# Enhancing quality of life in severe post-COVID-19 survivors through multidisciplinary care

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**Tailored multidisciplinary care is pivotal in enhancing meaningful outcomes, such as health-related quality of life and symptom burden, following severe COVID-19** https://bit.ly/4aZWoWR

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## Abstract

***Background*** COVID-19 survivors who were hospitalised continue to experience long-term multisystemic sequelae and symptoms, impacting their health-related quality of life (HRQoL). The complexity of post-COVID-19 conditions underscores the importance of adopting a multidisciplinary, patient-centric approach to ensure ongoing care. This study aims to assess HRQoL and post-COVID symptoms in a cohort of severe COVID-19 survivors depending on their participation in a multidisciplinary programme.

***Methods*** This prospective study was conducted in a post-COVID clinic staffed by a multidisciplinary team (physical rehabilitator, nutritionist, psychologist, including experts in pulmonary rehabilitation, nutrition, psychology and others). Subjects over 18 years old who were hospitalised due to severe COVID-19 during the acute phase and had attended the post-COVID clinic within the first 3 months following discharge were included. Subjects who were unable or unwilling to provide informed consent to participate in the protocol were excluded. Linear mixed-effect models were employed to examine changes in 12-Item Short-Form Health Survey (SF-12) component scores. The resolution of post-COVID symptom clusters was compared using the Cox model.

***Results*** A total of 730 patients were included, with a mean±SD age of 55.78±15.43 years; 60.55% were male and 90.62% required mechanical ventilation during hospitalisation. Programme attendants demonstrated improved SF-12 physical and mental component scores at 3 and 12 months. A reduction in the prevalence of post-COVID symptoms was observed in both groups, with greater reductions in those attending the programme.

***Conclusion*** Our study showed that patients enrolled on the multidisciplinary programme experienced improvements in fatigue, musculoskeletal, gastrointestinal, neuropsychiatric and respiratory symptoms, along with enhanced SF-12 mental and physical component scores.

## Introduction

In Mexico, COVID-19 became the leading cause of death in 2020–2021 [1], with fatality rates ranging from 20% to 50% among hospitalised patients suffering from severe forms of the disease [2]. It has been observed that ∼60–80% of COVID-19 survivors who were hospitalised continue to experience long-term multisystemic sequelae and associated symptoms [3, 4]. When these symptoms persist for >2 weeks and extend beyond 3 months after the initial infection, they are classified as post-COVID-19 conditions [5]. The persistence of these symptoms, including dyspnoea, weakness and fatigue, has been associated with increased healthcare costs, reduced patient and caregiver productivity [6], and an elevated risk of adverse outcomes such as disability [7], and diminished quality of life [8].

The complexity of post-COVID-19 conditions underscores the importance of adopting a multidisciplinary, patient-centric approach to ensure ongoing care, prevent long-term morbidity and mortality [9], and facilitate a swift return to daily life for affected individuals.

Critically ill patients due to severe COVID-19 may experience post-intensive care syndrome [10], which encompasses physical, cognitive and mental impairments that could continue into the long term [11] and negatively affect quality of life. Strategies targeted to improve recovery in this specific group of patients may impact these outcomes and have emerged as a priority after the pandemic [12].

Multidisciplinary programmes tailored to COVID-19 survivors aim to provide comprehensive care that enables patients and healthcare institutions to achieve meaningful outcomes [13, 14]. In addition to addressing a wide range of symptoms, these programmes also consider patient-reported outcomes (PROs), including health-related quality of life (HRQoL) and post-COVID symptoms, to assess the effectiveness of interventions [15]. These PROs offer valuable insights into the well-being and recovery experiences of patients [16], playing a pivotal role in enhancing healthcare systems [17].

This study aims to assess HRQoL and post-COVID symptoms persistence in a cohort of COVID-19 survivors receiving care at a post-COVID clinic within a tertiary care institution. Our hypothesis is that multidisciplinary interventions provided to severe COVID-19 survivors will lead to improvements in PROs.

## Methods

The strengthening of the reporting of observational studies in epidemiology (STROBE) checklist was employed to report this study [18]. The study was conducted in accordance with the Declaration of Helsinki, and approved by the Ethics Committee of the Instituto Nacional de Enfermedades Respiratorias “Ismael Cosío Villegas” (approval number: C57–21). All participants provided informed consent.

### *Study design*

This is a prospective study conducted as part of a clinical programme designed to improve long-term outcomes in severe COVID-19 survivors. In response to the early months of the pandemic, a post-COVID clinic was established at a tertiary-level referral centre dedicated to patients experiencing sequelae from severe COVID-19. This clinic is staffed by a multidisciplinary team, including experts in pulmonary rehabilitation, nutrition, psychology and various medical specialties (figure 1). The initial visit comprises three appointments, which are regularly scheduled for patients approximately 10 to 12 weeks after their hospital discharge. The evaluation will be conducted over 18 months of follow-up, with a focus on improvements in HRQoL and post-COVID symptoms over time and an exploration of factors associated with the persistence of poor outcomes during follow-up.

At the first appointment, patients undergo a comprehensive battery of medical examinations, in accordance with international guidelines, aimed at detecting systemic sequelae associated with COVID-19 [9]. These examinations include blood tests, lung computed tomography scans and pulmonary function tests. Subsequently, during the second appointment, patients receive assessments from nutritionists, rehabilitation physicians and psychologists. Those patients who require treatment by these specialties receive follow-up. In addition, patients identified as requiring care from another medical specialty, such as nephrology, gastroenterology, psychiatry, geriatrics, neurology, endocrinology or haematology, were referred. A follow-up or second appointment is scheduled with primary care physicians approximately 3 months following the initial assessment. At the third appointment, otolaryngology and respiratory medicine specialists assess the presence of upper and lower respiratory sequelae to determine the patient’s treatment plan. All patients received tailored interventions according to identified needs by each discipline, receiving rehabilitation sessions, psychological interventions, nutrition assessment and treatment, and specialised medical management for the identified sequelae.

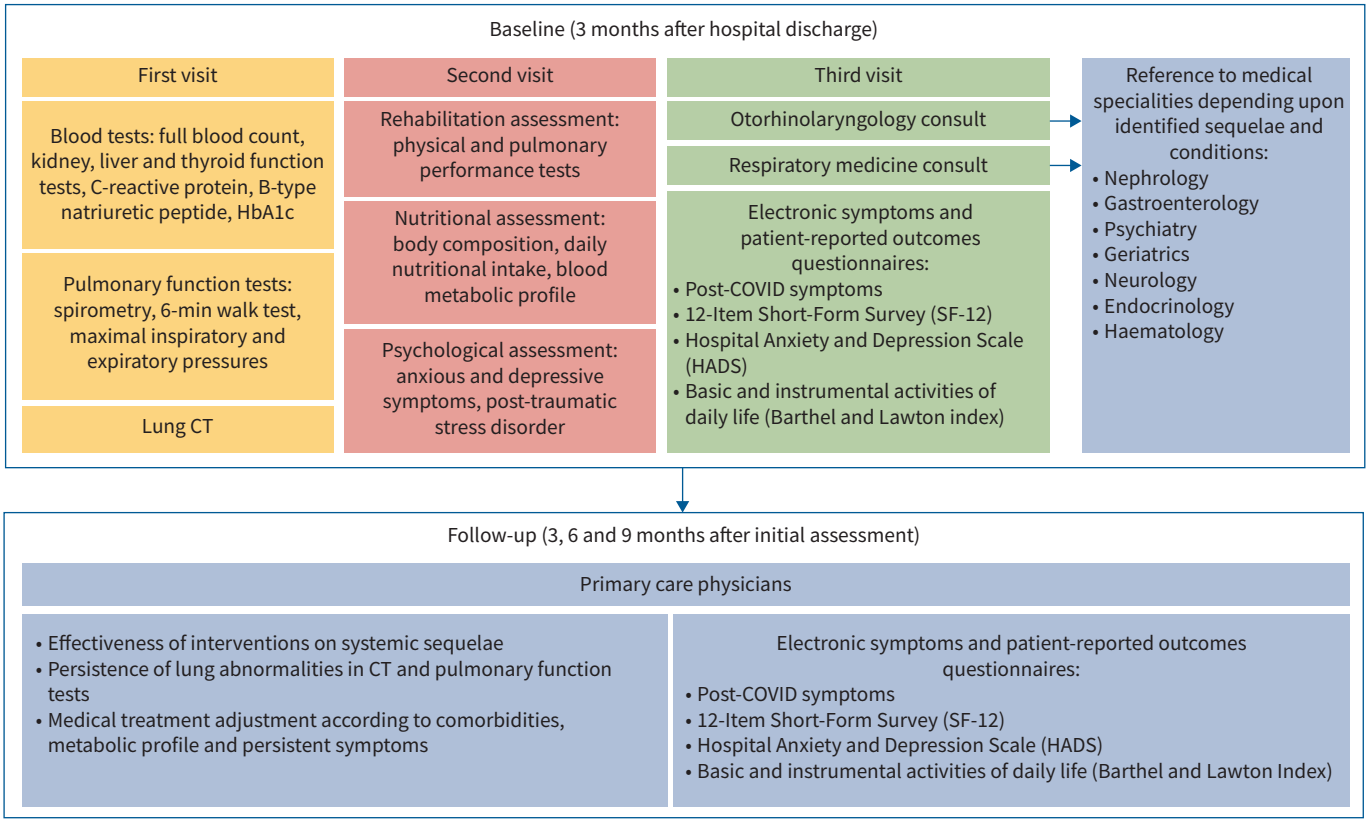


**FIGURE 1** Post-COVID clinic pathway. Post-COVID patients participated in a multidisciplinary programme that encompassed nutritional, psychological and rehabilitation interventions, in addition to tailored medical specialist care based on identified requirements. CT: computed tomography.

Patients were classified as having completed the multidisciplinary assessment if they attended all the baseline appointments and consultations with medical specialists.

### *Participants*

Patients 18 years and older hospitalised in a tertiary care centre due to severe COVID-19 underwent an initial assessment as part of our programme, typically occurring around 12 weeks after discharge. COVID-19 diagnosis was confirmed through a PCR test using an oropharyngeal swab upon hospital admission. Every patient was hospitalised between 2020 and early 2021, and received standardised management for that time, which consisted mainly of steroids, anticoagulants and ventilatory support. Patients who were unable or unwilling to provide informed consent to participate in the protocol were excluded. Before the first appointment, patients were screened through our telemedicine platform to detect any early complications post-hospitalisation. The 3-month period allowed us to evaluate longer-term consequences known as post-COVID conditions based on the World Health Organization consensus [5]. Consecutive sampling was employed.

### *Data collection*

A list of post-COVID symptoms, in accordance with the initial reports on long-COVID-19, was presented to patients to identify any sequelae and provide suitable management. Additionally, various other PROs, such as HRQoL, were investigated. The initial visit survey encompassed demographic information, including age, sex, employment status, educational background, place of residence and medical history, which incorporated comorbidities and COVID-19 vaccination status. Information regarding the severity of the infection, interventions during hospitalisation and ventilatory support requirements was sourced from both medical records and patient accounts.

### *Outcomes*

We evaluated HRQoL using the 12-Item Short-Form Health Survey (SF-12) [19], a Spanish-validated instrument [20]. This abbreviated version of the 36-Item Short-Form Health Survey comprises 12 items

with 3–5 point Likert scales and assesses eight dimensions, encompassing general health, vitality, physical and social functioning, bodily pain, physical and emotional role, and mental health.

A survey regarding post-COVID symptoms was carried out by considering the primary long-term effects of COVID-19 or post-COVID condition [21]. The list of post-acute sequelae after SARS-CoV-2 infection is based on the most prevalent symptoms identified in a cohort of 1990 patients, including fatigue, brain fog, dizziness, palpitations, weakness, headaches, tremors, and muscle and abdominal pain [21]. Responses were gathered in a binary format to signify whether these symptoms were present or absent. To identify common patterns of post-COVID symptoms, they were categorised by systemic involvement in neuropsychiatric (cognitive complaints, headache, anxious symptoms, depressive symptoms, insomnia), cardiovascular (angina, palpitations, lower limbs oedema), musculoskeletal (muscular weakness, osteomuscular pain), gastrointestinal (abdominal pain, diarrhoea, constipation, appetite loss, nausea) and respiratory symptoms (dyspnoea, pleuritic pain, cough, wheezing), as determined through health database analyses [22]. A cluster was considered present if the patient had any of the symptoms in that group and absent if they did not exhibit any of those symptoms.

Responses to the surveys were documented on the REDCap system during each quarterly evaluation. The initial responses were collected in face-to-face meetings when patients attended their first appointment, whereas primary care physicians carried out follow-up assessments remotely.

### *Statistical analysis*

Categorical variables were presented as frequency (%), while continuous variables were expressed as mean±SD or median (interquartile range) as appropriate. The normality of distribution was assessed using the Kolmogorov–Smirnov test. Comparisons between two groups were conducted using the Chi-square or exact Fisher test as needed for categorical variables, and t-test and Mann–Whitney U test for normally parametric and non-parametric continuous variables, respectively.

The SF-12 questionnaires were scored using the standard algorithm [23], to derive both Physical and Mental Health Component Scores. The questionnaire items were scored and weighted to calculate the aggregate scores.

In this study, we employed a mixed-effects maximum likelihood regression model to analyse the relationship between SF-12 scores, a measure of physical HRQoL, and various independent variables assessed at the first evaluation. The independent variables included age, sex, ischaemic heart disease, ventilatory mechanical support, smoking history, COVID-19 immunisation, diabetes, hypertension and COPD. This analysis was conducted in relation to attendance at the multidisciplinary post-COVID programme, and marginal plots were used to validate the model's assumptions.

A comparison of the differences in the resolution of post-COVID symptom clusters between patients who attended and those who did not attend the multidisciplinary programme was performed using Kaplan–Meier curves and the log-rank test. A univariable and multivariable Cox proportional hazards model for recurrent event data was conducted to identify risk factors for symptom cluster resolution, using interval-censored and goodness-of-fit tests to assess the proportional hazards assumption. The multivariate models were adjusted by bivariate analysis for variables with $p<0.20$ (supplementary material). Results were reported as hazard ratios (HR) with 95% confidence intervals (CI). Study data were collected and managed using REDCap electronic data capture tools hosted at Instituto Nacional de Enfermedades Respiratorias 'Ismael Cosío Villegas', REDCap [24, 25]. REDCap (Research Electronic Data Capture) is a secure, web-based software platform designed to support data capture for research studies, providing: 1) an intuitive interface for validated data capture; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages; and 4) procedures for data integration and interoperability with external sources.

All statistical analyses were carried out using STATA version 13 (Stata Corp., College Station, TX, USA). A p-value of <0.05 was considered statistically significant.

## Results

### *Patient characteristics*

910 patients were discharged following hospitalisation for severe COVID-19 during the study period. All patients were invited for an initial assessment upon discharge, scheduled with the assistance of the social work department. Among these, 816 patients met the inclusion criteria; however, 86 individuals (10.53%)

were lost to follow-up due to missing data. As a result, 730 patients were included in the subsequent analyses (figure 2).

Table 1 presents the baseline characteristics of the 730 patients, both those who attended and those who did not attend the multidisciplinary programme. The mean±SD age was 55.78±15.43 years, with 442 patients (60.55%) being male. All patients had experienced severe COVID-19 pneumonia, necessitating hospitalisation due to a high demand for oxygen supply. Of these patients, 662 (90.62%) required mechanical ventilatory support. The majority (n=510, 69.86%) had received the complete COVID vaccine regimen. The most prevalent comorbidity was hypertension (n=238, 32.60%), followed by diabetes (n=210, 28.77%), chronic lung disease (n=117, 16.03%) and ischaemic heart disease (n=42, 5.75%). No discernible differences were observed in baseline characteristics or comorbidities between the two groups.

A total of 418 (57.26%) participants responded to the 3-month follow-up, 226 (30.95%) at 6 months, 192 (26.30%) at 9 months, 402 (55.06%) at 12 months, 105 (14.38%) at 15 months and 140 (19.17%) at 18 months, respectively.

### *Health-related quality of life*

The SF-12 questionnaire scores revealed a predominant improvement in the initial 6 months, particularly in the mental component, and a gradual enhancement, especially within the first 12 months, for the physical component. A statistically significant difference was observed in the physical component score of the SF-12, with higher scores among those who engaged in the multidisciplinary programme at 3 months (43.06±9.73 *versus* 39.30±10.26, p=0.017). In terms of the mental component, a progressive enhancement

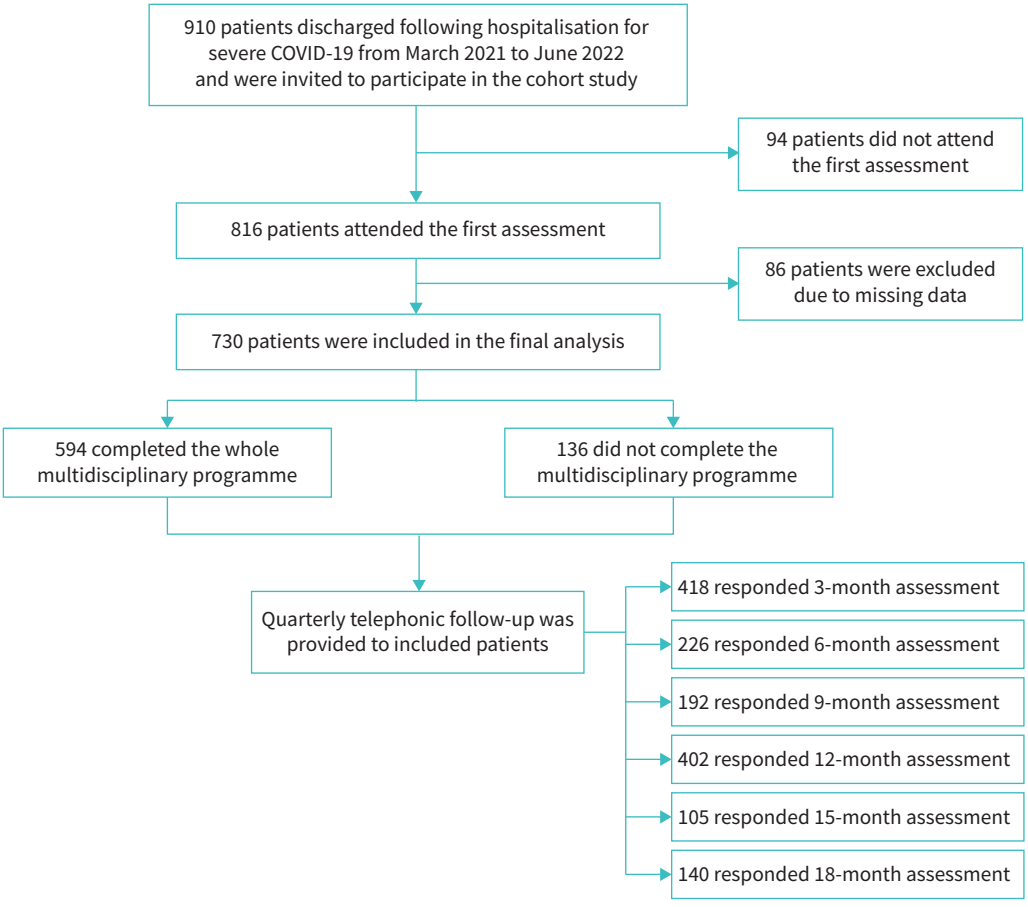


FIGURE 2 Flowchart of the post-COVID cohort. Upon discharge, patients who had been hospitalised for severe COVID-19 were offered participation in the multidisciplinary programme. Out of the 910 discharged patients, 730 were eligible for inclusion in the study. A total of 594 patients attended the multidisciplinary assessment, while 136 did not. Quarterly follow-ups by telephone were conducted to assess quality of life and symptoms.

**TABLE 1** Baseline characteristics of the study cohort

| | All | Programme non-attendants | Programme attendants | p-value |
|---|---|---|---|---|
| **Patients, n** | 730 | 136 | 594 | |
| **Age years, mean±SD** | 55.78±15.4 | 55.40±15.4 | 55.87±15.5 | 0.32 |
| **Male sex, n (%)** | 442 (60.6) | 79 (58.0) | 363 (61.1) | 0.52 |
| **With partner, n (%)** | 453 (62.1) | 85 (62.5) | 368 (62.1) | 0.98 |
| **COVID vaccine, n (%)** | 510 (69.9) | 94 (69.1) | 416 (70.0) | 0.79 |
| **Smoking history, n (%)** | 151 (20.7) | 28 (20.6) | 123 (20.7) | 0.68 |
| **Mechanical ventilation, n (%)** | 662 (90.6) | 121 (88.1) | 541 (91.0) | 0.45 |
| **Hypertension, n (%)** | 238 (32.6) | 48 (35.3) | 190 (31.1) | 0.46 |
| **Diabetes, n (%)** | 210 (28.8) | 45 (33.1) | 165(27.8) | 0.22 |
| **Chronic lung disease, n (%)** | 117 (16.0) | 29 (21.3) | 88 (14.8) | 0.07 |
| **Ischaemic heart disease, n (%)** | 42 (5.8) | 10 (7.4) | 32 (5.4) | 0.38 |
| **Thyroid disease, n (%)** | 43 (5.9) | 8 (5.9) | 35 (5.9) | 0.99 |

p-values are reported for comparison between attendants and non-attendants to the multidisciplinary programme.

in scores was noted within the initial 6 months, followed by a gradual decline at 12 and 18 months. A predominant improvement was observed in the group that participated in the multidisciplinary programme compared to those who did not at 3 months (54.60±8.47 *versus* 52.46±8.83, p=0.009) and 12 months (55.63±6.35 *versus* 52.96±8.18, p=0.013) (table 2).

The estimated adjusted differences in the physical and mental component score of SF-12 were significantly higher in those patients who attended the multidisciplinary programme *versus* those who did not attend (2.178 points/assessment, 95% CI 0.827–3.547, p=0.002 for the mental component and 2.638 points/assessment, 95% CI 1.419–3.857, p<0.001 for the physical component score) (figure 3).

In table 3 multivariate adjusted analyses show that the most substantial improvement was observed at the 15-month assessment for the physical component (10.41; 95% CI 7.877–12.958; p<0.001) and at 6 months for the mental component score (6.788; 95% CI 5.369–8.206; p<0.001). Scores in the physical component were adversely affected by comorbid conditions such as ischaemic heart disease (−4.559; 95% CI −6.515– −2.602), chronic lung disease (−5.251; 95% CI −7.615– −2.887) and hypertension (−1.624; 95% CI −2.641– −0.606).

These same comorbidities also had a detrimental impact on the SF-12 mental component scores, albeit to a lesser extent, resulting in a decrease of 4.443 points for ischaemic heart disease (95% CI −6.198– −2.688; p<0.001), 3.735 for chronic lung disease (95% CI −5.862– −1.609; p<0.001) and 0.983 points for hypertension (95% CI −1.898– −0.068; p=0.035).

In terms of the impact of post-COVID symptoms on HRQoL, the most significant adverse effects on the physical component score were observed in cases of fatigue (−5.498; 95% CI −6.464– −4.533; p<0.001), the respiratory symptoms cluster (−4.297; 95% CI −4.772– −3.815) and cardiovascular symptoms (−3.640; 95% CI −4.523– −2.757; p<0.001).

On the mental component score, the most substantial impacts were due to fatigue (−4.397; 95% CI −5.28– −3.515; p<0.001), the respiratory symptoms cluster (−2.723; 95% CI −3.171– −2.274) and cardiovascular symptoms (−2.532; 95% CI −3.331– −1.733; p<0.001) (table 3).

### *Post-COVID symptom clusters*

We observed a decrease in the prevalence of post-COVID symptoms in both groups, with a more pronounced reduction in patients who attended the post-COVID programme (figure 4). Kaplan–Meier survival curves were generated, accounting for age, sex, comorbidities and mechanical ventilation.

Sustained improvement in nearly every symptom cluster was noted throughout the entire follow-up period. Gastrointestinal symptoms, such as diarrhoea, nausea and abdominal pain, continued for up to 1 year post-discharge but displayed significant improvement following the 12-month assessment.

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**TABLE 2** Post-COVID symptom cluster and physical and mental composite subscores at baseline, 3-, 12- and 18-month assessments

| | First assessment | | | 3-month assessment | | | 12-month assessment | | | 18-month assessment | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Total | Programme attendants | Programme non-attendants | Total | Programme attendants | Programme non-attendants | Total | Programme attendants | Programme non-attendants | Total | Programme attendants | Programme non-attendants |
| **Patients, n** | 730 | 594 | 136 | 418 | 375 | 43 | 402 | 360 | 42 | 140 | 114 | 26 |
| **SF-12 physical subscore, mean±SD** | 38.2±11.1 | 38.7±11.1 | 37.1±10.7 | 42.7 ±9.8 | **43.1±9.7** | **39.3±10.3** | 47.9±21.9 | 47.9±8.5 | 47.4±9.2 | 46.7±9.8 | 46.6±9.8 | 47.1±27.5 |
| **SF-12 mental subscore, mean±SD** | 50.3±11.6 | 50.6±11.6 | 49±11.4 | 54.3±8.5 | 54.6±8.4 | 52.46±8.8 | 55.3±6.5 | **55.6±6.3** | **52.9±8.1** | 51.9±8.1 | 52.0±8.6 | 51.4±5.6 |
| **Fatigue** | 234 (32.0) | 176 (29.6) | 58 (42.6) | 121(28.9) | 108 (28.8) | 13 (30.2) | 98 (24.4) | 86 (23.9) | 12 (28.6) | 53 (37.9) | 43 (37.7) | 10 (38.5) |
| **Respiratory symptoms** | | | | | | | | | | | | |
| Dyspnoea | 492 (67.4) | 397 (66.8) | 95 (69.9) | 278 (66.5) | 245 (65.3) | 33 (76.7) | 193 (48.0) | 167 (46.4) | 26 (61.9) | 78 (55.7) | 65 (57.0) | 13 (50) |
| Pleuritic pain | 36 (4.9) | **24 (4.0)** | **12 (8.8)** | 19 (4.6) | 16 (4.3) | 3 (6.1) | 11 (2.7) | 11 (3.0) | 0 (0) | 7 (5) | 7 (6.1) | 0 (0) |
| Cough | 115 (15.6) | **80 (13.4)** | **35 (25.7)** | 79 (18.9) | 68 (18.1) | 11 (25.6) | 49 (12.1) | 45 (12.5) | 4 (9.5) | 32 (22.9) | 25 (21.9) | 7 (26.92) |
| Wheezing | 49 (6.7) | 39 (6.6) | 10 (7.4) | 11 (2.6) | **7 (1.9)** | **4 (9.3)** | 4 (1) | 3 (0.8) | 1 (2.4) | 4 (2.9) | 4 (3.5) | 0 (0) |
| **Neuropsychiatric symptoms** | | | | | | | | | | | | |
| Cognitive complaints | 101 (13.5) | **73 (12.3)** | **28 (20.6)** | 43(10.3) | 37 (9.9) | 6 (13.1) | 39 (9.7) | **33 (9.2)** | **6 (14.3)** | 26 (25.7) | 29 (25.4) | 7 (26.9) |
| Headache | 117 (16.0) | **85 (14.3)** | **32 (23.5)** | 50(12.0) | 42 (11.2) | 8 (18.6) | 24 (6.0) | 21 (5.8) | 3 (7.1) | 20 (14.3) | 16 (14.0) | 4 (15.3) |
| Anxious symptoms | 74 (10.1) | **51 (8.6)** | **23 (16.9)** | 24 (5.7) | 22 (5.9) | 2 (4.7) | 9 (2.2) | **6 (1.7)** | **3 (7.1)** | 13 (9.3) | 11 (9.7) | 2 (7.7) |
| Depressive symptoms | 69 (9.5) | 53 (8.9) | 16 (11.8) | 33 (7.9) | 28 (7.5) | 5 (11.6) | 19 (4.7) | 15 (4.1) | 4 (9.5) | 14 (10.00) | 12 (10.6) | 2 (7.7) |
| Insomnia | 92 (12.7) | **66 (11.1)** | **26 (19.1)** | 31 (7.9) | 26 (6.9) | 5 (11.6) | 12 (3.0) | 11 (3.1) | 1 (2.4) | 4 (4) | 4 (4.2) | 0 (0) |
| **Cardiovascular symptoms** | | | | | | | | | | | | |
| Angina | 31 (4.3) | **20 (3.4)** | **11 (8.1)** | 5 (1.2) | 5 (1.3) | 0 (0.0) | 4 (1) | 4 (1.1) | 0 (0) | 4 (2.9) | 4 (3.5) | 0 (0) |
| Palpitations | 38 (5.2) | 27 (4.6) | 11 (8.1) | 37 (8.9) | 32 (8.5) | 5 (11.6) | 24 (6.0) | 21 (5.8) | 3 (7.1) | 19 (13.6) | 17 (14.9) | 2 (7.7) |
| Lower limb oedema | 60 (8.2) | **41 (6.9)** | **19 (14.0)** | 43(10.2) | 36 (9.6) | 7 (16.3) | 34 (8.4) | 30 (8.3) | 4 (9.5) | 24 (17.1) | 22 (19.3) | 2 (7.7) |
| **Musculoskeletal symptoms** | | | | | | | | | | | | |
| Muscular weakness | 136 (18.6) | **102(17.1)** | **34 (25.0)** | 98(23.4) | 87 (23.2) | 11 (25.6) | 55 (13.7) | 50(13.9) | 5 (11.9) | 28 (2) | 20 (17.5) | 8 (30.8) |
| Osteomuscular pain | 87 (11.9) | **57 (9.6)** | **30 (22.0)** | 60(14.4) | 55 (14.7) | 5 (11.6) | 34 (8.5) | 31 (8.7) | 3 (7.1) | 13(10) | 12 (10.5) | 1 (3.9) |
| **Gastrointestinal symptoms cluster** | | | | | | | | | | | | |
| Abdominal pain | 42 (5.8) | **28 (4.7)** | **14 (10.3)** | 6 (1.4) | 6 1.6) | 0(0) | 3 (0.7) | 2 (0.6) | 1 (2.4) | 0(0) | 0 (0) | 0(0) |
| Diarrhoea | 50 (60.9) | 36 (6.1) | 14 (10.3) | 6 (1.4) | 6 (1.6) | 0(0) | 7 (1.7) | **3 (0.8)** | **4 (9.6)** | 2 (1.9) | 1 (1.1) | 1 (7.1) |
| Constipation | 78 (10.7) | 59 (9.9) | 19 (14.0) | 11 (2.6) | 10 (2.7) | 1 (2.3) | 2 (0.5) | 2 (0.6) | 0(0) | 0 (0) | 0 (0) | 0(0) |
| Appetite loss | 35 (4.8) | 25 (4.2) | 10 (7.4) | 5 (1.2) | 4 (1.1) | 1 (2.3) | 4 (1) | 4 (1.1) | 0(0) | 4 (2.9) | 4 (3.5) | 0(0) |
| Nausea | 30 (4.1) | 24 (4.0) | 6 (4.4) | 6 (1.4) | 5 (1.3) | 1 (2.3) | 1 (0.2) | 1 (0.3) | 0(0) | 6 (4.3) | 5 (4.4) | 1 (3.9) |

Data are presented as n (%) unless otherwise specified. Data in bold indicate a p-value <0.05. t-test or Mann–Whitney U test was performed to compare SF-12 scores according to programme attendance on each assessment. Chi-square or exact Fisher test as needed was employed to compare proportion of symptoms according to programme attendance on each assessment.

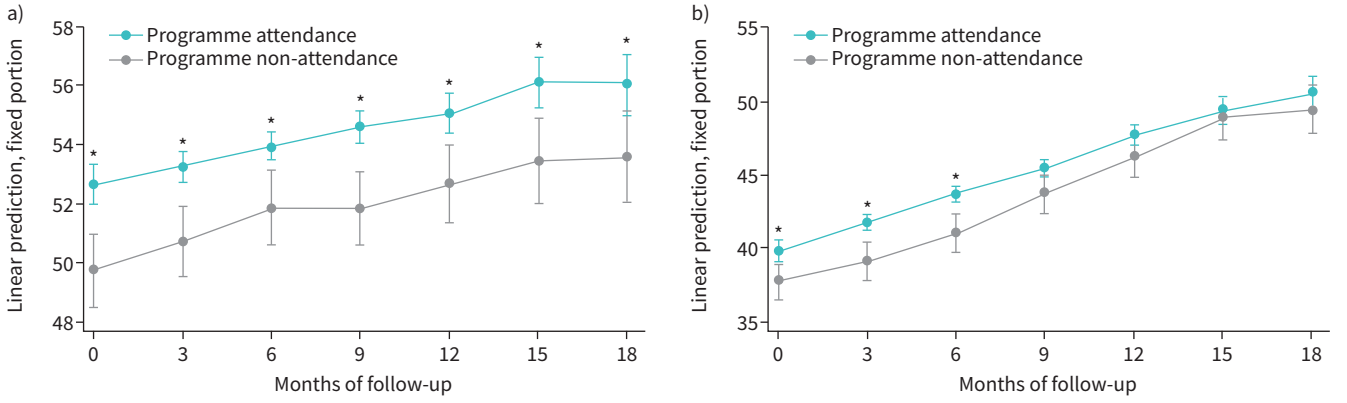


FIGURE 3 Linear mixed-effect model for changes in physical and mental composite scores of SF-12 among patients who participated in the multidisciplinary programme compared to those who did not. a) SF-12 mental composite score changes at follow-up according to programme attendance (regression coefficient 2.178 points/month, 95% CI 0.827–3.547, p=0.002). b) SF-12 physical composite score changes at follow-up according to programme attendance (regression coefficient 2.638 points/month, 95% CI 1.419–3.857, p<0.001). SF-12: 12-item short-form survey. *p<0.05.

### *Prognostic factors for post-COVID symptom clusters resolution*

After adjustment for baseline characteristics, covariates related to hospitalisation and comorbidities through Cox proportional hazards model for recurrent event data, attendance to the multidisciplinary programme was associated with greater improvement for post-COVID symptom clusters, conferring a HR of 0.81 (95% CI 0.68–0.96) for persistence of fatigue, HR 0.78 (95% CI 0.66–0.92) for persistence of respiratory symptoms, HR 0.62 (95% CI 0.46−0.83) for persistence of neuropsychiatric symptoms, HR 0.77 (95% CI

TABLE 3 Linear mixed-effect model for slope coefficient differences in physical and mental composite of SF-12 scores adjusted by programme attendance, months of follow-up, comorbidities and post-COVID symptom clusters

| | Regression coefficient of changes in physical composite SF-12 | 95% confidence interval | p-value | Regression coefficient of changes in mental composite SF-12 | 95% confidence interval | p-value |
|---|---|---|---|---|---|---|
| **Post-COVID programme attendance** | 2.2 | 0.8–3.5 | 0.002 | 2.6 | 1.4–3.8 | <0.001 |
| **3-month assessment** | 4.6 | 3.4–5.8 | <0.001 | 4.1 | 2.9–5.2 | <0.001 |
| **6-month assessment** | 6.2 | 4.7–7.7 | <0.001 | 6.8 | 5.4–8.2 | <0.001 |
| **9-month assessment** | 8.3 | 6.6–10.1 | <0.001 | 5.6 | 4.1–7.2 | <0.001 |
| **12-month assessment** | 9.6 | 8.3–10.8 | <0.001 | 5.1 | 3.9–6.3 | <0.001 |
| **15-month assessment** | 10.4 | 7.9–12.9 | <0.001 | 4.6 | 2.2–6.9 | <0.001 |
| **18-month assessment** | 8.9 | 7.2–10.8 | <0.001 | 1.7 | 0.1–3.3 | 0.048 |
| **Ischaemic heart disease** | −4.6 | −6.5– −2.6 | <0.001 | −4.4 | −6.2– −2.7 | <0.001 |
| **Chronic lung disease** | −5.3 | −7.6– −2.9 | <0.001 | −3.7 | −5.9– −1.6 | 0.001 |
| **Hypertension** | −1.6 | −2.6– −0.6 | 0.002 | −0.9 | −1.9– −0.1 | 0.035 |
| **Respiratory symptoms cluster** | −4.3 | −4.8– −3.8 | <0.001 | −2.7 | −3.2– −2.3 | <0.001 |
| **Fatigue** | −5.5 | −6.5– −4.5 | <0.001 | −4.4 | −5.3– −3.5 | <0.001 |
| **Gastrointestinal symptoms cluster** | −2.2 | −2.6– −1.8 | <0.001 | −2.5 | −2.9– −2.2 | <0.001 |
| **Cardiovascular symptoms cluster** | −3.6 | −4.5– −2.8 | <0.001 | −2.5 | −3.3– −1.7 | <0.001 |
| **Musculoskeletal symptoms cluster** | −2.6 | −3.1– −2.1 | <0.001 | −1.2 | −1.7– −0.8 | <0.001 |
| **Neuropsychiatric symptoms cluster** | −2.6 | −3.1– −2.2 | <0.001 | −5.8 | −6.4– −5.2 | <0.001 |

Factors with a p-value <0.10 by unadjusted analysis entered to adjusted analysis for age and sex.

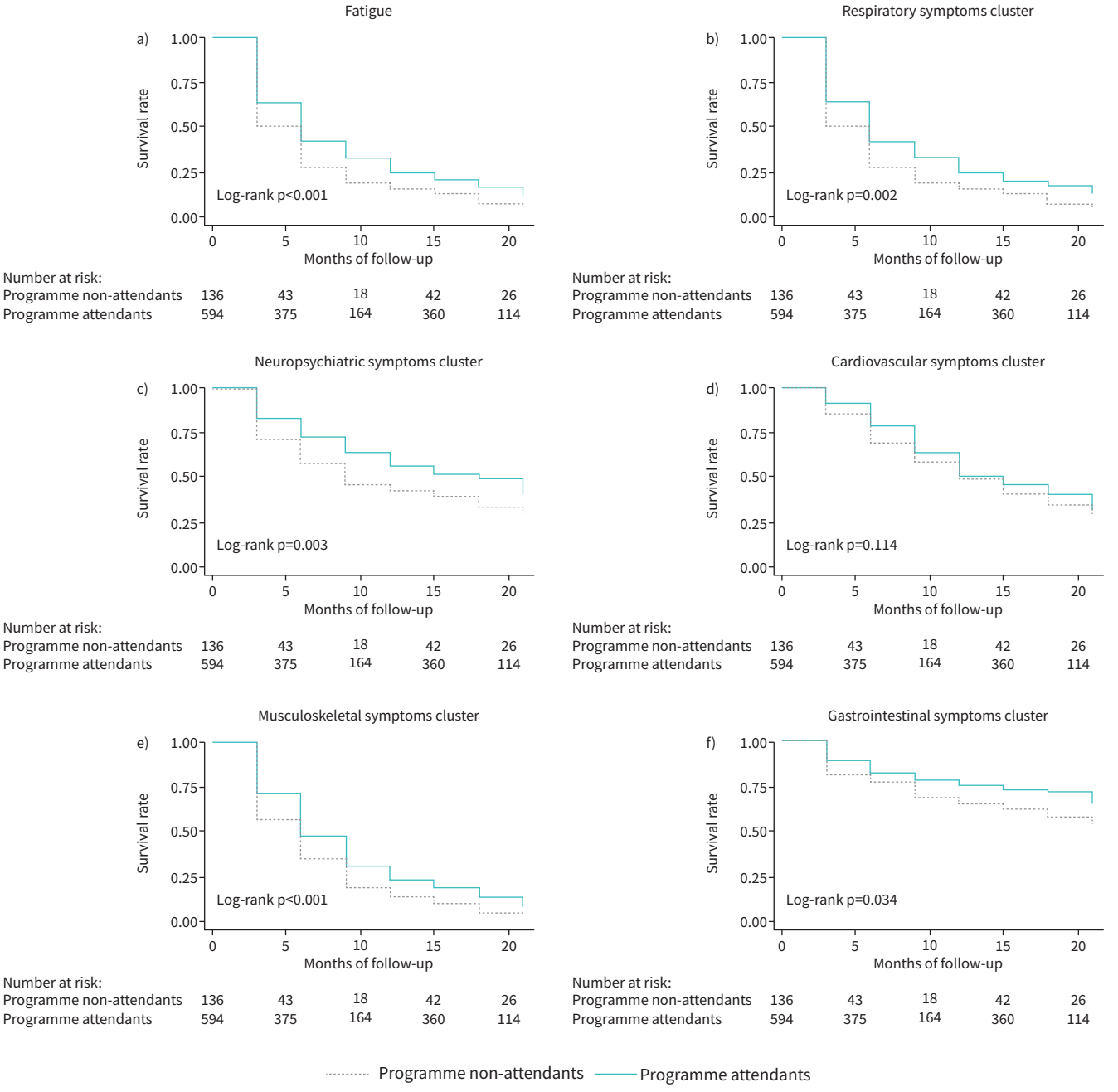


**FIGURE 4** Kaplan–Meier curves depicting time to resolution of post-COVID symptom clusters over 18-month follow-up, after adjustment by baseline characteristics and comorbidities. Overall resolution of post-COVID symptoms in patients who attended compared to patients who did not attend the multidisciplinary programme: a) fatigue (p<0.001), b) respiratory symptoms (p=0.002), c) neuropsychiatric symptoms (p=0.003), d) cardiovascular symptoms (p=0.114), e) musculoskeletal symptoms (p< 0.001) and f) gastrointestinal symptoms (p=0.034).

0.54–1.09) for persistence of cardiovascular symptoms, HR 0.74 (95% CI 0.60–0.90) for persistence of musculoskeletal symptoms and HR 0.69 (95% CI 0.47–1.00) for persistence of gastrointestinal symptoms (figure 5).

## Discussion

In this research, we have successfully elucidated the favourable impact of participation in a comprehensive, multidisciplinary programme. This programme incorporates psychological and nutritional interventions, physical and pulmonary rehabilitation, and consultations with medical specialists, and it is tailored to address the multifaceted consequences of severe COVID-19.

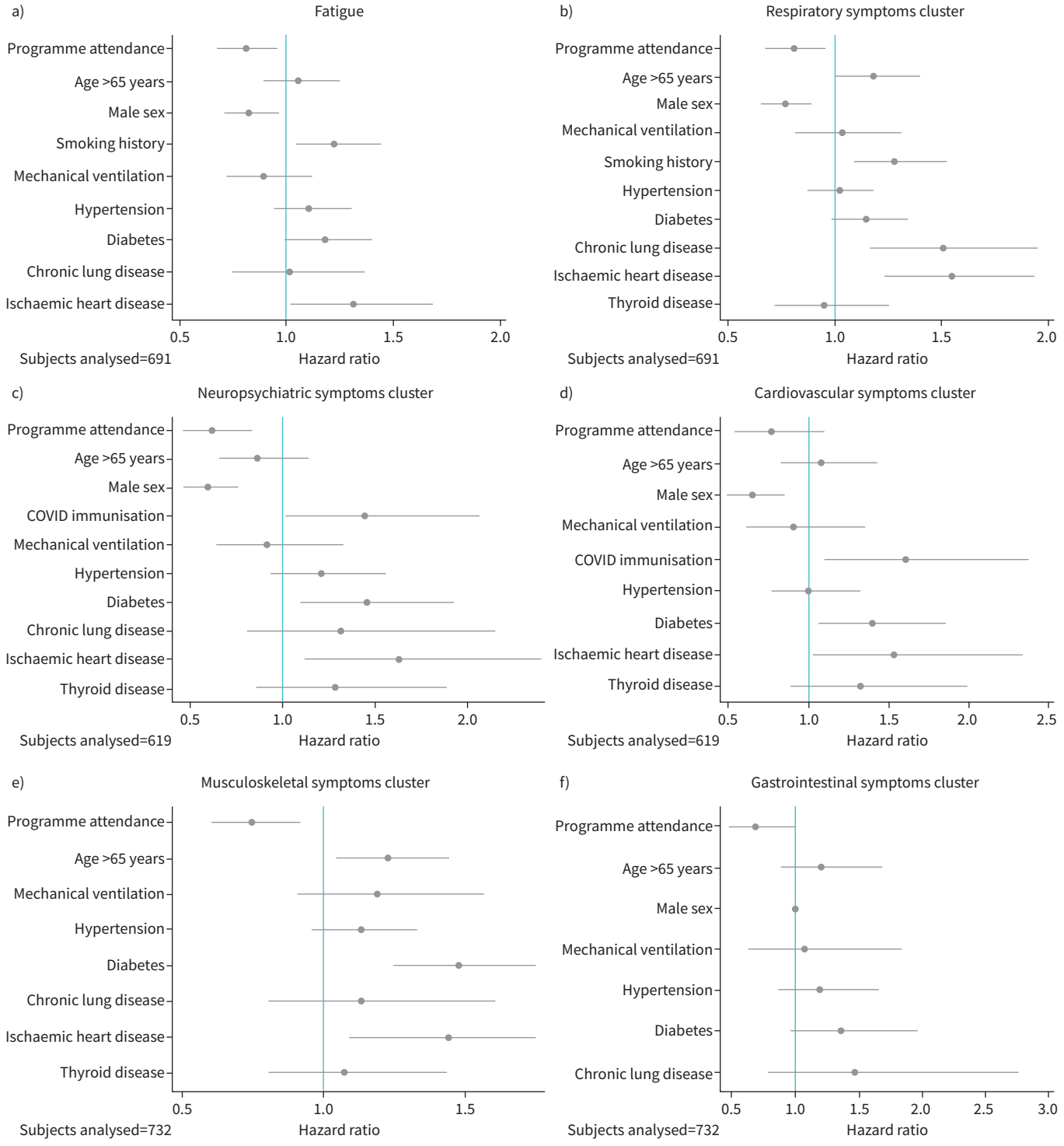


**FIGURE 5** a–f) Multivariate Cox proportional hazards model for recurrent event data for persistence of post-COVID symptom clusters at the end of follow-up in all patients included. A hazard ratio <1.0 indicates a greater probability of symptoms resolution. The multivariate models were adjusted by bivariate analysis for variables with p<0.20.

Individuals who have survived severe COVID-19 often encounter a substantial load of sequelae and multisystemic symptoms, which detrimentally impact their quality of life and hinder their capacity to reintegrate into their daily activities [26]. Despite the high symptom burden observed at the outset of the study, the multidisciplinary programme significantly benefited all symptom clusters.

The advantages of participating in the comprehensive assessment remained evident for up to 1 year after the commencement of the follow-up, with participants achieving higher scores on both the physical and mental components of HRQoL questionnaires right from the outset of the programme. The most substantial enhancements were noticed within the first 15 months for the physical component of HRQoL and at 6 months for the mental component. Certain comorbidities, such as ischaemic heart disease, chronic lung disease and hypertension, were associated with more modest improvements in these scores, underscoring the importance of personalised interventions for these patients and emphasising the necessity of attending integrated care programmes following a severe illness.

We did indeed observe a significant enhancement in the mental component of the SF-12 and the cluster of neuropsychiatric symptoms among programme participants. Within the multidisciplinary programme, a psychological screening was administered to identify symptoms of depression, anxiety and post-traumatic stress, followed by subsequent care for those requiring it. The interventions encompassed psychoeducation, cognitive-behavioural therapy [27] and biofeedback [28], all underpinned by a substantial body of evidence supporting their efficacy.

The psychiatry service extended medical follow-up to patients treated during their COVID-19 hospitalisation and to those referred by other departments within the post-COVID programme. A subset of these individuals received specialised, integrated treatment in external facilities, such as cognitive rehabilitation. The patient's progressive recovery is associated with a comprehensive restoration of functionality in critical life domains, including the physical, psychological, mental, social, occupational and academic spheres [29].

In the context of musculoskeletal alterations, the hypothesised mechanism in COVID-19 involves factors such as advanced age and pre-existing metabolic and inflammatory conditions, including diabetes, obesity, cardiovascular and pulmonary diseases, cancer, and so forth [30]. Besides, once the virus enters and replicates in cells, it disrupts cellular functions, leading to cell death and tissue dysfunction. In conjunction with hypoxia, proinflammatory cytokines in hypercatabolic conditions are associated with oxidative stress that causes severe myocyte damage. In addition, in subjects recovering from moderate-to-severe COVID-19, more significant impairment has been observed due to prolonged hospital stays, glucocorticoid use and mechanical ventilation requirements [31]. The aforementioned risk exposures predispose individuals to enduring musculoskeletal disorders, which hold significant implications, as muscle constitutes the body's largest tissue vital for movement and daily activities and plays a role in glucose metabolism, and reduced muscle mass has been associated with an adverse prognosis [31].

As part of the multidisciplinary management approach, subjects underwent nutritional care, which encompassed a comprehensive evaluation of body composition, blood metabolic profiles and daily dietary intake. This evaluation aimed to identify changes in body composition, including dynapenia, muscle depletion, sarcopenia, obesity and sarcopenic obesity, and to detect alterations in the metabolic profile indicative of malnutrition, undernutrition, as well as dyslipidaemias, disruptions in glucose metabolism and metabolic syndrome risk. Rehabilitation intervention was composed of physical therapy using superficial and deep heat, mechanotherapy, massage therapy and stretching to control pain, regain arch mobility and muscle elasticity of all four limbs, and then progress to mobility and finally strengthening and re-education of the respiratory pattern. The nutritional and rehabilitation interventions were personalised to cater to the specific requirements of each patient, with a focus on enhancing endothelial function, mitigating metabolic and cardiovascular risks, and ameliorating changes in body composition.

Our cohort of patients needed intensive care during hospitalisation, and most of them received mechanical ventilation. Evidence about the effectiveness of follow-up programmes in this subset of patients is contradictory, and the design of robust methods for addressing the special needs of critical patients has been proposed [32]. Other multicentre studies have incorporated a lower proportion of critical patients, identifying factors associated with non-recovery in their population, including factors such as female sex, multimorbidity and acute severe illness [33]. In our study, improvement was observed independently of the severity of acute illness, with a focus on patients with specific needs, such as those with ischaemic heart disease or chronic lung disease, for whom tailored interventions should be prioritised.

Regarding limitations, it should be noted that not all patients responded to quarterly follow-up assessments, although the majority provided their outcomes for a minimum of three assessments during the follow-up period. Nonetheless, every patient was included as per the study protocol.

Another limitation is a possible selection bias as our hospital is a tertiary pulmonary centre, so the subjects recruited had severe COVID-19, which limits the generalisability of the results to subjects with COVID who did not require hospitalisation as in the primary level of care offered in other health centres.

### *Conclusion*

Our study demonstrated that individuals participating in a multidisciplinary programme experienced improvements in musculoskeletal, fatigue and respiratory symptoms, as well as enhanced SF-12 mental and physical component scores. Comparable findings have been identified in studies involving pulmonary rehabilitation interventions for post-COVID-19 patients, resulting in improvements in fatigue, dyspnoea, exercise capacity, pulmonary function, respiratory muscle strength and overall quality of life [34].

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Ethics statement: The study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of the Instituto Nacional de Enfermedades Respiratorias “Ismael Cosío Villegas” (approval number: C57-21). All participants provided informed consent.

Author contributions: Conceptualisation and methodology, validation, and formal analysis: D.J. Cataneo-Piña, A. Castorena-Maldonaldo, D. González-Islas, S. Galicia-Amor, L. Gochicoa-Rangel and V. Pelaez-Hernández; investigation; D.J. Cataneo-Piña, A. Castorena-Maldonaldo, D. González-Islas, S. Galicia-Amor, L. Gochicoa-Rangel, V. Pelaez-Hernández, A. Orea-Tejeda and A.D. Gutiérrez-Álvarez; patient recruitment: D.J. Cataneo-Piña, A. Castorena-Maldonaldo, D. González-Islas, S. Galicia-Amor, L. Gochicoa-Rangel, V. Pelaez-Hernández, A. Orea-Tejeda, A.D. Gutiérrez-Álvarez, J. Rojas-Serrano, E. Ortiz-Reyes, A. Mendoza-Méndez, Á. Mendoza-Escamilla, S. Fabre-Alonso and C. López-García; writing (original draft preparation): D.J. Cataneo-Piña, A. Castorena-Maldonaldo, D. González-Islas, S. Galicia-Amor, L. Gochicoa-Rangel, V. Pelaez-Hernández, A. Orea-Tejeda, A.D. Gutiérrez-Álvarez, J. Rojas-Serrano, E. Ortiz-Reyes, A. Mendoza-Méndez, Á. Mendoza-Escamilla, S. Fabre-Alonso, C. López-García, M. Radillo-Gil, C.G. Hernández Favela, I. Buendía-Roldán, S. Moraz-Perez, J. Salas-Hernández and P. Santillán-Doherty; writing (review and editing): D.J. Cataneo-Piña, A. Castorena-Maldonaldo, D. González-Islas, S. Galicia-Amor, L. Gochicoa-Rangel, V. Pelaez-Hernández, A. Orea-Tejeda, A.D. Gutiérrez-Álvarez, J. Rojas-Serrano, E. Ortiz-Reyes, A. Mendoza-Méndez, Á. Mendoza-Escamilla, S. Fabre-Alonso, C. López-García, M. Radillo-Gil, C.G. Hernández Favela, I. Buendía-Roldán, S. Moraz-Perez, J. Salas-Hernández and P. Santillán-Doherty. All authors contributed to the article and approved the submitted version.

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