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

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Abstract

Background Recovery trajectories from coronavirus disease 2019 (COVID-19) call for longitudinal investigation. We aimed to characterise the kinetics and status of clinical, cardiopulmonary and mental health recovery up to 1 year following COVID-19.

Methods Clinical evaluation, lung function testing (LFT), chest computed tomography (CT) and transthoracic echocardiography were conducted at 2, 3, 6 and 12 months after disease onset. Submaximal exercise capacity, mental health status and quality of life were assessed at 12 months. Recovery kinetics and patterns were investigated by mixed-effect logistic modelling, correlation and clustering analyses. Risk of persistent symptoms and cardiopulmonary abnormalities at the 1-year follow-up were modelled by logistic regression.

Findings Out of 145 CovILD study participants, 108 (74.5%) completed the 1-year follow-up (median age 56.5 years; 59.3% male; 24% intensive care unit patients). Comorbidities were present in 75% (n=81). Key outcome measures plateaued after 180 days. At 12 months, persistent symptoms were found in 65% of participants; 33% suffered from LFT impairment; 51% showed CT abnormalities; and 63% had low-grade diastolic dysfunction. Main risk factors for cardiopulmonary impairment included pro-inflammatory and immunological biomarkers at early visits. In addition, we deciphered three recovery clusters separating almost complete recovery from patients with post-acute inflammatory profile and an enrichment in cardiopulmonary residuals from a female-dominated post-COVID-19 syndrome with reduced mental health status.

Conclusion 1 year after COVID-19, the burden of persistent symptoms, impaired lung function, radiological abnormalities remains high in our study population. Yet, three recovery trajectories are emerging, ranging from almost complete recovery to post-COVID-19 syndrome with impaired mental health.

Introduction

As of 6 July 2022, the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic has resulted in >540 million cases and >6.3 million deaths worldwide, including 4.5 million cases and 20 057 deaths in Austria (population 8.9 million) [1]. The acute phase of disease manifests within a broad clinical

spectrum including respiratory, neurological and cardiological symptoms ranging from mild to fatal disease courses [2]. Additionally, disease course may often vary in duration and severity of symptoms. Long-term health consequences have been analysed by various previously published studies, leading to the definition of post-coronavirus disease 2019 (COVID-19) syndrome or post-COVID-19 condition (persisting symptoms 3 months from the onset of COVID-19 that last for ⩾2 months and cannot be explained by an alternative diagnosis) [3, 4]. These conditions are predominantly defined in terms of time, including heterogeneous manifestations of physical, neurocognitive and psychological impairment [5]. Yet, only a few COVID-19 recovery studies have longitudinally captured both physical and health-related quality-of-life consequences, restricting comprehensive knowledge about the recovery phase and residual burden of disease [6, 7]. We previously characterised the early cardiopulmonary recovery of COVID-19 survivors [8, 9]. Herein, we aim to describe the evolution of recovery up to 1 year and its impact on physical performance and mental health.

Methods

Study design and approval

CovILD is a prospective, multicentre, observation cohort study (ClinicalTrials.gov identifier NCT04416100) [8, 9]. The participants were recruited between April and June 2020 at the department of internal medicine II at the Medical University of Innsbruck, St Vinzenz Hospital, Zams and Karl Landsteiner Rehabilitation Facility, Münster (all located in Tyrol, Austria). Inclusion criteria were age ⩾18 years and a symptomatic PCR-confirmed SARS-CoV-2 infection. Out of 190 individuals screened for participation, 145 were enrolled. Reasons for nonparticipation were mainly logistical (e.g. distance from the follow-up centre in Innsbruck precluding completion of the study visits, n=27) or rejection of study participation (n=18). Follow-up visits were scheduled at 2, 3, 6 and 12 months after diagnosis. Participants having completed the 1-year follow-up (n=108; table 1) were included in the current analysis. Main reasons for participant dropout were loss of contact and incomplete follow-up visits (figure 1). During the recruitment phase, steroids were not considered a standard therapy in oxygen-dependent COVID-19 patients. However, steroids were administered in cases of nonresolving pneumonia (20 out of 108) beginning from week 4 post-diagnosis at the discretion of the physician [9].

The study was performed in accordance with the Declaration of Helsinki and the European data policies. All participants gave written informed consent. The study protocol was approved by the ethics committee at the Medical University of Innsbruck (approval number 1103/2020).

Procedures

For every follow-up visit, self-reported COVID-19 symptoms (fever, night sweating, dermatological manifestations, cough, smell disorders, sleep disorders, hair loss and gastrointestinal symptoms, surveyed by single yes/no questions), dyspnoea (modified British Medical Research Council dyspnoea score ⩾1) and physical performance rating (Eastern Cooperative Oncology Group reduced performance score ⩾1), laboratory testing, lung function tests (LFTs), transthoracic echocardiography (TTE) and high-resolution computed tomography (CT) [10, 11] were examined [8, 9, 12]. Pulmonary imaging findings defined by the Fleischner Society [13] were graded for every lobe using the following CT severity score: 0: none; 1: minimal (subtle ground-glass opacities (GGOs)); 2: mild (several GGOs, subtle reticulation); 3: moderate (multiple GGOs, reticulation, small consolidation); 4: severe (extensive GGOs, consolidation, reticulation with distortion); and 5: massive (massive findings, parenchymal destruction). The maximum score was 25 (i.e. maximum score 5 per lobe). LFT impairment was defined as forced expiratory volume in 1 s (FEV_1), forced vital capacity (FVC), diffusion capacity of the lung for carbon monoxide (D_{LCO}), total lung capacity (TLC) <80% predicted or FEV_1/FVC ratio <70% pred. TTE was performed according to the European Society of Cardiology and European Association of Cardiovascular Imaging recommendations [14].

Additionally, the 1-year follow-up evaluation included 6-min walk test (6MWT), and rating of fatigue, quality of life (QoL) and mental health. The 6MWT was conducted according to the American Thoracic Society guidelines [15]. Fatigue was quantified using the 11-item Chalder Fatigue Scale (CFS) (Likert and bimodal; significant fatigue: bimodal CFS ⩾4) [16].

QoL was evaluated using the European Quality of Life Five-Dimension Five-Level tool (EQ-5D-5L) with mobility, self-care, usual activities, pain/discomfort and anxiety/depression subscores (impairment: subscore >1) [17]. The EQ-5D-5L visual analogue scale (VAS; 0–100, impairment <73 [18]) was used to gauge self-perceived general health. Additionally, resilience (Brief Resilient Coping Scale (BRCS) [19]), somatic symptom disorder (Somatic Symptom Disorder – B Criteria Scale, 12 items (SSD-12) [20]) and perceived mental stress (four-item Perceived Stress Scale (PSS) [21]) were assessed at the 1-year follow-up.

TABLE 1 Baseline characteristics of the study cohort and the coronavirus disease 2019 (COVID-19) severity groups

|	CovILD cohort	Ambulatory COVID-19	Moderate COVID-19	Severe COVID-19	Significance, p-value[#]	Effect size[#]
Participants	108	27	55	26		
Sex					0.039	V=0.31
Female	41 (44)	67 (18)	35 (19)	27 (7)		
Male	59 (64)	33 (9)	65 (36)	73 (19)		
Age, years	56 (49–68; 19–87)	47 (38–55; 19–70)	62 (53–72; 27–87)	56 (52–64; 44–79)	<0.001	η^2=0.19
Weight class[¶]					NS (0.31)	V=0.17
Normal	39 (42)	56 (15)	29 (16)	42 (11)		
Overweight	43 (46)	33 (9)	51 (28)	35 (9)		
Obese	19 (20)	11 (3)	20 (11)	23 (6)		
Smoking					NS (0.23)	V=0.19
Never-smoker	63 (68)	81 (22)	53 (29)	65 (17)		
Ex-smoker	34 (37)	15 (4)	44 (24)	35 (9)		
Active smoker	2.8 (3)	3.7 (1)	3.6 (2)	0 (0)		
Comorbidity present	75 (81)	41 (11)	85 (47)	88 (23)	<0.001	V=0.46
Metabolic disease	42 (45)	19 (5)	49 (27)	50 (13)	NS (0.087)	V=0.27
Diabetes	15 (16)	3.7 (1)	15 (8)	27 (7)	NS (0.18)	V=0.23
Hypercholesterolaemia	21 (23)	3.7 (1)	31 (17)	19 (5)	NS (0.084)	V=0.27
Cardiovascular disease	40 (43)	7.4 (2)	47 (26)	58 (15)	0.0025	V=0.39
Pulmonary disease	19 (20)	11 (3)	22 (12)	19 (5)	NS (0.62)	V=0.11
Malignancy	9.3 (10)	3.7 (1)	15 (8)	3.8 (1)	NS (0.31)	V=0.19
Immune deficiency	5.6 (6)	0 (0)	3.6 (2)	15 (4)	NS (0.13)	V=0.25
Chronic kidney disease	6.5 (7)	0 (0)	5.5 (3)	15 (4)	NS (0.18)	V=0.22
Gastrointestinal disease	13 (14)	0 (0)	20 (11)	12 (3)	NS (0.14)	V=0.24
Steroid therapy[+]	19 (20)	3.7 (1)	16 (9)	38 (10)	0.033	V=0.32
Rehabilitation	104	27	53	24	<0.001	V=0.5
None	68 (71)	89 (24)	81 (43)	17 (4)		
Inpatient	25 (26)	0 (0)	13 (7)	79 (19)		
Outpatient	6.7 (7)	11 (3)	5.7 (3)	4.2 (1)		

Data are presented as n, % (n) or median (interquartile range; range), unless otherwise stated. NS: nonsignificant. [#]: comparison between the COVID-19 severity strata (categorical variables Chi-squared test with Cramer V effect size statistic; numeric variables Kruskal–Wallis test with η^2 effect size statistic; p-values corrected for multiple testing using the Benjamini–Hochberg method; [¶]: overweight: body mass index (BMI) >25 kg·m^{-2}, obese: BMI >30 kg·m^{-2}; [+]: steroid therapy in cases of nonresolving pneumonia beginning from week 4 post-diagnosis at the discretion of the physician.

Participants were classified as ambulatory (outpatients, World Health Organization (WHO) Ordinal Scale for Clinical Improvement 1–2), moderate (inpatients, no mechanical ventilation, WHO scale 3–4) and severe COVID-19 survivors (inpatients, mechanical ventilation and/or intensive care unit (ICU) stay, WHO scale 5–8) (table 1) [22]. The variable list and stratification scheme is provided in the supplementary methods and supplementary table S1.

Serological markers were determined by the International Organization for Standardization-certified central laboratory of the University Hospital Innsbruck. C-reactive protein (CRP; elevated >0.5 mg·L^{-1}), interleukin (IL)-6 (elevated >7 pg·mL^{-1}), procalcitonin (elevated >0.15 µg·L^{-1}), N-terminal pro-brain natriuretic peptide (NT-proBNP; elevated >150 pg·mL^{-1}) and serum ferritin (elevated male $\geqslant$300 µg·L^{-1}, female $\geqslant$150 µg·L^{-1}) were determined using a Roche Cobas 8000 analyser (Basel, Switzerland) and D-dimer (elevated >500 µg·L^{-1}) with a Siemens BCS-XP instrument using the Siemens D-Dimer Innovance reagent (Erlangen, Germany). Anti-S1/S2 protein SARS-CoV-2 immunoglobulin (Ig)G was quantified with LIAISON chemoluminescence assay (DiaSorin, Saluggia, Italy), expressed as manufacturer's arbitrary units (AU) and stratified by quartiles (Q1: 0–54 AU, Q2: 54–109 AU, Q3: 109–168 AU, Q4: 168–1160 AU).

Analysis end-points
The primary, 1-year follow-up end-point was the evolution of 1) COVID-19 related symptoms; 2) LFT impairment; 3) CT abnormalities; or 4) TTE abnormality up to the 1-year follow-up in patients stratified by acute COVID-19 severity (table 2). The secondary end-points were measures of physical performance (6-min walk distance, fatigue), mental health and QoL.
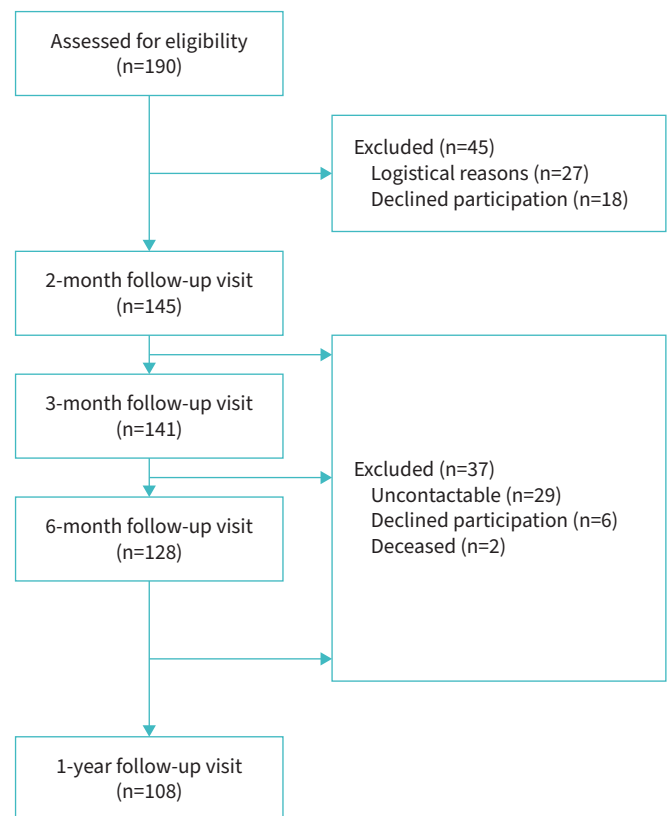
FIGURE 1 Flow diagram of study inclusion and analysis.

Statistical analysis

Numeric variables are presented as medians (interquartile range (IQR)). Categorical variables are presented as percentages of complete answers. Statistical analysis was performed using R (version 4.2.0; R Foundation for Statistical Computing). Differences in frequency distribution were determined using the Chi-squared test with Cramer V effect size statistic. Differences in numeric variables were analysed using the Mann–Whitney U-test with r effect size statistic or Kruskal–Wallis test with η^2 effect size statistic. Correlation was investigated with Kendall's τ-b test. Kinetics of binary variables were investigated with

TABLE 2 Key outcome measures of participants according to coronavirus disease 2019 (COVID-19) severity groups at the 1-year follow-up

	CovILD cohort	Ambulatory COVID-19	Moderate COVID-19	Severe COVID-19	Significance, p-value[#]	Effect size, Cramer V[#]
Symptoms present	65 (68) n=105	59 (16) n=27	67 (36) n=54	67 (16) n=24	NS (0.86)	0.068
LFT abnormality[¶]	33 (35) n=106	22 (6) n=27	32 (17) n=53	46 (12) n=26	NS (0.32)	0.18
CT abnormality (CT score ⩾1)[+]	51 (52) n=101	13 (3) n=23	52 (27) n=52	85 (22) n=26	<0.001	0.5
Diastolic dysfunction	63 (67) n=107	30 (8) n=27	69 (37) n=54	85 (22) n=26	0.001	0.42

Data are presented as % (n) or n, unless otherwise stated. LFT: lung function test; CT: computed tomography; NS: nonsignificant. [#]: COVID-19 severity groups compared with Chi-squared test with Cramer V effect size statistic; p-values corrected for multiple testing using the Benjamini–Hochberg method; [¶]: abnormality in LFT >80% predicted value (forced expiratory volume in 1 s (FEV_1), forced vital capacity (FVC); diffusion capacity of the lung for carbon monoxide; total lung capacity) or >70% predicted value cut-offs (FEV_1/FVC ratio); [+]: any abnormality in chest CT, severity score ⩾1.

second-order mixed-effect logistic modelling [23]. Time differences in numeric variables were assessed by Friedman test with Kendall's W effect size statistic. Clustering was accomplished with the partitioning around medoids (PAM) algorithm (simple matching distance) [24].

For multiparameter modelling, least absolute shrinkage and selection operator (LASSO) logistic regression was used [25, 26]; model performance in the training data and 10-fold cross-validation was evaluated by receiver operating characteristic [27, 28].

Results

Cohort characteristics

Out of 145 CovILD study participants, 108 completed the 1-year follow-up between 16 March and 1 June 2021 (median (IQR) 380 (370–390) days after diagnosis) (figure 1). Males constituted 59% of the collective and median (IQR) age was 56 (49–68) years. The fraction of overweight (body mass index (BMI) >25 kg·m^{-2}) or obese (BMI >30 kg·m^{-2}) participants was 62%; 37% of participants had a tobacco-smoking history. Comorbidities were present in 75% of participants, with metabolic (42%) or cardiovascular disease (40%) as leading conditions. Concerning acute COVID-19 severity, 25% of participants were classified as ambulatory, 51% as moderate and 24% as severe. Mild COVID-19 patients demonstrated a higher fraction of females, lower median age and fewer comorbidities than severe COVID-19 convalescents. One-third (32%) of participants attended COVID-19-related rehabilitation (table 1).

18.5% (n=20) participants with nonresolving pneumonia in the course of moderate or severe COVID-19 were administered systemic steroids at the discretion of the physician beginning from week 4 post-diagnosis (table 1). Such post-acute steroid therapy was found to be significantly associated with higher obesity and comorbidity rates and tended to be linked to more frequent dyspnoea, reduced physical performance, self-reported sleep problems and lung CT and LFT abnormalities in the long-term follow-up (data not shown).

Kinetics of symptom and cardiopulmonary recovery up to the 1-year follow-up

At the 1-year assessment, 65% of participants still suffered from COVID-19 related symptoms. The symptom frequencies did not differ significantly between acute disease severity subsets (table 2). The leading persistent complaints were reduced physical performance (39%), significant fatigue (36%), self-reported sleep disorders (29%) and exertional dyspnoea (23%) (figure 2a). Interestingly, longitudinal data analysis revealed a substantial deceleration of symptom recovery and relapse in the late convalescent period (6–12 months) as compared to the early convalescent period (0–3 months) in each COVID-19 severity subset (figure 2b). Protracted recovery was particularly evident for reduced physical performance and self-reported sleep problems (supplementary figure S1).

LFT impairment was detected in 33% of participants and tended to be more frequent in moderate and severe patients than in ambulatory participants (table 2). In the entire collective, FEV$_1$ (16%), FVC (15%) and D_{LCO} impairment (15%) were the most frequent findings. The fraction of individuals with D_{LCO} <80% pred tended to be higher in moderate and severe COVID-19 convalescents (figure 3a). A significant reduction frequency of LFT abnormality during the follow-up was discerned only in severe, but not in mild or moderate, COVID-19 (figure 3b).

At the 1-year follow-up, 51% of participants demonstrated any structural lung alterations (CT severity score ⩾1) and 18% had moderate-to-severe CT findings (CT severity score >5). The percentage of both any (Chi-squared test p<0.001 effect size: V=0.5) or moderate-to-severe alterations (Chi-squared test p<0.001, effect size V=0.45) were significantly linked to COVID-19 severity (table 2, figure 4a). Significant resolution of structural lung alterations was observed in the entire collective over time with the highest extent of recovery in moderate COVID-19 (λ=37; ambulatory λ=15; severe λ=12) (figure 4b).

Reduced cardiac ejection fraction in TTE, defined as left ventricular ejection fraction <55%, was found in only two (2%) patients. Nearly two-thirds of participants were affected by diastolic dysfunction (63%; grade I 58%; grade II 4.7%), with a significant association to COVID-19 disease severity (table 2, figure 5a). Furthermore, percentages of diastolic dysfunction increased significantly in the severe COVID-19 subset, especially between the 6-month and 1-year follow-up (figure 5b).

Physical performance, quality of life and mental health following COVID-19

Reduced exercise capacity in 6MWT was evident in 56% of the collective and comparable in the COVID-19 severity subsets. Self-perceived overall health rating (EQ-5D-5L VAS) was close to the generalised adult population [18, 29]. A great majority of the participants reported no deficits of mobility,
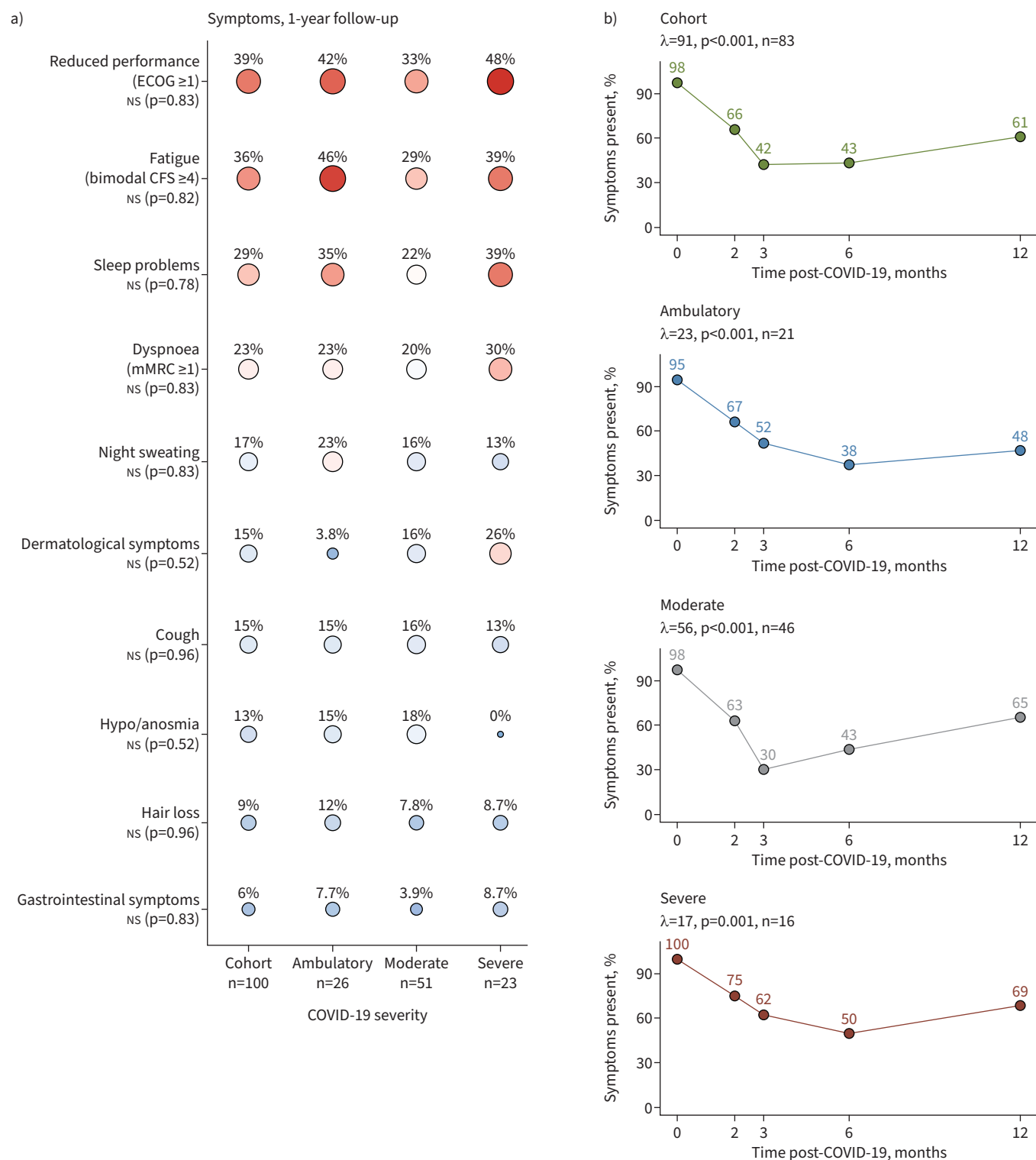
FIGURE 2 Coronavirus disease 2019 (COVID-19) symptom recovery. Presence of COVID-19 symptoms (reduced performance: Eastern Cooperative Oncology group score (ECOG) ⩾1; fatigue: bimodal Chalder Fatigue Score (CFS) ⩾4; dyspnoea: modified Medical Research Council (mMRC) score ⩾1; self-reported: sleep problems, night sweating, cough, hair loss, hyposmia/anosmia, dermatological and gastrointestinal symptoms) was analysed 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. Differences between the COVID-19 severity strata were investigated by Chi-squared test corrected for multiple testing using the Benjamini–Hochberg method. Percentages are represented by point size and colour code. 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- and 6-month and 1-year follow-up. Participants with the complete longitudinal dataset were included in the analysis. The symptom kinetic was

analysed by second-order mixed-effect logistic modelling and likelihood ratio test (full *versus* 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 dataset are presented. NS: nonsignificant.

self-care or usual activity (EQ-5D-5L). Yet, elevated pain/discomfort and anxiety/depression scores were observed in 36% and 28% of participants, respectively. Except for the somatic symptom disorder rating, which peaked in severe COVID-19, there were no significant differences in the investigated mental health readouts between the COVID-19 severity subsets (table 3).

Cardiopulmonary parameters (LFT, D_{LCO}, CT severity score, diastolic dysfunction) correlated neither with persistent symptoms nor with QoL, general health perception, stress or with exercise capacity assessed by 6MWT. Number of symptoms, dyspnoea, impairment of physical performance impairment and fatigue correlated significantly with poor self-perceived health, constrained usual activity, pain/discomfort as well as anxiety/depression and stress scoring. Self-reported sleep disorders were strongly associated with an impaired usual activity and, to a lesser extent, with anxiety/depression signs. Persistent cough correlated with poorer general health rating, impaired usual activity, pain/discomfort and anxiety/depression. Additionally, higher CT abnormality grading correlated with increased frequency of diastolic dysfunction and poorer D_{LCO} (figure 6). In a direct analysis of physical performance and mental health rating, participants with persistent COVID-19-related symptoms had significantly worse self-perceived general health, mobility, usual activity as well as higher scores of pain/discomfort, depression/anxiety and stress. By contrast, effects of cardiopulmonary abnormalities at the 1-year follow-up were not significant (supplementary figures S2 and S3).

COVID-19 recovery clusters
Three subsets of study participants, the COVID-19 recovery clusters, were identified by PAM algorithm [24] with respect to the presence of persistent symptoms, diastolic dysfunction, CT and LFT deficits, self-perceived stress and EQ-5D-5L measures of QoL, general and mental health (supplementary figure S4). The largest cluster (cluster 1) included individuals with nearly complete recovery from COVID-19 symptoms and cardiopulmonary deficits as well as excellent physical performance, mental health and QoL rating. In cluster 2, high symptom frequencies and 6MWT deficits were observed. Individuals in cluster 2 demonstrated only minor QoL and mental health deficits comparable with cluster 1. Patients in cluster 3 had the highest rates of 6MWT deficits and the highest burden of persistent symptoms, and one-third of them experienced a relapse of dyspnoea between the 6- and 12-month follow-up. Cluster 3 was additionally characterised by poor self-perceived health, low rating of usual activity as well as signs of pain/discomfort, depression/anxiety, mental stress and high levels of somatisation (SSD-12). Resilient coping (BRCS) was comparable between the recovery clusters (figures 7 and 8, supplementary figure S5). As identified by permutation importance analysis, the most influential clustering factors were impaired usual activity, signs of anxiety/depression, pain/discomfort, dyspnoea and presence of any persistent symptoms (supplementary figure S4C). Accordingly, the clusters differed primarily in mental health, QoL features and symptoms. There were no significant differences in diastolic dysfunction and LFT abnormalities across the clusters. Yet, the second cluster revealed an enrichment of structural cardiopulmonary findings, but without significant impact on quality of life or mental health (figures 7 and 8, supplementary figure S5). Concerning the demographic and clinical background, cluster 3 comprised mostly females and severe COVID-19 survivors with low median age. In turn, cluster 2 was predominantly male with high percentages of elderly and moderate COVID-19 convalescents (supplementary figure S6, supplementary table S3).

Prediction of long-term symptoms and cardiopulmonary abnormalities by demographic parameters and post-acute biomarkers
Symptom number, self-reported sleep problems during acute COVID-19 and elevated NT-proBNP at the 2-month follow-up were identified as the most important risk factors for persistent symptoms at the 1-year follow-up. Male sex, age 51–65 years and hypercholesterolaemia were linked to a lower persistent symptom risk. However, the sensitivity of symptom prediction was low (training data 0.44, cross-validation 0.2) (supplementary figure S7).

Elevated IL-6 and D-dimer at the 2-month follow-up, as well as comorbidity, were linked to higher risk, whereas male sex and night sweating during acute COVID-19 were associated with lower frequency of LFT findings (supplementary figure S8). Diabetes, male sex and reduced physical performance during acute COVID-19 were associated with higher radiological abnormality risk. Furthermore, high anti-S1/S2
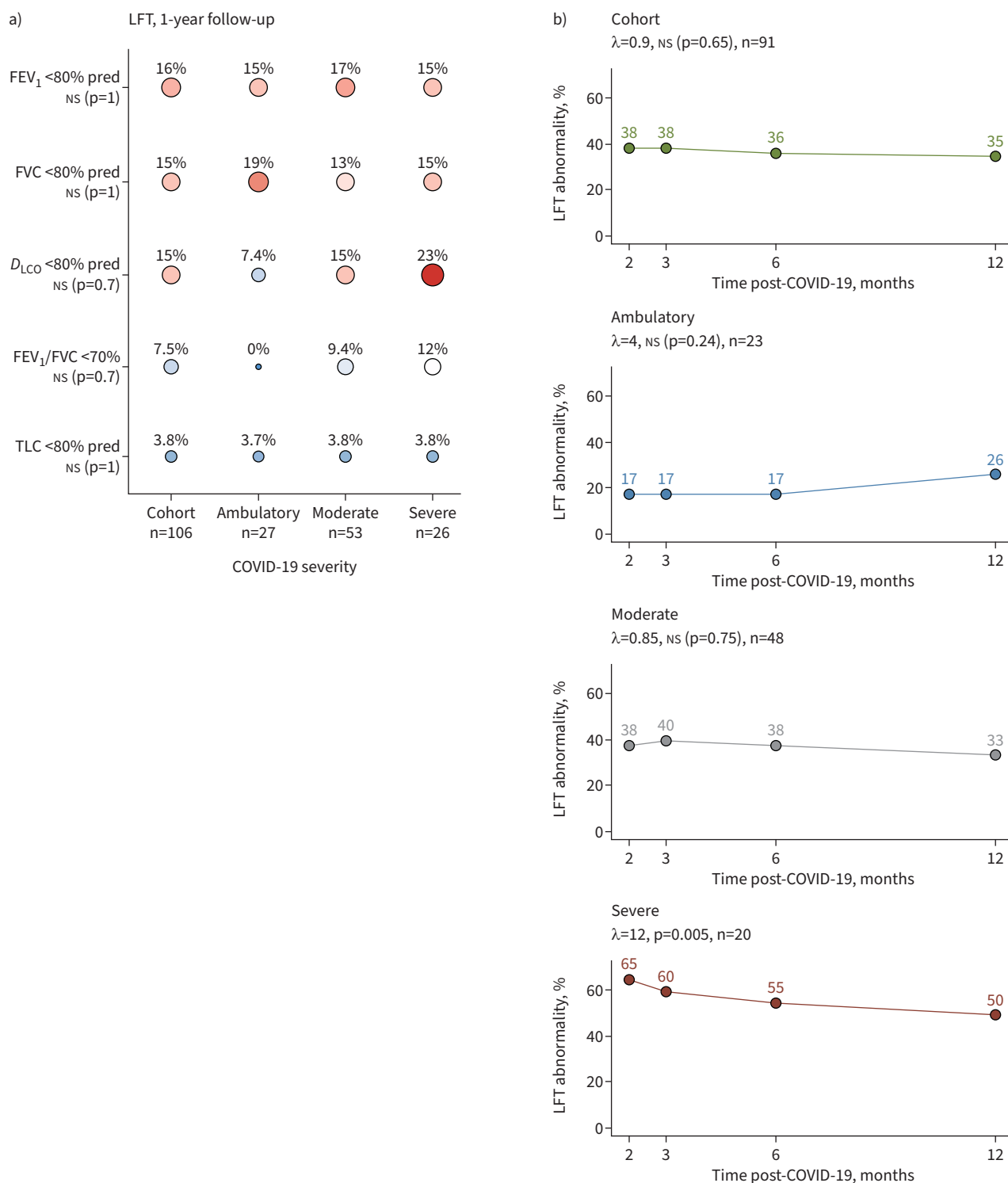
FIGURE 3 Functional lung recovery. Lung function testing (LFT) was analysed in the entire study collective and in ambulatory, moderate and severe coronavirus disease 2019 (COVID-19) survivors. a) Percentages of individuals with particular LFT abnormalities at the 1-year follow-up. Differences between the COVID-19 severity strata were investigated by Chi-squared test corrected for multiple testing using the Benjamini–Hochberg method. Percentages are represented by point size and colour code. p-values are displayed in the y-axis; numbers of complete observations are indicated in the x-axis. b) Percentages of individuals with any LFT abnormality (forced expiratory volume in 1 s (FEV_1), forced vital capacity (FVC), diffusion capacity of the lung for carbon monoxide (D_{LCO}) or total lung capacity (TLC): <80% predicted or FEV_1/FVC ratio <70% pred) at the 2-, 3- and 6-month and 1-year follow-up. Participants with the complete longitudinal dataset were included in the analysis. The LFT finding kinetic was analysed by second-order mixed-effect logistic modelling and likelihood ratio test (full versus null model). p-values were corrected for multiple testing using the Benjamini–Hochberg method. Likelihood ratio (λ), p-values and numbers of participants with the complete longitudinal dataset are presented. NS: nonsignificant.
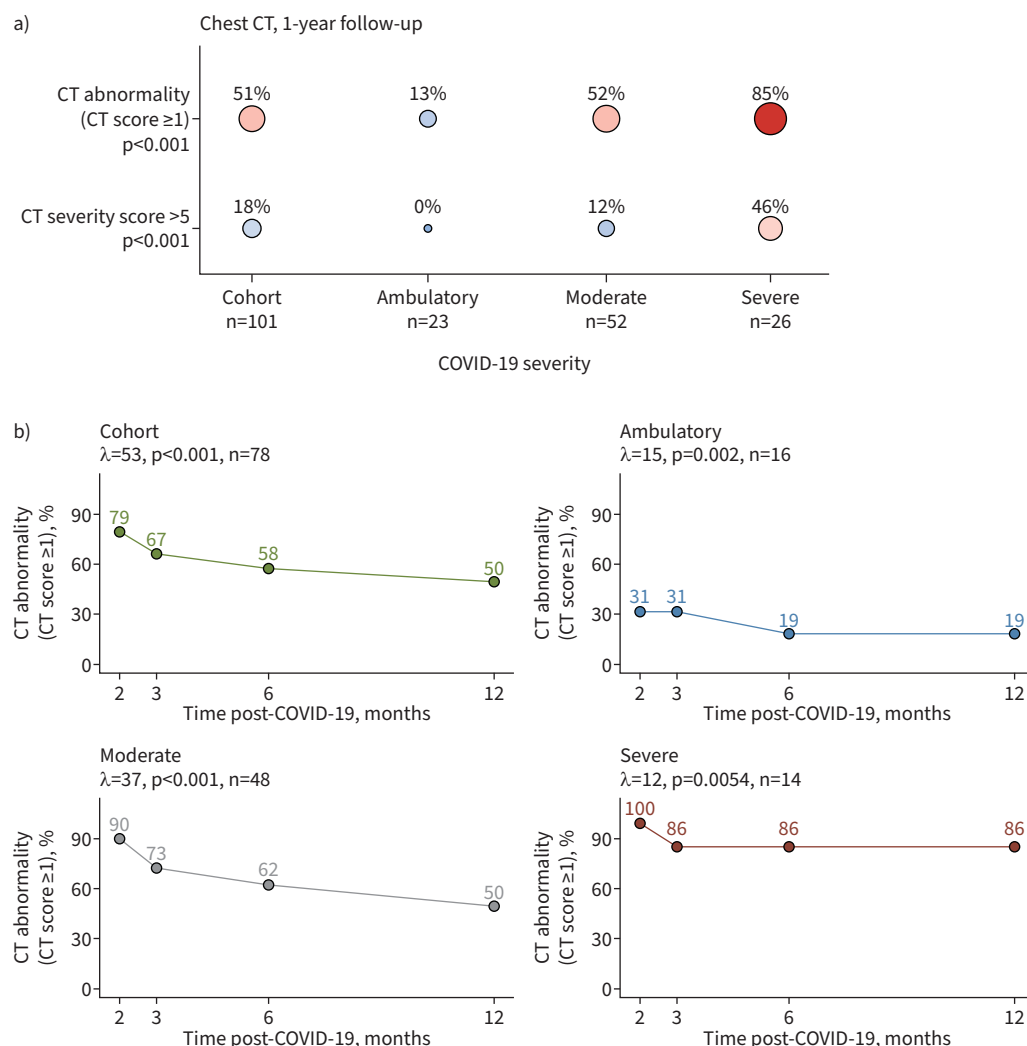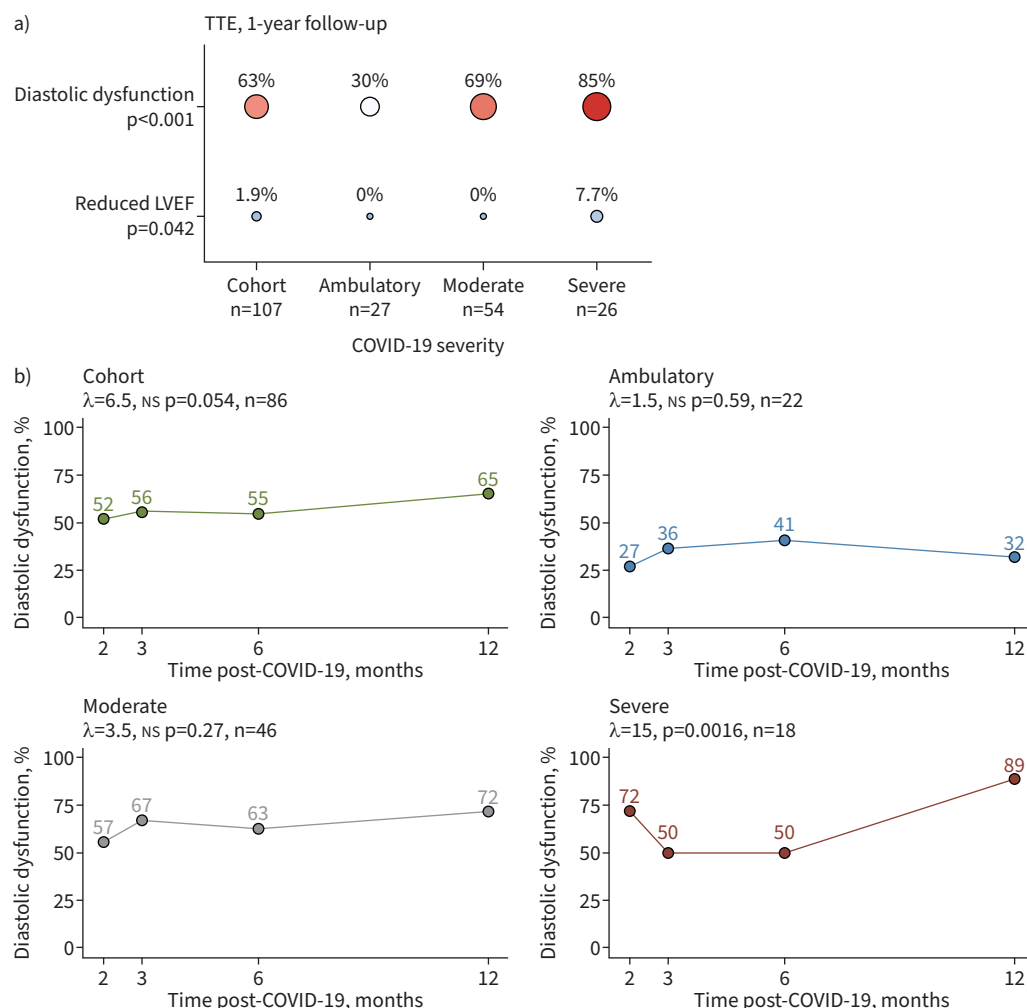
FIGURE 4 Radiological lung recovery. Chest computed tomography (CT) was analysed in the entire study collective and in ambulatory, moderate and severe coronavirus disease 2019 (COVID-19) survivors. a) Percentages of individuals with any chest CT abnormality (CT severity score ⩾1) and CT abnormalities scored >5 severity score points at the 1-year follow-up. Differences between the COVID-19 severity strata were investigated by Chi-squared test corrected for multiple testing using the Benjamini–Hochberg method. Percentages are represented by point size and colour code. 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- and 6-month and 1-year follow-up. Participants with the complete longitudinal dataset were included in the analysis. The CT finding kinetic was analysed by second-order mixed-effect logistic modelling and likelihood ratio test (full versus null model). p-values were corrected for multiple testing using the Benjamini–Hochberg method. Likelihood ratio (λ), p-values and numbers of participants with the complete longitudinal dataset are presented.

IgG titres (fourth quartile), elevated inflammatory (CRP, IL-6) and coagulation biomarkers (D-dimer) at the 2-month follow-up were unfavourable risk predictors for CT abnormalities (supplementary figures S9 and S10).

Discussion

Results of our longitudinal study in a mixed-severity COVID-19 patient collective show that the frequencies of symptoms, abnormal lung function, CT and cardiological findings declined substantially during early convalescence and reached a plateau 6 months after COVID-19. Specifically, for LFT and CT abnormalities and diastolic dysfunction, the frequencies at the 1-year follow-up were higher in severe

FIGURE 5 Cardiological recovery. Transthoracic echocardiography (TTE) was performed in the entire study collective and in ambulatory, moderate and severe coronavirus disease 2019 (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. Differences between the COVID-19 severity strata were investigated by Chi-squared test corrected for multiple testing using the Benjamini–Hochberg method. Percentages are represented by point size and colour code. 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- and 6-month and 1-year follow-up. Participants with the complete longitudinal dataset were included in the analysis. The diastolic dysfunction kinetic was analysed by second-order mixed-effect logistic modelling and likelihood ratio test (full *versus* null model). p-values were corrected for multiple testing using the Benjamini–Hochberg method. Likelihood ratio (λ), p-values and numbers of participants with the complete longitudinal dataset are presented. NS: nonsignificant.

COVID-19 than in ambulatory or moderate disease. Furthermore, presence of COVID-19-related symptoms was largely independent of cardiopulmonary findings and COVID-19 severity. Importantly, these persistent symptoms negatively affected patients' quality of life, exertional capacity and mental and self-perceived general health.

1 year after COVID-19, impaired LFT affected only a minority of patients, in line with recent studies [30–33]. Comparable to longitudinal reports there was a significant improvement over 12 months in severe COVID-19 survivors, but the frequency of patients with abnormal lung function plateaued at a higher level in the severe group [30, 32]. Among them, every fourth patient presented a reduced D_{LCO} that may reflect residual parenchymal damage and pulmonary vascular disease [34–36]. Although half of our patients displayed radiological lung alterations, no progressive or specific interstitial lung disease subtypes were

TABLE 3 12-month submaximal exercise performance and mental health across coronavirus disease 2019 (COVID-19) severity groups

|	CovILD cohort	Ambulatory	Moderate	Severe	Significance, p-value[#]	Effect size[#]
6MWD, m	550 (490–630; 270–760) n=102	580 (540–640; 400–740) n=26	540 (460–620; 270–760) n=51	520 (480–620; 310–700) n=25	NS (0.18)	η^2=0.034
6MWD versus ref., m	−13 (−75–42; −230–140) n=102	−27 (−83–25; −230–120) n=26	−3.6 (−63–47; −230–130) n=51	−25 (−67–39; −210–140) n=25	NS (0.5)	η^2=0.0013
6MWD <ref.	56 (57) n=102	62 (16) n=26	51 (26) n=51	60 (15) n=25	NS (0.74)	V=0.099
Fatigue score (Likert CFS)	12 (11–16; 0–32) n=101	11 (11–17; 0–26) n=27	12 (11–15; 1–24) n=51	13 (11–23; 1–32) n=23	NS (0.52)	η^2=−3.5e−05
Fatigue (bimodal CFS ⩾4)	37 (38) n=103	44 (12) n=27	31 (16) n=52	42 (10) n=24	NS (0.55)	V=0.13
General health score (EQ-5D-5L VAS)	85 (75–90; 40–100) n=102	85 (75–94; 40–100) n=27	85 (80–90; 50–100) n=51	80 (70–90; 40–100) n=24	NS (0.66)	η^2=−0.0071
Impaired general health (VAS <73, EQ-5D-5L)	19 (19) n=102	19 (5) n=27	14 (7) n=51	29 (7) n=24	NS (0.43)	V=0.16
Mobility impairment score (EQ-5D-5L)	1 (1–1; 1–3) n=103	1 (1–1; 1–2) n=27	1 (1–1; 1–3) n=52	1 (1–1.2; 1–3) n=24	NS (0.33)	η^2=0.013
Impaired mobility (score >1, EQ-5D-5L)	14 (14) n=103	11 (3) n=27	9.6 (5) n=52	25 (6) n=24	NS (0.32)	V=0.18
Self-care impairment score (EQ-5D-5L)	1 (1–1; 1–2) n=103	1 (1–1; 1–1) n=27	1 (1–1; 1–2) n=52	1 (1–1; 1–2) n=24	NS (0.32)	η^2=0.014
Impaired self-care (score >1, EQ-5D-5L)	2.9 (3) n=103	0 (0) n=27	1.9 (1) n=52	8.3 (2) n=24	NS (0.32)	V=0.18
Activity impairment score (EQ-5D-5L)	1 (1–1; 1–3) n=103	1 (1–1.5; 1–3) n=27	1 (1–1; 1–3) n=52	1 (1–2; 1–3) n=24	NS (0.18)	η^2=0.033
Impaired usual activity (score >1, EQ-5D-5L)	18 (19) n=103	26 (7) n=27	9.6 (5) n=52	29 (7) n=24	NS (0.18)	V=0.23
Pain/discomfort score (EQ-5D-5L)	1 (1–2; 1–4) n=103	1 (1–2; 1–3) n=27	1 (1–2; 1–4) n=52	1.5 (1–2; 1–4) n=24	NS (0.28)	η^2=0.019
Pain/discomfort (score >1, EQ-5D-5L)	36 (37) n=103	41 (11) n=27	27 (14) n=52	50 (12) n=24	NS (0.27)	V=0.2
Anxiety/depression score (EQ-5D-5L)	1 (1–2; 1–5) n=103	1 (1–2; 1–4) n=27	1 (1–1; 1–3) n=52	1 (1–2; 1–5) n=24	NS (0.23)	η^2=0.027
Anxiety/depression (score >1, EQ-5D-5L)	28 (29) n=103	30 (8) n=27	21 (11) n=52	42 (10) n=24	NS (0.32)	V=0.18
Stress score (PSS)	5 (3–8; 0–11) n=102	4 (1–6.5; 0–11) n=27	5 (2.8–8; 0–11) n=52	8 (5–9.5; 0–11) n=23	NS (0.061)	η^2=0.068
Elevated stress (PSS >5)	49 (50) n=102	33 (9) n=27	48 (25) n=52	70 (16) n=23	NS (0.15)	V=0.25
SSD-12	7 (3–13; 0–30) n=101	5 (2–10; 0–25) n=27	5 (2–9.8; 0–30) n=50	16 (6.8–22; 0–30) n=24	0.03	η^2=0.087
Resilience score (BRCS)	16 (13–18; 4–20) n=100	18 (14–19; 4–20) n=27	16 (12–18; 4–20) n=49	16 (14–17; 4–20) n=24	NS (0.23)	η^2=0.026
Resilience (BRCS)[¶]	100	27	49	24	NS (0.55)	V=0.14
Low	29 (29)	22 (6)	35 (17)	25 (6)		
Medium	26 (26)	19 (5)	27 (13)	33 (8)		
High	45 (45)	59 (16)	39 (19)	42 (10)		

Data are presented as median (interquartile range; range), n or % (n), unless otherwise stated. 6MWD: 6-min walk distance; ref.: reference value; CFS: 11-item Chalder Fatigue Score; EQ-5D-5L: European Quality of Life Five-Dimension Five-Level tool; VAS: visual analogue scale; PSS: 4-item Perceived Stress Scale; SSD-12: 12-item Somatic Syndrome Disorder – B criteria scale; BRCS: Brief Resilient Coping Score; NS: nonsignificant. [#]: comparison between the COVID-19 severity strata. Categorical variables: Chi-squared test with Cramer V effect size statistic; numeric variables: Kruskal–Wallis test with η^2 effect size statistic. p-values corrected for multiple testing using the Benjamini–Hochberg method. [¶]: low: 4–13 points, medium: 14–16 points, high: 17–21 points in the BRCS scale.

found [12]. As we showed recently, former ICU patients had the highest frequency of chest imaging abnormalities [12, 37]. Based on the plateau of radiological recovery curve after 6 months, we do not expect any further structural improvement in these patients.
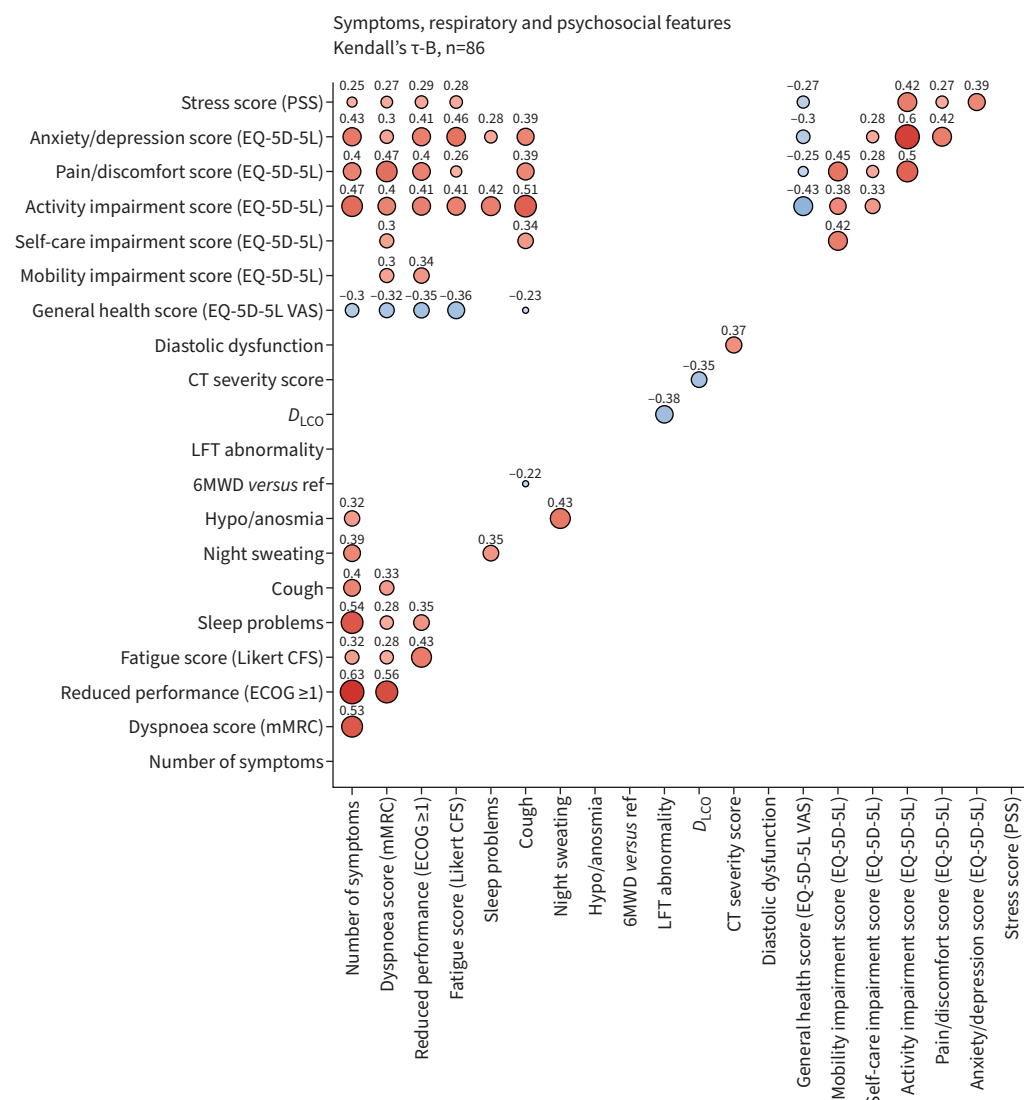
FIGURE 6 Correlation of symptoms, physical performance, cardiopulmonary findings, mental health and quality of life at the 1-year follow-up. Association of coronavirus disease 2019 (COVID-19) symptoms (number of symptoms; modified Medical Research Council (mMRC) dyspnoea score; reduced performance (Eastern Cooperative Oncology Group (ECOG) score ⩾1); Likert Chalder Fatigue Score (CFS); and self-reported sleep problems, cough, night sweating and hyposmia/anosmia); mobility (6-min walk distance (6MWD) *versus* the reference value (ref.)); any lung function testing (LFT) abnormality; diffusion capacity of the lung for carbon monoxide (D_{LCO}); chest computed tomography (CT) severity score; diastolic dysfunction; self-perceived general health (European Quality of Life Five-Dimension Five-Level (EQ-5D-5L) tool visual analogue scale (VAS)); quality of life and mental health scoring (EQ-5D-5L); and stress (four-item Perceived Stress Scale (PSS)) at the 1-year follow-up. Pairwise correlations were investigated using Kendall's τ-b test. p-values were corrected for multiple testing using the Benjamini–Hochberg method. τ coefficients for significant correlations are presented. τ-values are represented by point size and colour code. The number of complete observations is indicated.

The high prevalence of low-grade diastolic dysfunction in the CovILD cohort might reflect an exacerbating cardiopulmonary comorbidity as supported by age, comorbidity number and diabetes being risk factors for diastolic dysfunction in our cohort. Yet, correlation with anti-S1/S2 antibody titres and COVID-19 severity suggests that diastolic dysfunction may represent a late cardiac sequela of severe COVID-19 [38]. In line with our previous reports, comorbidities, male gender and elevated IL-6, D-dimer and anti-S1/S2 IgG levels at the 2-month follow-up are key risk factors of persistent cardiopulmonary findings at 1 year after COVID-19 [9, 39]. This defines potential biomarkers and time windows for future therapy trials, *e.g.* with anti-inflammatory drugs, to improve structural outcomes.
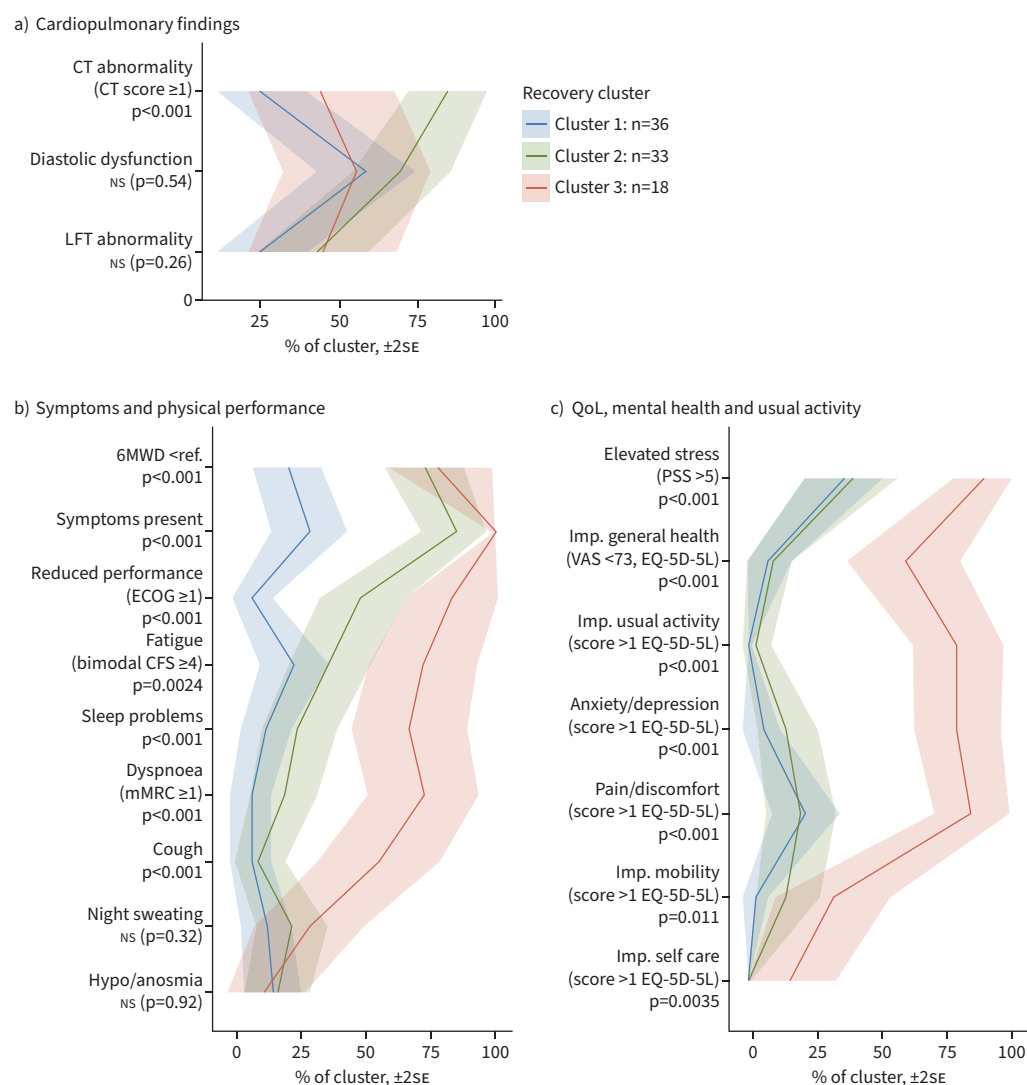
FIGURE 7 Coronavirus disease 2019 (COVID-19) recovery clusters. Clustering of the study participants in respect to symptoms (any symptom present; modified Medical Research Council (mMRC) dyspnoea score ⩾1; reduced performance (Eastern Cooperative Oncology Group (ECOG) score ⩾1); bimodal Chalder Fatigue Score (CFS) ⩾4; self-reported sleep problems, cough, night sweating and hyposmia/anosmia; mobility (6-min walk distance (6MWD) *versus* the reference value (ref.)); cardiopulmonary abnormalities (any chest computed tomography (CT) abnormality (CT severity score ⩾1); any lung function testing (LFT) abnormality; diastolic dysfunction); significant stress (four-item Perceived Stress Scale (PSS) >5); impaired self-perceived general health (impaired (imp.) European Quality of Life Five-Dimension, Five-Level (EQ-5D-5L) visual analogue scale (VAS) <73); as well as features of quality of life and mental health (EQ-5D-5L; cut-off score >1) at the 1-year follow-up. Clustering analysis was done with the partitioning around medoids algorithm, simple matching distance). Differences in frequency of the a) cardiopulmonary, b) symptom and mobility as well as c) self-perceived general health, quality of life (QoL) and mental health clustering variables between the recovery clusters were analysed by Chi-squared test. p-values were corrected for multiple testing using the Benjamini–Hochberg method. Lines represent the estimated percentages of the feature in the cluster, tinted regions represent 2×SEM intervals. p-values are indicated in the y-axis. NS: nonsignificant.

1 year after COVID-19, two-thirds of patients still suffered from COVID-19-related symptoms. Consistent with recent observations, the burden of both respiratory and nonrespiratory complaints did not differ between severity groups [33, 40]. Specifically, we confirm that respiratory symptoms such as dyspnoea and cough are among the most prevalent symptoms with high relevance for quality of life and mental and self-perceived general health [7, 33, 40, 41]. Unexpectedly, persistent symptoms, including respiratory
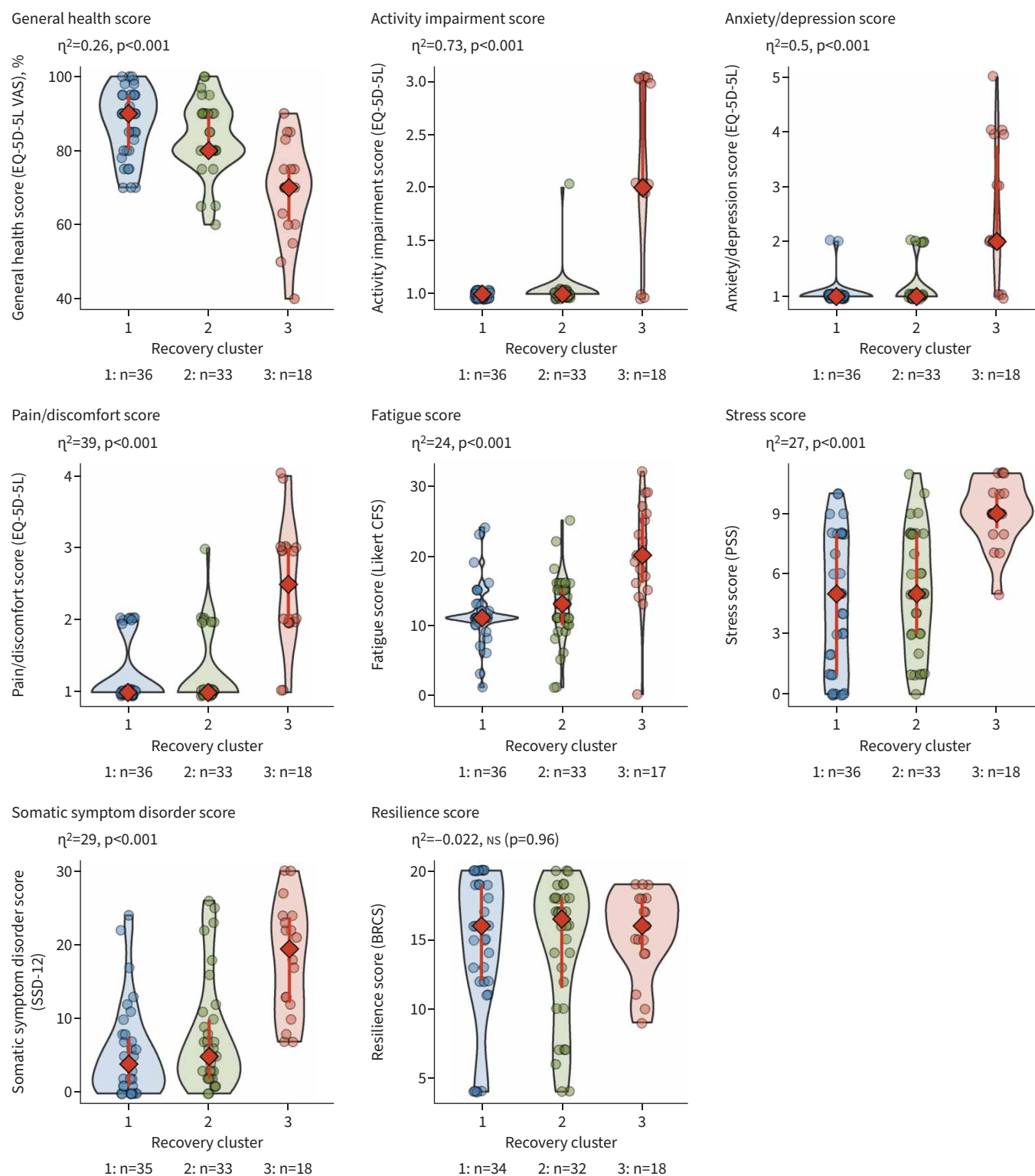
FIGURE 8 Quality of life, general health and rating of fatigue, stress, somatic symptom disorder and resilience were assessed at the 1-year follow-up and compared between the coronavirus disease 2019 (COVID-19) recovery clusters. Statistical significance was determined by Kruskal–Wallis test with η^2 effect size statistic. p-values were corrected for multiple testing with the Benjamini–Hochberg method. Effect size statistic, p-values and numbers of participants assigned to the clusters are presented. EQ-5D-5L: European Quality of Life Five Dimensions, Five Levels; VAS: visual analogue scale; CFS: Chalder Fatigue Score; SSD-12: Somatic Syndrome Disorder – B criteria scale; PSS: four-item Perceived Stress Scale; BRCS: Brief Resilient Coping Scale; NS: nonsignificant.

complaints, were neither associated with comorbidities, smoking history nor LFT deficits or residual chest CT abnormalities. Recent studies employing cardiopulmonary exercise testing could not elaborate a consistent pattern of cardiopulmonary findings correlating with the sensation of dyspnoea [42]. Analogously, functional or structural cardiopulmonary findings were not associated with exertional capacity assessed by 6MWT.

These observations are corroborated by clustering, which revealed three recovery phenotypes. In line with a recent report, a large subgroup of patients demonstrated almost complete recovery at physical and mental levels [33]. A second group revealed persistent symptoms and an enrichment of structural cardiopulmonary findings, but without significant impact on quality of life or mental health. A third, female-dominated phenotype faced persistent symptoms, predominantly dyspnoea and fatigue, negatively affecting quality of life and mental health 1 year after COVID-19. The latter cluster well reflects major characteristics of the recent clinical case definition of the post-COVID-19 condition and highlights a phenotype that is mechanistically poorly understood and a major challenge in post-COVID-19 follow-up [4]. The elevated scores for somatisation in the individuals grouped in cluster 3 is consistent with the concept of a functional aetiology. This group showed sufficient recovery on ancillary investigations but on the other hand high symptom burden and a striking proportion of dyspnoea relapses, which are characteristic for psychosomatic conditions (*e.g.* dysfunctional breathing). All of these findings indicate that clinical management of such individuals requires early physical and mental rehabilitation.

Our study bears limitations. Participant enrolment took place in the early phase of the pandemic, prior to the emergence of SARS-CoV-2 variants and widespread use of early corticosteroids/anticytokine therapies, vaccination programmes and novel antiviral treatments that are now considered standard of care. Thus, a generalisation to all disease courses has to be made with caution. In particular, as steroid therapy was nonsystemically administered in cases of nonresolving pneumonia, we were not able to corroborate therapeutic effects of such intervention on cardiopulmonary recovery. Furthermore, objectified findings prior to COVID-19 infection and a control cohort that can address SARS-CoV-2 specificity are lacking. Despite these aspects, and low a sample size with a considerable dropout rate at 12 months, the longitudinal character consistently reflected trajectories of symptoms, function, and imaging after COVID-19.

In summary, we present a comprehensive description of the temporal resolution of symptoms, functional and structural cardiopulmonary abnormalities in the first 12 months of COVID-19 convalescence. 6 months after COVID-19, the maximum recovery of pulmonary findings is widely reached. Residual functional and cardiopulmonary deficits are mostly mild, nonprogressive, remain subclinical and are predominantly found in severe COVID-19 survivors with protracted elevation of inflammation, coagulation and immunological biomarkers at the early follow-up. Independent of acute COVID-19 severity and residual cardiopulmonary findings, the interaction of persistent symptoms, dyspnoea, fatigue, reduced physical performance, mental health and quality of life needs to be addressed by a multidisciplinary rehabilitation approach.

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