6-month and 1-year follow-up. Participants with the complete longitudinal data set were included in the analysis. The recovery was modeled 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 (λ), p values and numbers of participants with the complete longitudinal data set are presented in the plot captions.
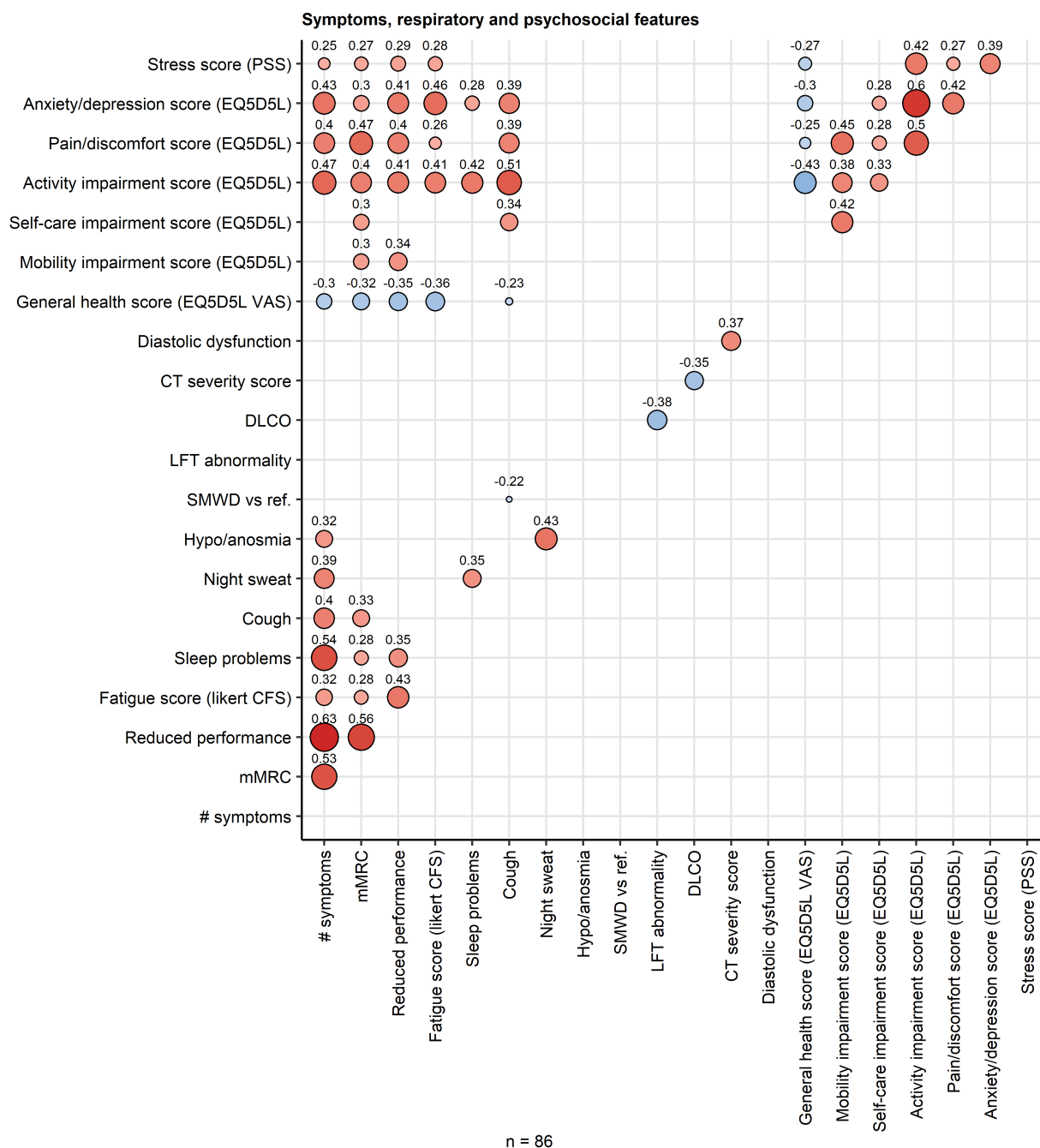
Figure 6. Symptoms, cardiopulmonary findings and mental health.

Association of COVID-19 symptoms, cardiopulmonary abnormality as well as scores of fatigue, health self-perception, quality of life, mental health and stress scoring at the 1-year follow-up (**Supplementary Tables S1** and **S2**) was analyzed by pairwise Kendall's τ correlation test. P values were corrected for multiple testing with the Benjamini-Hochberg

method. τ coefficients for significant correlations are presented. Point size and color codes for the τ value. The number of complete observations is indicated under the plot.

mMRC: modified medical research council dyspnea scale; #: number of, LFT: lung function testing; DLCO: diffusion lung capacity for carbon monoxide; CT: chest computed tomography; SMWD vs ref.: six minute walking distance, difference versus the reference value; EQ5DL: European quality of life 5 dimensions; VAS: visual analogue scale; PSS: perceived stress score; CFS: Chalder fatigue score.
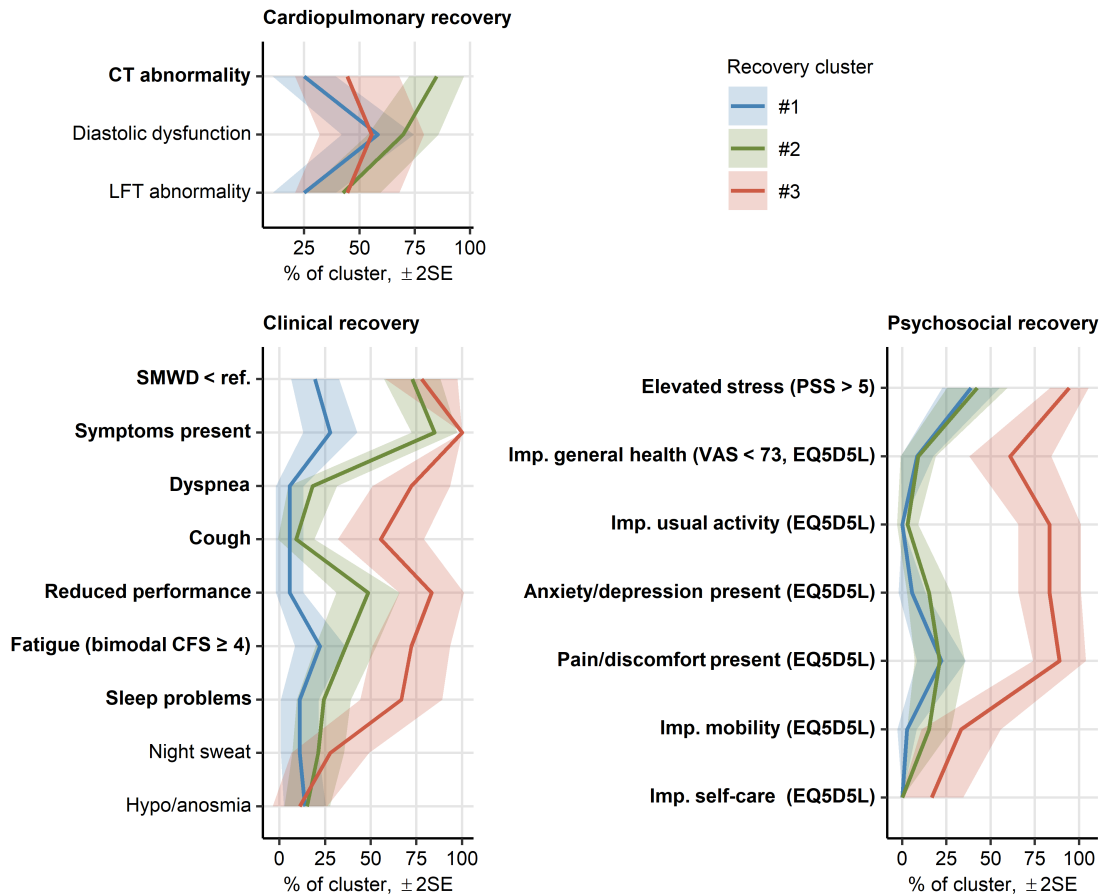
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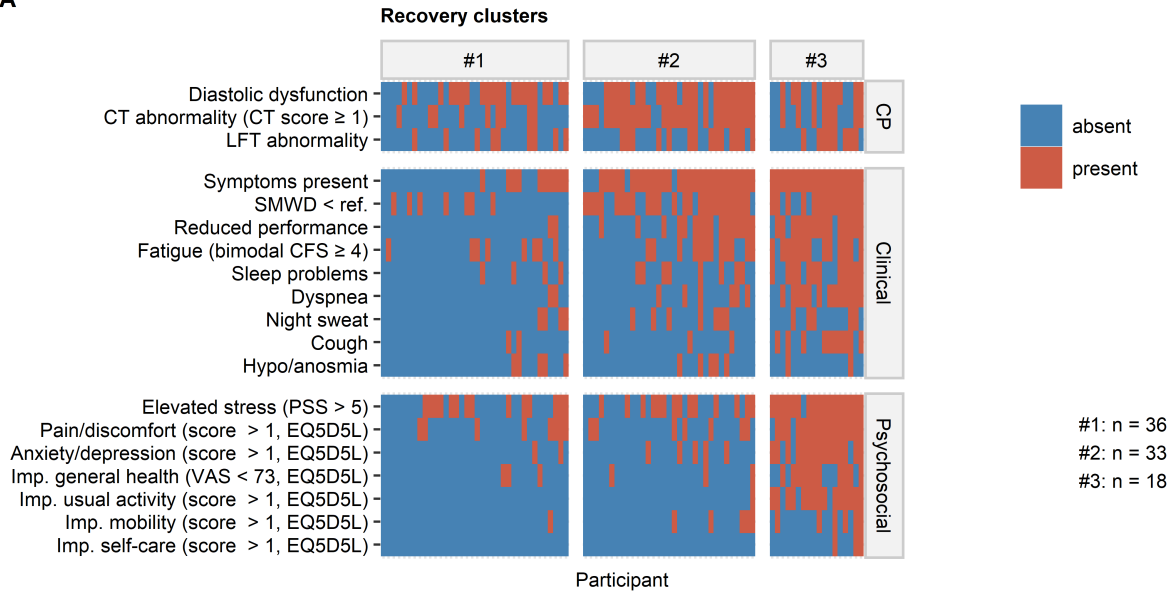
Figure 7. Clusters of clinical and psychosocial COVID-19 recovery.

Clustering of the study participants in respect to 19 binary symptom, cardiopulmonary and psychosocial features recorded at the 1-year follow-up (**Supplementary Table S1** and **S2**) was analyzed by the PAM algorithm (PAM: partitioning around medoids, simple matching distance).

(A) Assignment of the study participants to the recovery clusters. Percentages of variance associated with the UMAP components are presented in the plot axes. Numbers of participants assigned to the clusters are presented next to the plot.

(B) Differences in frequency of the clustering variables between the recovery clusters were analyzed by χ^2. 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 2×SEM intervals. Features significantly differing between the clusters are labeled in bold.

CP: cardiopulmonary, imp.: impaired, EQ5DL: European quality of life 5 dimensions; VAS: visual analogue scale; CFS: Chalder fatigue score; PSS: perceived stress score; SMWD < ref: six-minute walking distance below the reference value. LFT: lung function testing; CT: chest computed tomography.
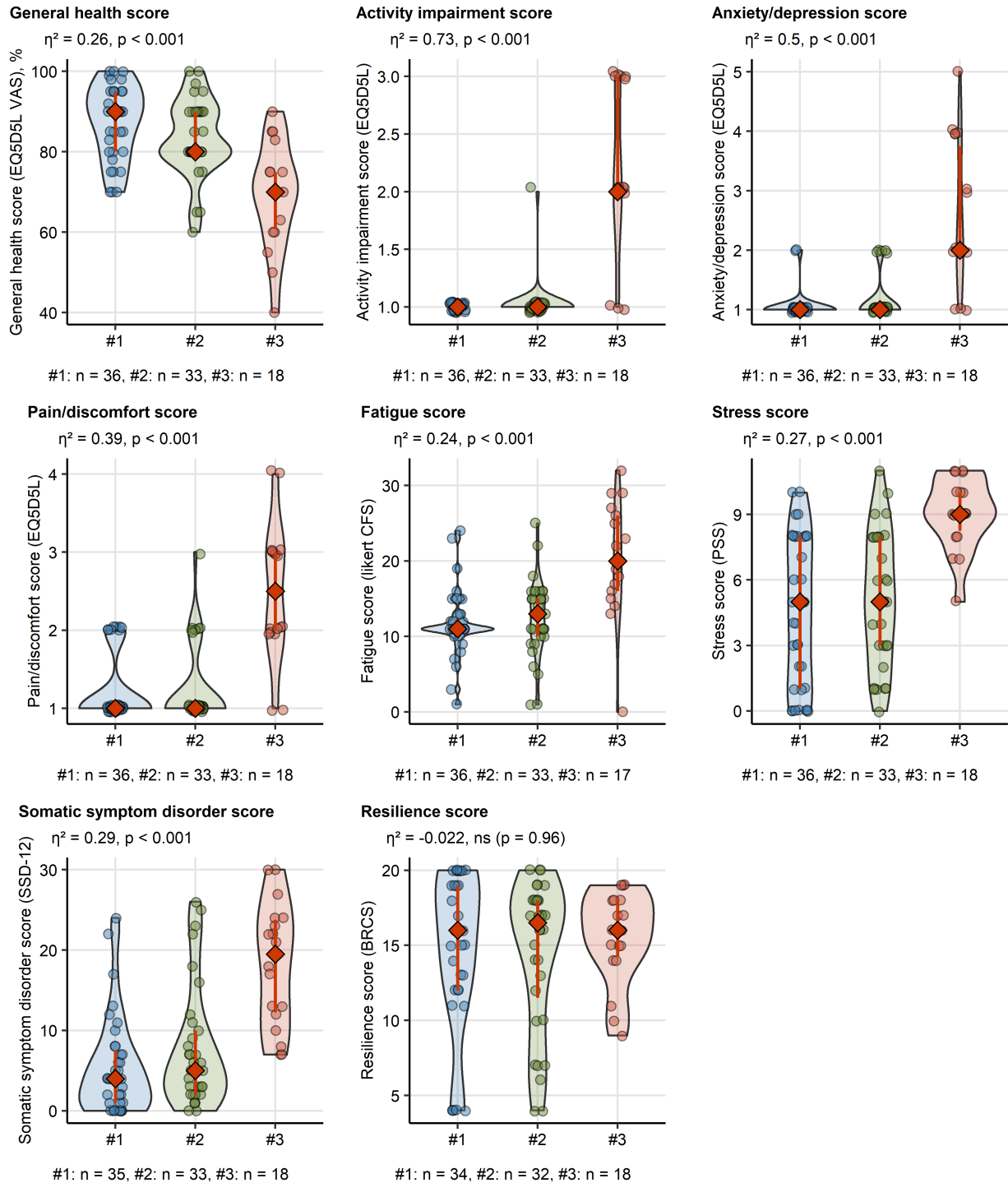
Figure 8. Quality of life, fatigue and mental health rating in the COVID-19 recovery clusters.

Quality of life, general health and rating of fatigue, stress, somatic symptom disorder and resilience were assessed at the 1-year follow-up were compared between the COVID-19 recovery clusters (**Figure 7**, **Supplementary Figure S9**). Statistical significance was determined by Kruskal-Wallis test with η^2 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 to the plots.

EQ5DL: European quality of life 5 dimensions; VAS: visual analogue scale; CFS: Chalder fatigue score; SSD-12: somatic syndrome disorder - B criteria scale; PSS: perceived stress score; BRCS: brief resilient coping scale.