Long COVID is not the same for everyone: a hierarchical cluster analysis of Long COVID symptoms 9 and 12 months after SARS-CoV-2 test

Marta Moniz[1*], Carolina Ruivinho[1], Ana Rita Goes[1], Patrícia Soares[1,2] and Andreia Leite[1,2]

Abstract

Background Identifying symptom clusters in Long COVID is necessary for developing effective therapies for this diverse condition and improving the quality of life of those affected by this heterogeneous condition. In this study, we aimed to identify and compare symptom clusters at 9 and 12 months after a SARS-CoV-2 positive test and describe each cluster regarding factors at infection.

Methods This is a cross-sectional study with individuals randomly selected from the Portuguese National System of Epidemiological Surveillance (SINAVE) database. Individuals who had a positive RT-PCR SARS-CoV-2 test in August 2022 were contacted to participate in a telephonic interview approximately 9 and 12 months after the test. A hierarchical clustering analysis was performed, using Euclidean distance and Ward's linkage. Clustering was performed in the 35 symptoms reported 9 and 12 months after the SARS-CoV-2 positive test and characterised considering age, sex, pre-existing health conditions and symptoms at time of SARS-CoV-2 infection.

Results 552 individuals were included at 9 months and 458 at 12 months. The median age was 52 years (IQR: 40–64 years) and 59% were female. Hypertension and high cholesterol were the most frequently reported pre-existing health conditions. Memory loss, fatigue or weakness and joint pain were the most frequent symptoms reported 9 and 12 months after the positive test. Four clusters were identified at both times: no or minor symptoms; multi-symptoms; joint pain; and neurocognitive-related symptoms. Clusters remained similar in both times, but, within the neurocognitive cluster, memory loss and concentration issues increased in frequency at 12 months. Multi-symptoms cluster had older people, more females and more pre-existing health conditions at 9 months. However, at 12 months, older people and those with more pre-existing health conditions were in joint pain cluster.

Conclusions Our results suggest that Long COVID is not the same for everyone. In our study, clusters remained similar at 9 and 12 months, except for a slight variation in the frequency of symptoms that composed each cluster. Understanding Long COVID clusters might help identify treatments for this condition. However, further validation of the observed clusters and analysis of its risk factors is needed.

Keywords Symptoms cluster, Long COVID, Portugal, Public health

*Correspondence:
Marta Moniz
martafmoniz@gmail.com
Full list of author information is available at the end of the article

Moniz *et al. BMC Infectious Diseases*   (2024) 24:1001

Page 2 of 16

Introduction

The outbreak caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which resulted in COVID-19 disease, has rapidly evolved into a global pandemic [1]. While the infection acute phase has been extensively documented, emerging evidence suggests that a substantial proportion of individuals experience long-term symptoms that are not yet fully understood. These are often referred to as "Long COVID" or "post-COVID condition (PCC)" [2], and can significantly impact the quality of life and functional capacity of affected individuals [3], posing significant challenges to public health worldwide.

Different individual characteristics associated with different symptomatology and contradictory evidence regarding the risk factors for Long COVID symptoms [4–6] indicate that Long COVID is not a uniform syndrome. Previous studies have assessed potential Long COVID symptom clusters. A systematic review of such studies showed that neurological clustering was consistently identified, followed by cardiorespiratory and systemic/inflammatory [7]. Yet only eight studies were included, and the number and characteristics of clusters identified varied widely. Kenny et al. identified musculoskeletal and pain-related symptoms, cardiorespiratory symptoms and lower number of reported symptoms [8]; Nayani et al. identified loss of smell and taste, neurological symptoms and multiple symptoms classes [9]; Gentilotti et al. identified chronic fatigue-like syndrome, respiratory syndrome, chronic pain syndrome and neurosensorial syndrome [10]; Goldhaber et al. identified gastrointestinal, musculoskeletal, neurocognitive, airway and cardiopulmonary clusters [11]; Torrel et al. identified multisystemic, multisystemic – predominantly dysautonomous, heterogeneous, taste & smell, and menstrual & sexual alterations [12]; van den Houdt et al. identified moderate inflammatory symptoms, high inflammatory symptoms, moderate malaise-neurocognitive symptoms, high malaise-neurocognitive-psychosocial symptoms, low overall symptoms, and high overall symptoms [13]. This might be due to the variability in symptom selection [11, 12], symptom collection [8, 9], and clustering methodology [8–12]. Studies analysing symptom clusters focused either on the early stages of post-infection symptoms (> 3 months [9, 12, 14] or later stages (≥ 12 months [10, 15–17]), and there is little evidence regarding symptoms cluster between these two periods. Thus, clustering of Long COVID symptoms requires further assessment.

Understanding Long COVID has been a complex challenge, indicating that its treatment is more likely to be paved with tailored interventions rather than a one-size-fits-all approach [18]. This knowledge may facilitate the design of tailored interventions and ultimately improve the overall quality of life for individuals affected by this condition [19]. Hence, this study aimed to identify and compare symptom clusters at 9 and 12 months after a SARS-CoV-2 positive test and describe each cluster regarding factors at infection.

Methods

Data collection and study population

This study included individuals who had a SARS-CoV-2 test notification from the National System of Epidemiological Surveillance (SINAVE) in August 2022 and lived in Lisbon and Tagus Valley, which comprises one-third of the country's population distributed between urban and rural, high and low population density areas. Individuals who had a positive RT-PCR SARS-CoV-2 test in August 2022, were residing in Lisbon and Tagus Valley region during the study period regardless of their nationality or immigration status, were 18 years old or older, and consented to participate were included in the study. Individuals without a valid landline or mobile phone registered; institutionalised (e.g. residential structures for the elderly, prisons); who died between the date of the test and the call; with language difficulties (languages not covered by the group of translators that were part of the team of investigators) or deafness, as well as advanced states of mental illness or dementia; who were emigrants on holidays in Portugal or Portuguese tourists; and who tested positive for SARS-CoV-2 after August 2022 but before completing the first questionnaire and before the second questionnaire, to ensure an homogenous time between the test and symptoms were excluded.

The General Directorate of Health (DGS) provided information on a list of potential participants in two phases: 1) names and contact numbers (landline or mobile) of a random sample of 10,000 individuals who had an RT-PCR SARS-CoV-2 test approximately 9 months before the beginning of data collection. Verbal informed consent was obtained over the telephone by a trained inquirer; 2) result of the test for SARS-CoV-2. The second phase was only applicable to the individuals who consented to participate in the study. A questionnaire was performed between June 12 and August 8 of 2023, through a 30-minute computer-assisted telephone interview. Calls were scheduled for the most convenient times for the participants, with a maximum of five call attempts at different hours. Information collected included individuals' sociodemographic information, previous health conditions, previous lifestyle behaviours (alcohol intake and smoking) and symptoms reported at the time of the SARS-CoV-2 test and during the interview. Three months after the first questionnaire, a second similar questionnaire was performed on those who accepted to continue in the study after

Moniz *et al. BMC Infectious Diseases*   (2024) 24:1001

Page 3 of 16

the first questionnaire. This second questionnaire only questioned the participant regarding symptoms felt and changes in health conditions 12 months after the test to assess the evolution of the participants health between the two time points. Further information on the data collection process and study population can be found in the published study protocol [20] and both questionnaires can be seen in Additional file 1.

Variables

We considered the presence of at least one symptom reported 9 and 12 months after the SARS-CoV-2 test for the clustering analysis. The symptoms considered included persistent or worsening of usual cough, difficulty breathing, runny nose, sore throat, chest pain, abdominal pain, vomiting or nausea, diarrhoea, fever $\geq 38°C$, chills, headache, joint pain, myalgia, change or loss of smell, change or loss of taste, fatigue or weakness, breathing pain, palpitations, loss of appetite, constipation, difficulties urinating, swollen ankle, balance issues, not feeling one side of the body or face, tingling, fainting, seizures, tremors, swallowing difficulties, chewing difficulties, tinnitus, insomnia, rash, concentration issues and memory loss. The symptoms were based on the International Severe Acute Respiratory and Emerging Infection Consortium (ISARIC)/WHO COVID-19 clinical characterisation protocol [20] and derived from the question "I would like you to tell me whether or not if, in the last 7 days, you have felt any or some of them, which you had not felt before the test was taken, 9 (and 12) months ago, in August 2022". Due to cluster analysis requirements, individuals with missing values were removed from the analysis.

Sex (male/female), age (in years), behavioural and clinical characteristics: smoking (yes/no), alcohol intake (never/ 2 to 4 times a month or less/ twice a week or more), overweight (yes/no) and pre-existing health conditions (COVID-19, hypertension, diabetes, high cholesterol, asthma, chronic bronchitis, pulmonary fibrosis, heart failure, reflux disease, psychiatric disease, myocardial infarction, stroke, deep vein thrombosis, pulmonary thromboembolism) and symptoms reported at the time of SARS-CoV-2 test (persistent cough or worsening of usual cough, difficulty breathing, runny nose, sore throat, chest pain, abdominal pain, vomiting or nausea, diarrhoea, fever $\geq 38°C$, chills, headache, joint pain, myalgia, change or loss of smell, change or loss of taste, fatigue or weakness) were also used to characterise individuals within each cluster. Body mass index equal or above 25.0 Kg/m^2 was considered overweight, based on the WHO criteria [21].

Statistical analysis

Categorical data was summarised as frequencies and percentages, and continuous data as mean (minimum and maximum) and median (alongside the corresponding interquartile range (IQR) presented as the 25th and 75th percentile).

A hierarchical clustering analysis was performed to identify clusters within the 35 symptoms reported 9 months after SARS-CoV-2 diagnosis. This method starts with each participant as its own cluster, combining the most "similar" participants based on closeness (Euclidean distance), continuing until the last two clusters merge into one cluster containing all participants. Wards linkage was used to assess the distance between each cluster. Hierarchical clustering works especially well with smaller datasets since it does not require the number of clusters to be specified in advance like other clustering methods. The optimal number of clusters was chosen based on visual inspection (dendrogram), symptoms included in each cluster (i.e. having symptoms in a cluster that were relatable between them), silhouette score and Dunn's index. The same methodology was also applied to the symptoms reported at 12 months to compare clusters. Data were analysed using R version 4.0.3 [22] and the hierarchical clustering was performed with *cluster* package (2.1.6) [23].

Results

Individuals' characteristics

We included 552 SARS-CoV-2 positive individuals who completed the questionnaire at 9 months and 424 at 12 months. At 9 months, the median age was 52 years (IQR: 40–64 years) and 59% were female. Considering characteristics of individuals before the test, most individuals did not smoke (79%) and were overweight (55%), but only 26% drank alcohol two times a week or more. Hypertension (30%) and high cholesterol (29%) were the most frequently reported diagnosed pre-existing health condition. Conversely, the less frequent pre-existing health conditions reported were pulmonary fibrosis (0.4%) and pulmonary thrombosis (0.5%). Considering the symptoms reported at the time of the test, runny nose, sore throat, headache, myalgia, fatigue or weakness were the ones with higher frequency. The distribution of characteristics before and at the time of the test for the individuals included at 12 months remained similar. Sociodemographic and clinical features of the study population can be found in Additional file 2.

Figure 1 shows the symptoms reported 9 (panel A), and 12 months (panel B) after the positive SARS-CoV-2 test. Memory loss, fatigue or weakness and joint pain were the most frequent symptoms at both times. However,
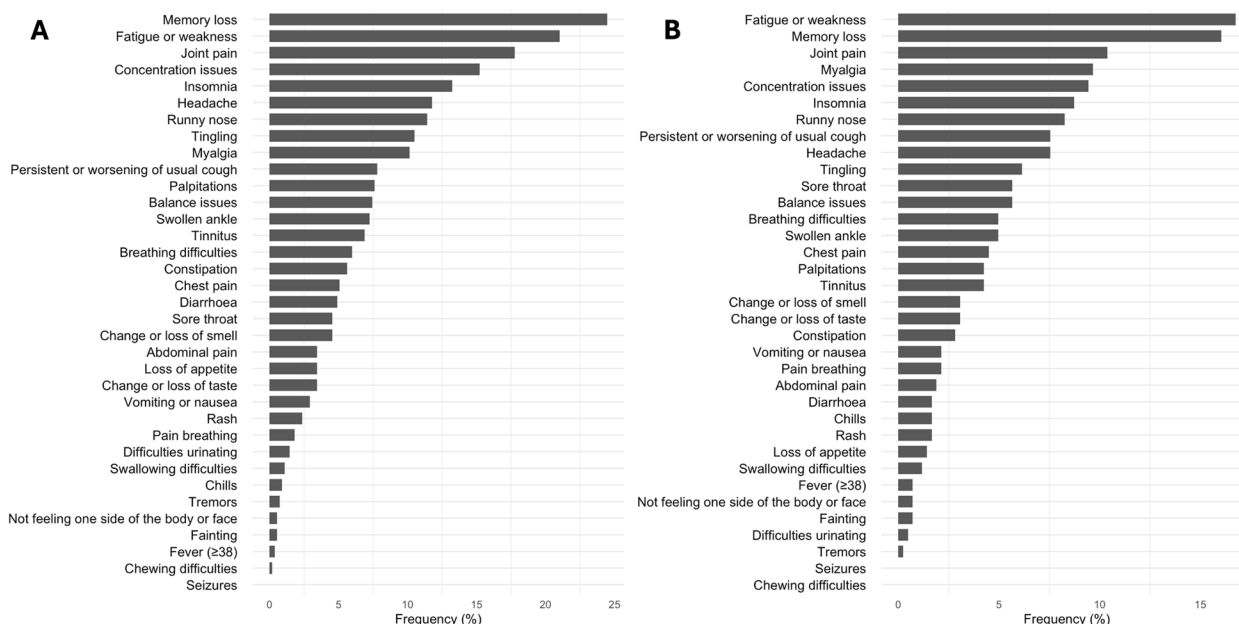
Fig. 1 Frequency of Long COVID symptoms 9 (**A**) and 12 (**B**) months after a SARS-CoV-2 positive test

all symptoms are reduced in frequency in the second moment.

Clustering analysis

Based on the dendrograms (Fig. 2), we considered two options: three and four clusters. Statistics for both options yielded similar metrics, although the option with four clusters was chosen because it was the most reasonable considering both statistic tests and cluster's explanation. Validation statistics for both options and the symptom distribution considering the option with three clusters are provided in Additional file 3, in Table 1 and Fig. 1, respectively.

Figures 3 and 4 show the distribution of the symptoms across the four clusters at 9 months. Cluster 1 ($n=368$, 67%) was characterised by individuals with no or minor symptoms, and the most frequent symptoms were runny nose (10%) and fatigue (10%). Cluster 2 ($n=47$, 8%) was characterised by individuals with a higher frequency of joint (85%) and myalgia (47%). Cluster 3 ($n=22$, 4%) included individuals with multiple symptoms across different organs, and the most frequent symptoms were fatigue (86%), memory loss (77%) and headache (77%). Cluster 4 ($n=115$, 21%) was characterised by individuals with cognitive-related symptoms, and the most frequent symptoms were memory loss (89%) and concentration issues (53%). Figures 5 and 6 show the distribution of the symptoms across the four clusters at 12 months, which remained similar to the clusters identified at 9 months but with some differences regarding symptoms

distribution. Cluster 1 ($n=327$, 71%) included individuals with no or minor symptoms, and the most prevalent symptoms were memory loss (6%), cough (5%) and runny nose (4%). Cluster 2 ($n=32$, 7%) included individuals with multiple symptoms across different organs, in which fatigue (84%) and myalgia (72%) were the most prevalent symptoms. Cluster 3 ($n=37$, 8%) was characterised by the individuals who reported mainly joint pain (57%) and fatigue (70%). Cluster 4 ($n=28$, 6%) included individuals with cognitive-related symptoms in which concentration issues (93%) was the most prevalent symptom, and all of them reported memory loss (100%).

The cluster characterised by minor or no symptoms remained the most frequent and the cluster characterised by cognitive-related symptoms went from the second most frequent to the least frequent. Overall, symptom's frequency fluctuated between the two time points. The cluster characterised by no or minor symptoms, had runny nose and fatigue as the most frequent symptoms at 9 months, while memory loss and cough were more common at 12 months. The cluster characterised by joint pain, showed myalgia as the second most frequent symptom at 9 months, with fatigue becoming more frequent at 12 months. In the multi-symptoms cluster, individuals reported fatigue most frequently at both time points. However, memory loss and headache were the second most frequent symptoms at 9 months, and myalgia at 12 months. In the neurocognitive-related symptoms cluster, memory loss and concentration issues were prevalent at both time points. Although the order of clusters 2 and 3
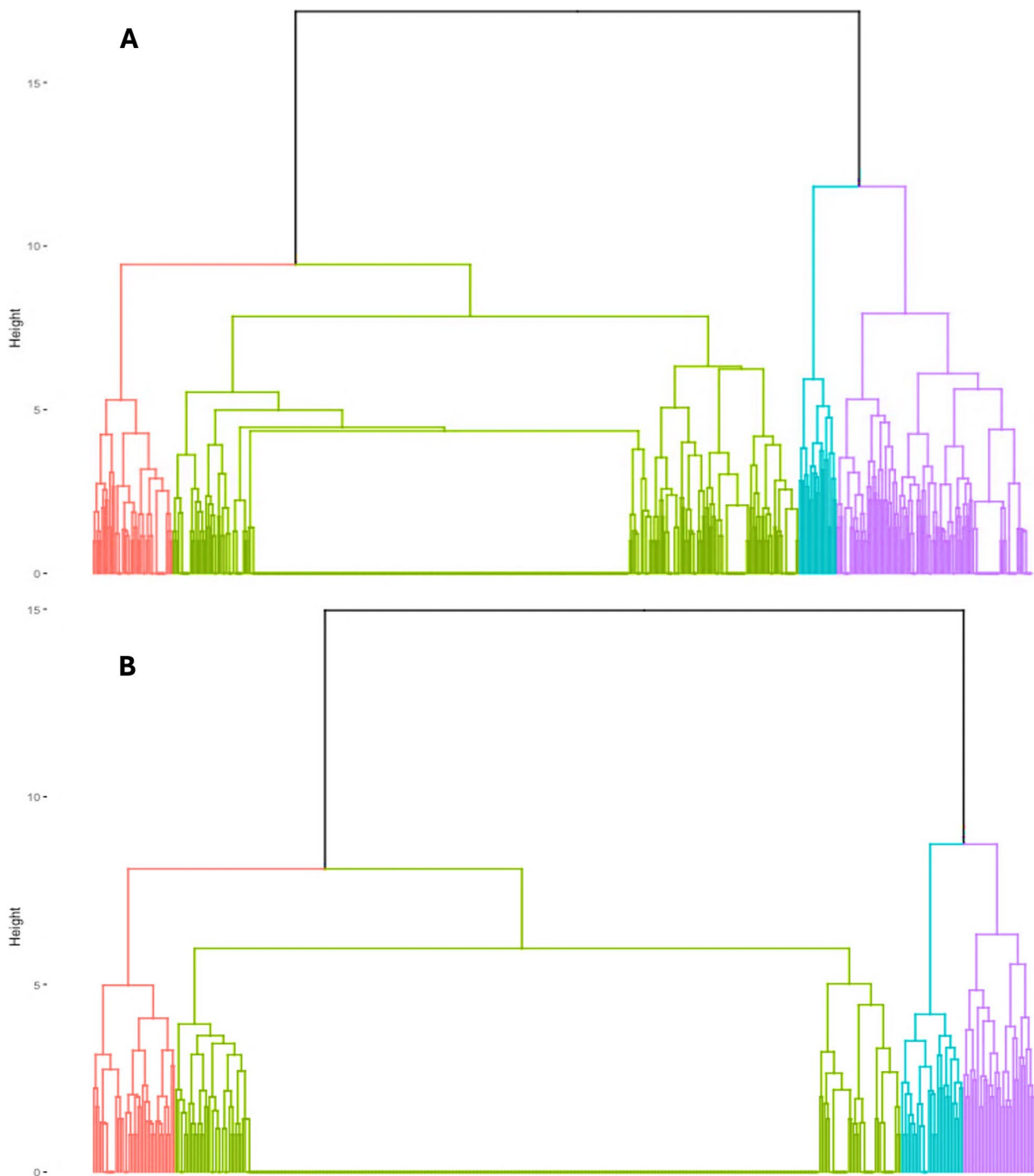
Fig. 2 Dendrogram based on hierarchical clustering analysis of 37 symptoms reported (**A**) 9 months after SARS-CoV-2 positive test, and (**B**) 12 months after SARS-CoV-2 positive test

have changed between the 9 and 12 months analysis, possibly due to the different data used, the clusters identified remained consistent over time.

Characteristics of the individuals per clusters

The characteristics of individuals in each symptom cluster at 9 months after SARS-CoV-2 test are shown in Table 1. Cluster 1, characterised by no or minor symptoms, had the highest median age (62 years) and the

Moniz *et al. BMC Infectious Diseases*   (2024) 24:1001
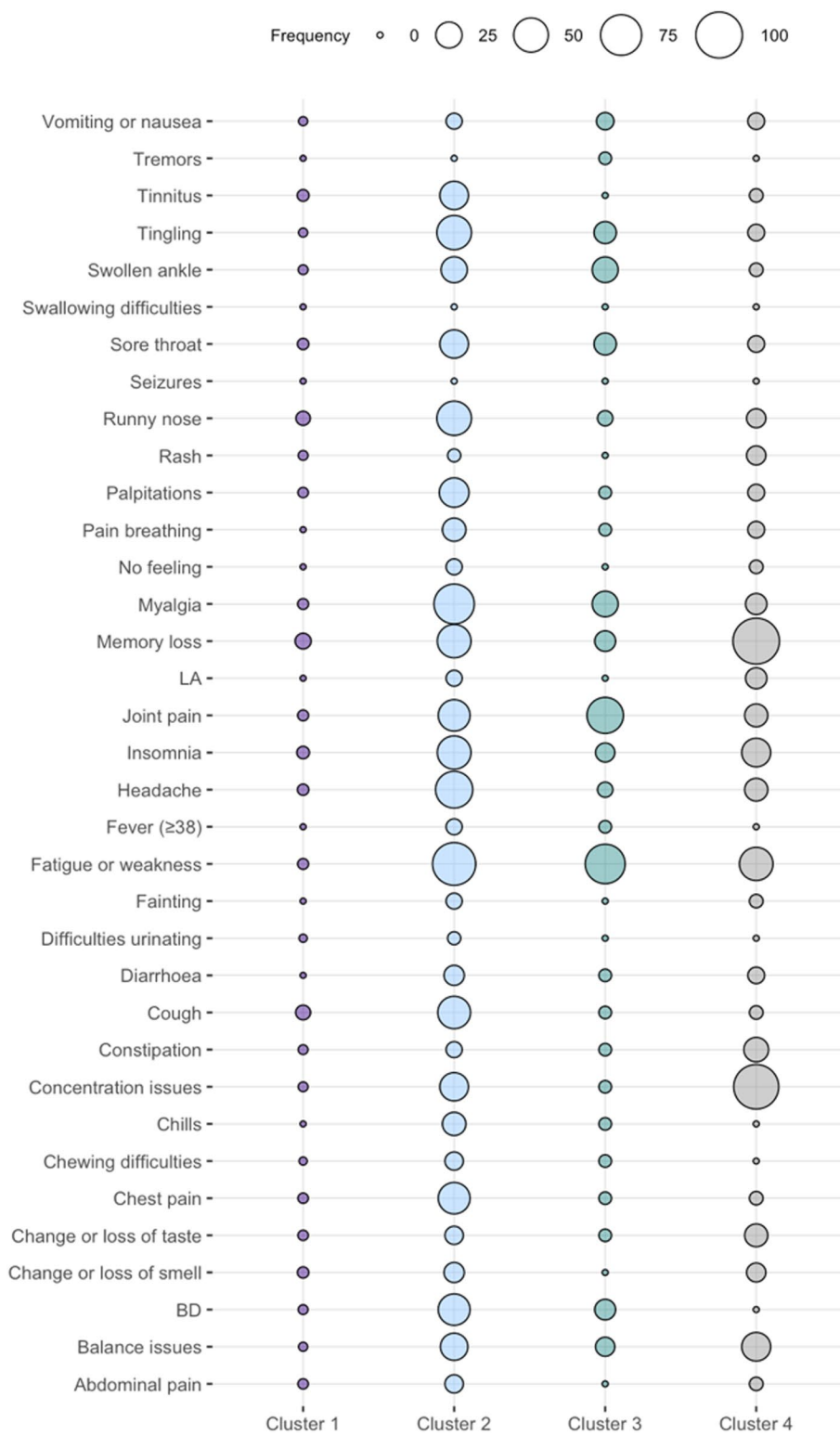
Page 6 of 16
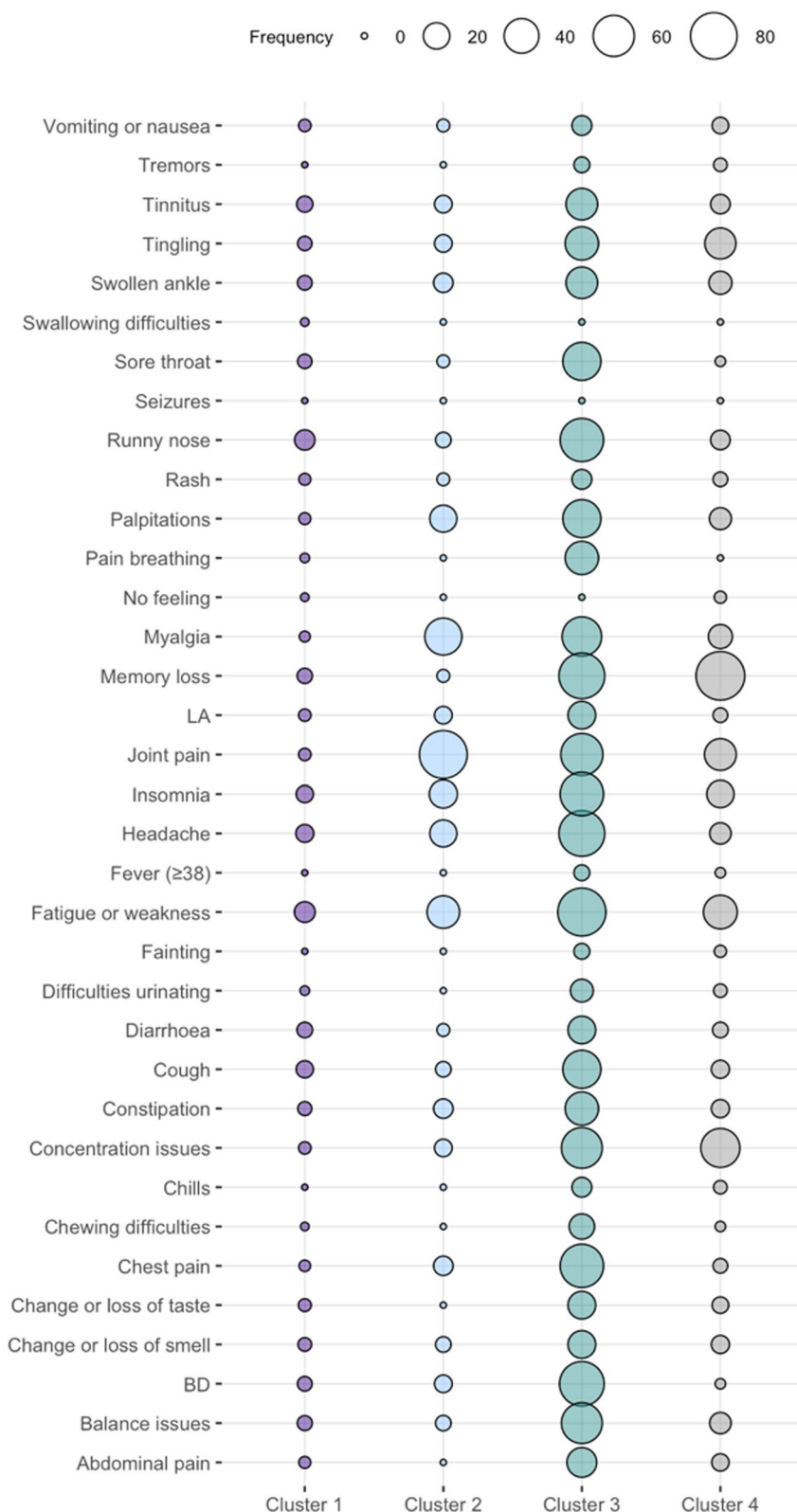
Fig. 3 Bubble plot of symptom cluster frequency derived from hierarchical clustering of Long COVID symptoms 9 months after a SARS-COV-2 positive test
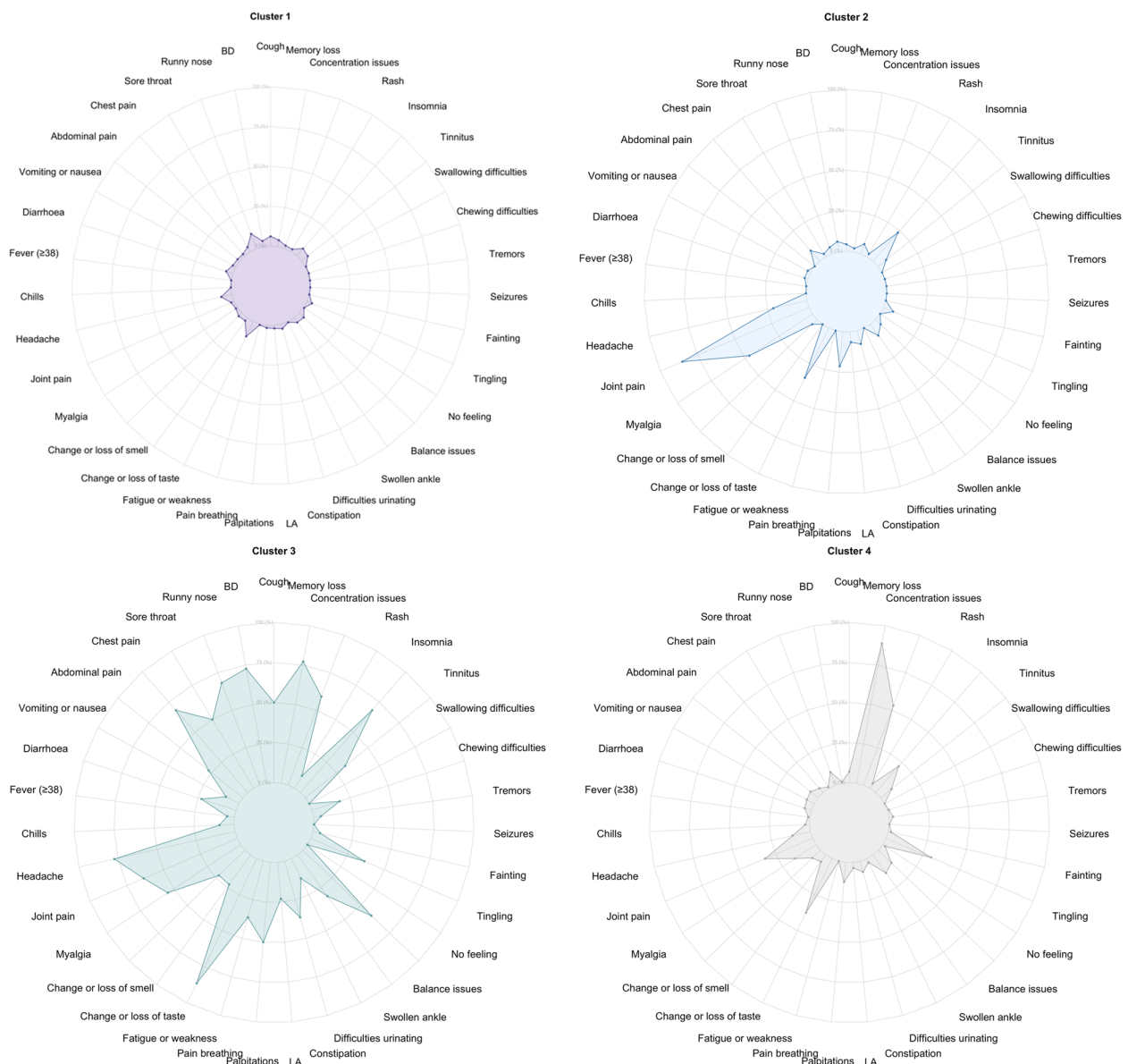
Fig. 4 Radar plots displaying the frequency of Long COVID symptoms across all four clusters. Abbreviations: LA: Loss of appetite; No feeling: Not feeling one side of the body or face; BD: Breathing difficulties

highest percentage of females (90%). Females were predominant in all clusters. Cluster 3 had the highest percentage of pre-existing health conditions. Fatigue and headache were consistently among the most frequent symptoms at testing in all clusters. In Cluster 3, these symptoms were particularly prevalent, with fatigue affecting 100% of individuals and headache affecting 86%. Hypertension and high cholesterol were the pre-existing health conditions most frequent in all clusters, and cluster 3 had the highest frequency of pre-existing health conditions.

Table 2 shows the characteristics of individuals in each symptom cluster at 12 months after SARS-CoV-2 test. Table 2 shows the characteristics of individuals in each symptom cluster at 12 months after SARS-CoV-2 test. Cluster 2, characterised by multiple symptoms, included the highest percentage of females (84%). Cluster 3 (joint pain) displayed the highest median age (58 years) and the highest frequency of tobacco consumption (30%). Cluster 4 presented the highest frequency of alcohol consumption (36%). Females were also predominant in all clusters at 12 months, and the frequency of pre-existing health

Fig. 5 Bubble plot of symptom cluster frequency derived from hierarchical clustering of Long COVID symptoms 12 months after a SARS-COV-2 positive test

Moniz *et al. BMC Infectious Diseases*   (2024) 24:1001

Page 9 of 16
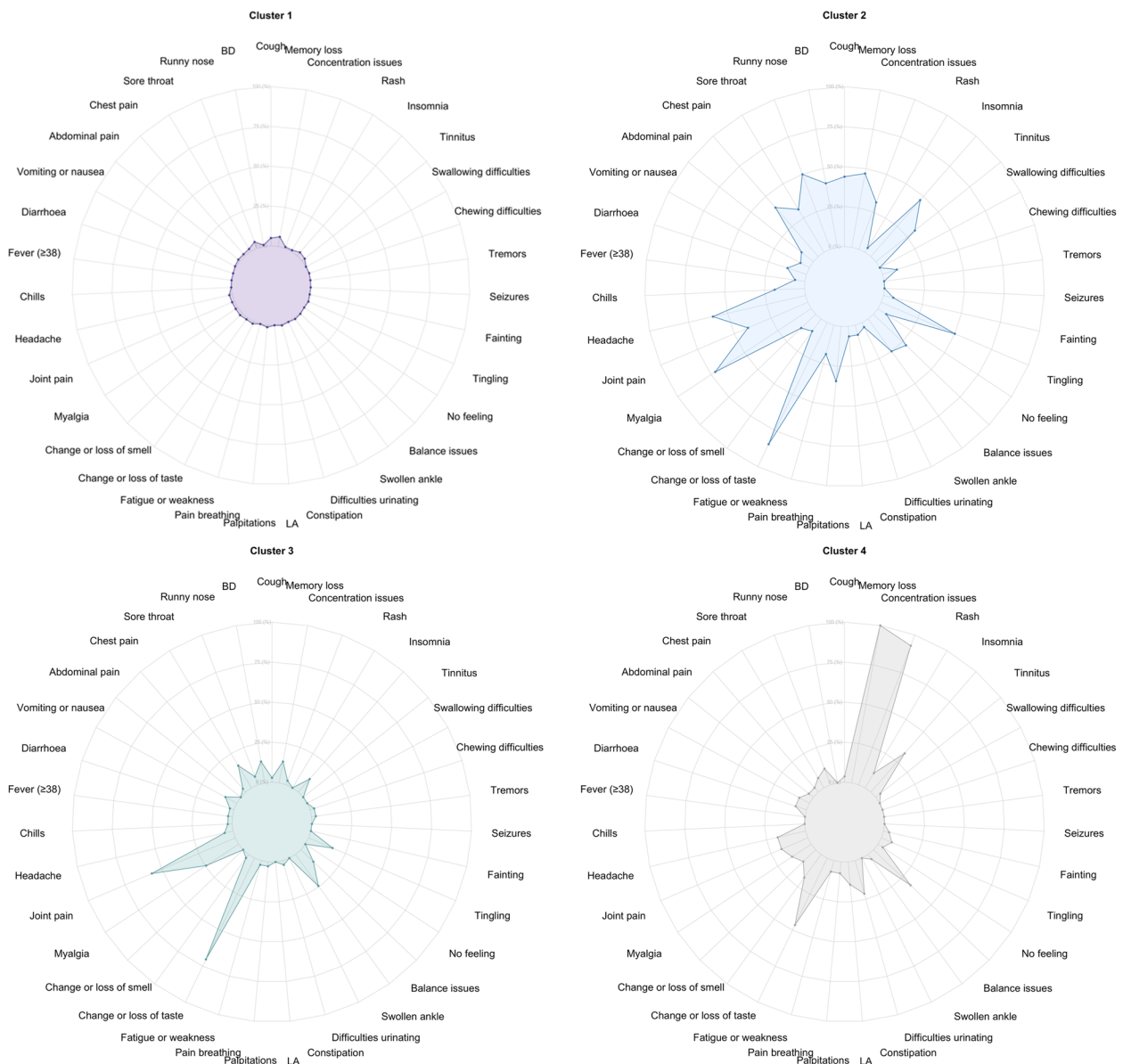
Fig. 6 Radar plots displaying the frequency of Long COVID symptoms across all four clusters. Abbreviations: LA: Loss of appetite; No feeling: Not feeling one side of the body or face; BD: Breathing difficulties

conditions was similar between clusters. Fatigue was the most frequent symptom at testing in all clusters, having the highest frequency in cluster 2, with 88%.

Discussion

In this study, we aimed to identify symptom clusters 9 and 12 months after a SARS-CoV-2 positive test and describe these clusters regarding symptoms, background demographic and clinical characteristics. Four clusters were identified at 9 and 12 months – no or minor symptoms, joint pain, multi-symptoms, and neurocognitive-related

symptoms. Symptom's frequencies and individuals' characteristics fluctuated between the two time points.

Our findings complement the literature analysing clusters of Long COVID symptoms [9–15, 24–28]. The cluster with no or minor symptoms (cluster 1) was the largest cluster in our study, comprising 60% of our study population, which is in line with similar studies where this cluster was also the largest, although with no distinctive characteristics [8, 14]. In 2023, Kenny et al. also identified this cluster, however, the most frequent symptoms between Long COVID phenotypes differed depending on

Table 1 Participants' sociodemographic and clinical characteristics by clusters 9 months after the positive SARS-CoV-2 test (*N* = 552)

	Clusters			
Variables	1 (*n* = 368)	2 (*n* = 47)	3 (*n* = 22)	4 (*n* = 115)
Age				
Mean (Range)	51.93 (19.00, 92.00)	53.21 (25.00, 86.00)	59.77 (22.00, 82.00)	53.22 (18.00, 87.00)
Median (IQR)	52.00 (39.75, 64.00)	52.00 (44.50, 61.00)	62.00 (50.50, 67.00)	52.00 (40.50, 64.50)
Sex (*n* = 546)				
Female	188 (51.51%)	32 (68.09%)	19 (90.48%)	81 (71.68%)
Male	177 (48.49%)	15 (31.91%)	2 (9.52%)	32 (28.32%)
Tobacco consumption[a] (*n* = 551)	76 (20.65%)	12 (26.09%)	5 (22.73%)	23 (20.00%)
Alcohol consumption				
Never	107 (29.08%)	14 (29.79%)	8 (36.36%)	24 (20.87%)
2 to 4 times a month or less	162 (44.02%)	26 (55.32%)	8 (36.36%)	62 (53.91%)
2 times a week or more	99 (26.90%)	7 (14.89%)	6 (27.27%)	29 (25.22%)
Overweight[a] (*n* = 544)	198 (54.25%)	28 (63.64%)	14 (63.64%)	61 (53.98%)
Pre-existing health conditions				
COVID-19[a] (*n* = 543)	74 (20.44%)	12 (26.09%)	6 (27.27%)	29 (25.66%)
Hypertension[a] (*n* = 550)	104 (28.26%)	14 (30.43%)	9 (40.91%)	36 (31.58%)
Diabetes[a] (*n* = 549)	39 (10.63%)	3 (6.52%)	1 (4.55%)	10 (8.77%)
High cholesterol[a] (*n* = 549)	106 (28.80%)	7 (15.56%)	7 (31.82%)	38 (33.33%)
Asthma[a] (*n* = 550)	31 (8.42%)	5 (10.87%)	2 (9.09%)	11 (9.65%)
Bronchitis[a] (*n* = 550)	13 (3.53%)	2 (4.35%)	3 (13.64%)	5 (4.39%)
Pulmonary fibrosis[a] (*n* = 549)	0 (0.00%)	1 (2.17%)	1 (4.55%)	0 (0.00%)
Heart failure[a] (*n* = 550)	16 (4.35%)	1 (2.17%)	6 (27.27%)	4 (3.51%)
Reflux disease[a] (*n* = 550)	33 (8.97%)	5 (10.87%)	6 (27.27%)	17 (14.91%)
Psychiatric condition[a] (*n* = 549)	49 (13.35%)	11 (23.91%)	6 (27.27%)	27 (23.68%)
Myocardial infarction[a] (*n* = 548)	11 (3.01%)	2 (4.35%)	1 (4.55%)	0 (0.00%)
Stroke[a] (*n* = 548)	9 (2.46%)	1 (2.17%)	1 (4.55%)	0 (0.00%)
Thrombosis[a] (*n* = 548)	5 (1.37%)	0 (0.00%)	2 (9.09%)	1 (0.88%)
Pulmonary thrombosis[a] (*n* = 549)	1 (0.27%)	0 (0.00%)	1 (4.55%)	1 (0.88%)
Pre-existing health condition[a]	264 (71.74%)	33 (70.21%)	18 (81.82%)	87 (75.65%)
Symptoms reported at the time of SARS-CoV-2 test				
Cough[a] (*n* = 546**)**	153 (41.80%)	21 (46.67%)	13 (59.09%)	54 (47.79%)
Breathing difficulties[a] (*n* = 549)	56 (15.26%)	8 (17.39%)	15 (68.18%)	22 (19.30%)
Runny nose[a] (*n* = 541)	181 (50.00%)	27 (58.70%)	14 (66.67%)	64 (57.14%)
Sore throat[a] (*n* = 544)	180 (49.18%)	26 (55.32%)	11 (57.89%)	64 (57.14%)
Chest pain[a] (*n* = 543)	28 (7.67%)	7 (15.22%)	7 (33.33%)	12 (10.81%)
Abdominal pain[a] (*n* = 546)	22 (6.01%)	2 (4.44%)	4 (18.18%)	13 (11.50%)
Vomiting or nause[a] (*n* = 548)	34 (9.29%)	6 (13.04%)	7 (31.82%)	21 (18.42%)
Diarrhoea[a] (*n* = 543)	39 (10.74%)	5 (10.87%)	3 (14.29%)	19 (16.81%)
Fever (≥ 38°C)[a] (*n* = 539)	161 (44.85%)	22 (48.89%)	9 (42.86%)	54 (47.37%)
Chills[a] (*n* = 540)	143 (39.83%)	23 (50.00%)	13 (61.90%)	70 (61.40%)
Headache[a] (*n* = 549)	196 (53.41%)	31 (65.96%)	19 (86.36%)	73 (64.60%)
Joint pain[a] (*n* = 542)	140 (38.57%)	32 (69.57%)	18 (85.71%)	58 (51.79%)
Myalgia[a] (*n* = 547)	179 (49.18%)	35 (74.47%)	18 (81.82%)	70 (61.40%)
Change or loss of smell[a] (*n* = 545)	72 (19.67%)	12 (27.27%)	11 (50.00%)	37 (32.74%)
Change or loss of taste[a] (*n* = 547)	72 (19.67%)	14 (30.43%)	9 (40.91%)	29 (25.66%)
Fatigue or weakness[a] (*n* = 548)	182 (49.86%)	33 (70.21%)	22 (100.00%)	91 (79.82%)
Any symptom[a]	337 (91.58%)	45 (95.74%)	22 (100.00%)	111 (96.52%)

[a] the category represented is "yes"

Table 2 Participants' sociodemographic and clinical characteristics by clusters 12 months after the positive SARS-CoV-2 test (*N*=424)

	Clusters			
Variables	**1** (*n*=327)	**2** (*n*=32)	**3** (*n*=37)	**4** (*n*=28)
Age				
Mean (Range)	52.60 (19.00, 92.00)	55.69 (26.00, 80.00)	55.73 (22.00, 89.00)	53.75 (18.00, 87.00)
Median (IQR)	51.00 (40.00, 65.50)	53.50 (43.75, 69.00)	58.00 (50.00, 62.00)	53.00 (39.50, 65.00)
Sex (*n*=418)				
Female	175 (54.01%)	26 (83.87%)	26 (72.22%)	20 (74.07%)
Male	149 (45.99%)	5 (16.13%)	10 (27.78%)	7 (25.93%)
Tobacco consumption[a]	63 (19.27%)	6 (18.75%)	11 (29.73%)	4 (14.29%)
Alcohol consumption				
Never	94 (28.75%)	12 (37.50%)	9 (24.32%)	8 (28.57%)
2 to 4 times a month or less	154 (47.09%)	13 (40.63%)	18 (48.65%)	10 (35.71%)
2 times a week or more	79 (24.16%)	7 (21.88%)	10 (27.03%)	10 (35.71%)
Overweight[a] (*n*=418)	173 (53.73%)	21 (65.63%)	22 (61.11%)	16 (57.14%)
Pre-existing health conditions				
COVID-19[a] (*n*=415)	63 (19.63%)	14 (46.67%)	8 (22.22%)	6 (21.43%)
Hypertension[a] (*n*=422)	101 (30.89%)	12 (38.71%)	10 (27.78%)	9 (32.14%)
Diabetes[a] (*n*=421)	33 (10.09%)	4 (13.33%)	5 (13.89%)	4 (14.29%)
High cholesterol[a] (*n*=422)	100 (30.58%)	14 (45.16%)	7 (19.44%)	13 (46.43%)
Asthma[a] (*n*=422)	27 (8.26%)	7 (22.58%)	4 (11.11%)	3 (10.71%)
Bronchitis[a] (*n*=421)	9 (2.75%)	4 (12.90%)	3 (8.33%)	1 (3.57%)
Pulmonary fibrosis[a] (*n*=421)	1 (0.31%)	1 (3.23%)	0 (0.00%)	0 (0.00%)
Heart failure[a] (*n*=422)	13 (3.98%)	2 (6.45%)	2 (5.56%)	2 (7.14%)
Reflux disease[a] (*n*=422)	30 (9.17%)	6 (19.35%)	5 (13.89%)	4 (14.29%)
Psychiatric condition[a] (*n*=421)	52 (15.95%)	10 (32.26%)	9 (25.00%)	9 (32.14%)
Myocardial infarction[a] (*n*=421)	8 (2.45%)	0 (0.00%)	1 (2.78%)	1 (3.57%)
Stroke[a] (*n*=421)	6 (1.84%)	1 (3.23%)	2 (5.56%)	1 (3.57%)
Thrombosis[a] (*n*=420)	4 (1.23%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Pulmonary thrombosis[a] (*n*=419)	1 (0.31%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Any pre-existing health condition[a]	241 (73.70%)	29 (90.63%)	28 (75.68%)	21 (75.00%)
Symptoms reported at the time of SARS-CoV-2 test				
Cough[a] (*n*=419)	144 (44.31%)	17 (53.13%)	18 (50.00%)	12 (46.15%)
Breathing difficulties[a] (*n*=423)	53 (16.21%)	15 (46.88%)	7 (19.44%)	6 (21.43%)
Runny nose[a] (*n*=414)	175 (55.03%)	16 (51.61%)	21 (56.76%)	16 (57.14%)
Sore throat[a] (*n*=419)	169 (52.32%)	18 (58.06%)	23 (62.16%)	12 (42.86%)
Chest pain[a] (*n*=419)	23 (7.10%)	6 (18.75%)	3 (8.33%)	4 (14.81%)
Abdominal pain[a] (*n*=421)	25 (7.69%)	5 (15.63%)	2 (5.41%)	3 (11.11%)
Vomiting or nausea[a] (*n*=422)	38 (11.69%)	8 (25.00%)	5 (13.51%)	4 (14.29%)
Diarrhoea[a] (*n*=416)	38 (11.84%)	8 (25.00%)	5 (13.89%)	6 (22.22%)
Fever (≥ 38°C)[a] (*n*=415)	149 (46.86%)	17 (53.13%)	13 (35.14%)	14 (50.00%)
Chills* (*n*=415)	142 (44.51%)	21 (65.63%)	18 (50.00%)	13 (46.43*)
Headache[a](*n*=422)	176 (53.99%)	28 (87.50%)	19 (51.35%)	18 (66.67%)
Joint pain[a] (*n*=416)	129 (40.31%)	24 (75.00%)	20 (54.05%)	16 (59.26%)
Myalgia[a] (*n*=415)	158 (48.77%)	25 (80.65%)	23 (62.16%)	21 (75.00%)
Change or loss of smell[a] (*n*=419)	62 (19.14%)	11 (35.48%)	13 (36.11%)	11 (39.29%)
Change or loss of taste[a] (*n*=421)	59 (18.10%)	10 (32.26%)	10 (27.78%)	11 (39.29%)
Fatigue or weakness[a] (*n*=419)	176 (54.66%)	28 (87.50%)	25 (67.57%)	20 (71.43%)
Any symptom[a]	303 (92.66%)	32 (100.00%)	35 (94.59%)	27 (96.43%)

[a] the category represented is "yes"

Moniz *et al. BMC Infectious Diseases*   (2024) 24:1001

Page 12 of 16

the SARS-CoV-2 variant at the time of infection: in the Alpha period, anosmia was more frequent in this cluster, whereas in the Omicron period, no single symptom predominated [29]. During our study period, Omicron was the predominant variant [30], and fatigue was the only symptom that stood out as more frequent but with minor differences from the other symptoms, which is in line with the aforementioned findings. Gerritzen et al. [15] and van den Houdt et al. [13] also observed a cluster with no or minor symptoms, although it included fewer individuals compared to the analogous cluster in our study.

The cluster characterised by joint pain included fewer individuals, which was also found in earlier studies [8, 10, 28]. Individuals in this cluster also had a higher frequency of joint pain and myalgia at the time of the test compared to the other clusters. Tobacco consumption was higher in this cluster, aligning with evidence suggesting a link between this habit and Long COVID pain-related symptoms [31]. Asthma was the pre-existing health condition most frequent in this cluster at 9 months, and at 12 months, asthma was more frequent in multi-symptoms cluster. This disease was associated with general fatigue in Long COVID by a cohort study in Japan [32] and, in fact, fatigue was among the most frequent symptoms reported in both clusters at both times, which seems to confirm this association. A clustering study found higher rates of diabetes and hypertension in this cluster [26], which was not the case in our study. The different magnitude of the studies (national survey vs. regional survey) or the period analysed (from < 1 month until > 6 months after SARS-CoV-2 positive test vs. 9 months) could be possible sources for this difference. Goldhaber et al. have also shown that older individuals were more likely to be in this cluster, however in our study, this was not the cluster with the highest median age at 9 months [11]. That study included individuals who tested positive for SARS-CoV-2 within 1 year period and of which one third had been hospitalised. Our study was community based, included individuals who tested positive for SARS-CoV-2 within 1 month period and less than 1% were hospitalised and individuals hospitalized due to SARS-CoV-2 infection tend to have higher rates of chronic diseases, namely diabetes [33]. Infection severity seems to be a shaping factor for Long COVID symptoms clustering by influencing the rates and specificity of Long COVID symptoms.

The multi-symptoms cluster was characterised by higher frequency of symptoms across several organs with no distinct organ affected, which was also identified in other studies [9, 12, 14, 24, 25, 34]. All the individuals in this cluster reported experiencing fatigue at the time of infection and at 9 and 12 months, which is in line with a previous study where fatigue was also the most common symptom in this cluster [9, 14, 25]. Individuals in this cluster also experienced a higher frequency of symptoms during the SARS-CoV-2 infection and had more pre-existing health conditions. This is in line with van den Houdt et al., which demonstrated that reporting a greater number of acute COVID-19 symptoms was associated with higher odds of belonging to the cluster with a higher prevalence of symptoms [13], and with Nayani et al. which demonstrated that individuals with a history of chronic diseases were more likely to be in this cluster [9]. Additionally, more females and older individuals were in this cluster, which is also shown in other studies [9, 14, 24, 34]. This might be related to other cluster characteristics, namely higher frequency of pre-existing health conditions since older individuals might be more likely to have other health conditions, however this association was not explored in this study. In our study, this cluster had the highest frequency of individuals with a previous infection of SARS-CoV-2, which is in line with previous findings that reinfection is associated with increased prevalence of Long COVID symptoms [26].

Neurocognitive-related symptoms cluster was the second largest cluster in our study. This cluster had been also identified in a meta-analysis with a pooled prevalence of 72% [7]. There are differences in the most frequent symptoms and even in the symptoms that comprise this cluster. In our study, at 9 months, the most frequent symptoms were memory loss and concentration issues, which were also identified in this cluster in other studies [9, 11, 14, 27]. However, studies also report higher frequencies of headache, insomnia, tingling or anosmia [7, 24]. A cardiorespiratory/cardiovascular cluster was also identified in the meta-analysis [7], comprising fatigue, dyspnoea, chest pain, myalgia, headache, and palpitations. In our study, fatigue was the most prevalent symptom and was distributed across clusters, namely no or minor symptoms, joint pain, and multi-symptoms; myalgia were more prevalent in joint pain cluster; and chest pain, headache, palpitations were more prevalent in multi-symptoms cluster. In this study, dyspnoea was also more frequent in multi-symptoms. The most prevalent pre-existing health condition in this cluster seems to be hypertension [24], which was the most prevalent pre-existing health condition in the multi-symptoms cluster found in this study, suggesting that this two may be related or overlapping. Additionally, individuals in this cluster appear to have experienced severe cases of SARS-CoV-2 infection, whereas in our study individuals had mainly mild cases [8].

A systematic review that analysed symptom clusters show that most symptoms tend to decrease in prevalence over time [7], which is in line with our study. Although evidence is not always consistent, since studies show that some symptoms can remain or increase over time

Moniz *et al. BMC Infectious Diseases*   (2024) 24:1001

Page 13 of 16

or even appear later on [7, 35–37]. The same systematic review also showed that post-exertional malaise continued to increase up to 1 year after SAR-CoV-2 infection [7]. Post-exertional malaise has been commonly reported by individuals with Long COVID and is characterised by fatigue- and pain-related symptoms following even minor physical or mental exercise [38]. In our study, fatigue remained relevant in multi-symptom clusters and even increased its frequency in the joint pain cluster between 9 and 12 months. Also, a prospective study showed that "feeling slowed down" and fatigue were less likely to improve at 12 months in older individuals [36], which was observed in our study. In fact, fatigue was the more frequent symptom at 12 months and, in Long COVID, it can encompass a variety of complaints, such as "brain fog" that can include concentration issues and memory impairments [39]. Memory loss and concentration issues increased their prevalence within the neuro-cognitive cluster. A cohort study also showed that the proportion of memory and cognitive impairment continues to increase up to 24 months after infection [37], which highlights the continued and future relevance of Long COVID as a public health challenge and the need for further reference. Memory loss and concentration issues are often associated with older age, as these faculties can begin to decline over time. Nevertheless, emerging evidence suggests that memory loss can manifest as a post-COVID symptom, affecting even younger demographics. Matias-Guiu et al. [40] found that cognitive issues were more prevalent among younger individuals with lower levels of education and Herrera et al. [41] demonstrated that, among predominantly mild cases of acute SARS-CoV-2 infection, cognitive issues appeared to be more frequent and severe in younger patients. Our sample primarily consists of middle-aged and older individuals, which could bias the findings of this cluster. However, studies that have also identified this cluster report a similar average age [9, 11, 14, 27].

Continuing to explore Long COVID symptoms, delving into specific symptoms and their evolution could assist public health authorities in directing prevention campaigns towards those at higher risk. Additionally, studying specific clusters may help developing evidence-based interventions and therapies as well as enable healthcare providers to intervene early, potentially mitigating the severity of long COVID symptoms and improving patient outcomes.

It is important to note that our study has certain limitations that must be considered. In our study, we defined "Long COVID symptoms" as having ≥ 1 symptom 9 or 12 months after the SARS-CoV-2 test. Given that Long COVID is a diagnosis of exclusion, we and most studies do not exclude other potential conditions. Different

methodological approaches, namely regarding symptom assessment and statistical analysis, were found, which might lead to different estimates. Also, although participants were asked about symptoms they experienced in the last 7 days and that they had not experienced before the SARS-CoV-2 test, reported symptoms could be due to other conditions. Symptoms were self-reported by participants and relied on their understanding of the questions being asked, memory of events, symptom definition and valorisation. We tried to use plain language and omit medical terms. Perhaps, with increasing identification of various complications over time, symptoms such as "balance issues" and "palpitations" can be linked to autonomic dysfunction and postural orthostatic tachycardia syndrome (POTS) that might be triggered by COVID-19 infection or COVID-19 vaccination [42], while "memory loss" or "concentration difficulties" have come to be recognised as post-COVID 'brain fog'. Also, despite adding relevant knowledge to Long COVID condition our study did not cover severe cases of SARS-CoV-2 infection. The severity of the infection appears to influence the frequency and specificity of Long COVID symptoms, thus playing a role in how these symptoms cluster. Another limitation was the lack of information on vaccination due to limited recall at the time of data collection [43, 44]. Linkage COVID-19 vaccination data could be employed in future studies. Although this is not a straightforward approach due to ethical issues, it could also be used as an addition to self-reported symptoms, which are an important indicator of individual's health behaviours. Although a 3-months follow-up can provide valuable insights into symptom clusters evolution, it may not be sufficient to fully capture the long-term progression and variability of Long COVID symptoms, which could affect the observed patterns. Future research with extended follow-up periods would be beneficial to gain a more comprehensive understanding of the persistence and fluctuation of symptoms over time.

To the best of our knowledge, this is the first study accessing Long COVID symptom clusters at 9 and 12 months, which adds relevant evidence from a European country and to the evolution of symptoms over time. Another important strength of our study is the exploration of clustering of an extensive range of Long COVID self-reported symptoms based on the International Severe Acute Respiratory and Emerging Infection Consortium (ISARIC) / WHO COVID-19 clinical characterisation [45]. This initiative aims to prevent illness and deaths from infectious disease outbreaks by offering a skilled and coordinated research response through a global federation of clinical research networks. This study also covered the Omicron phase and encompassed a broad spectrum of community-based cases, including

Moniz *et al. BMC Infectious Diseases*   (2024) 24:1001

Page 14 of 16

both PCR and rapid antigen tests. This inclusive methodology contrasts with many studies that focus solely on healthcare-seeking populations or pre-Omicron phases, allowing for a more representative analysis of Long COVID across different detection methods and timeframes.

The findings of the current study add important evidence to the body of work regarding the heterogeneity of Long COVID symptoms. Given the public health relevance that Long COVID has and will continue to have in the foreseeable future, it is important to continue deepening the research on this issue. Future studies should include larger samples to analyse the risk factors for the different clusters. Longer periods of infection should also be analysed to cover different variants and explore how they influence Long COVID symptom clusters.

Conclusion

We identified four clusters of symptoms within individuals who reported having one or more symptoms at 9 and 12 months after a positive SARS-Cov-2 infection. Clusters remained similar at 9 and 12 months, except for a slight variation in the frequency of symptoms that composed each cluster. All symptoms decreased frequency over time, however, within the neuro-cognitive cluster, memory loss and concentration issues increased their frequency at 12 months. Analysing Long COVID symptoms cluster could help to identify treatments for this condition which will remain a relevant public health issue in the years to come. Hence, further validation of the observed clusters and analysis of its risk factors is needed.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12879-024-09896-8.

> Supplementary Material 1.
>
> Supplementary Material 2.
>
> Supplementary Material 3.

Patient and public involvement
Patients and/or the public were not involved in the design, conduct, reporting or dissemination plans of this research.

Clinical trial number
Not applicable.

Availability of data and materials
Data are available upon reasonable request.

Declarations

Ethics approval and consent to participate
This study involved human participants and was approved by the Ethics Committee for Health of the Regional Health Administration of Lisbon and Tagus Valley (2151/CES/2022) and the Data Protection Officer of the General Directorate of Health. Verbal informed consent was obtained from the participants prior to the questionnaire.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

Author details
[1]Public Health Research Centre, Comprehensive Health Research Center, NOVA National School of Public Health, CHRC, REAL, CCAL, NOVA University Lisbon, Lisbon, Portugal. [2]National Institute of Health Doutor Ricardo Jorge, Lisbon, Portugal.

References
1. World Health Organization. WHO Director-General's opening remarks at the media briefing on COVID-19: 11 March 2020. Washington D.C.; 2020. p. 4. Available from: https://www.who.int/dg/speeches/detail/who-director-general-s-opening-remarks-at-the-media-briefing-on-covid-19---11-march-2020. Cited 30 Nov 2020.
2. World Health Organization. A clinical case definition of post COVID-19 condition by a Delphi consensus data. Geneva; 2021.
3. Natarajan A, Shetty A, Delanerolle G, Zeng Y, Zhang Y, Raymont V, et al. A systematic review and meta-analysis of long COVID symptoms. Syst Rev. 2023;12(1):88.
4. Chelly S, Rouis S, Ezzi O, Ammar A, Fitouri S, Soua A, et al. Symptoms and risk factors for long COVID in Tunisian population. BMC Health Serv Res. 2023;23(1):487.
5. Feter N, Caputo EL, Leite JS, Delpino FM, da Silva LS, Vieira YP, et al. Prevalence and factors associated with long COVID in adults from

Moniz *et al. BMC Infectious Diseases*   (2024) 24:1001

Page 15 of 16

Southern Brazil: Findings from the PAMPA cohort. Cad Saude Publica. 2023;39(12):e00098023.

6. Daniel CL, Fillingim S, James J, Bassler J, Lee A. Long COVID prevalence and associated characteristics among a South Alabama population. Public Health. 2023;221:135–41.

7. Kuodi P, Gorelik Y, Gausi B, Bernstine T, Edelstein M. Characterization of post-COVID syndromes by symptom cluster and time period up to 12 months post-infection: a systematic review and meta-analysis. Int J Infect Dis. 2023;134:1–7. https://doi.org/10.1016/j.ijid.2023.05.003.

8. Kenny G, McCann K, O'Brien C, Savinelli S, Tinago W, Yousif O, et al. Identification of distinct long COVID clinical phenotypes through cluster analysis of self-reported symptoms. Open Forum Infect Dis. 2022;9(4). Available from: https://dx.doi.org/10.1093/ofid/ofac060. Cited 22 Mar 2024.

9. Nayani S, Castanares-Zapatero D, De Pauw R, Van Cauteren D, Demarest S, Drieskens S, et al. Classification of post COVID-19 condition symptoms: a longitudinal study in the Belgian population. BMJ Open. 2023;13(10):e072726 Available from: https://bmjopen.bmj.com/content/13/10/e072726. Cited 2024 Mar 26.

10. Gentilotti E, Górska A, Tami A, Gusinow R, Mirandola M, Rodríguez Baño J, et al. Clinical phenotypes and quality of life to define post-COVID-19 syndrome: a cluster analysis of the multinational, prospective ORCHESTRA cohort. EClinicalMedicine. 2023;62:102107 https://www.thelancet.com/article/S2589537023002845/fulltext. Cited 2024 Mar 27.

11. Goldhaber NH, Kohn JN, Ogan WS, Sitapati A, Longhurst CA, Wang A, et al. Deep dive into the long haul: analysis of symptom clusters and risk factors for post-acute sequelae of COVID-19 to inform clinical care. Int J Environ Res Public Health. 2022;19(24). https://doi.org/10.3390/ijerph192416841. Cited 26 Mar 2024.

12. Torrell G, Puente D, Jacques-Aviñó C, Carrasco-Ribelles LA, Violán C, López-Jiménez T, et al. Characterisation, symptom pattern and symptom clusters from a retrospective cohort of Long COVID patients in primary care in Catalonia. BMC Infect Dis. 2024;24(1):82 Cited 2024 Mar 22.

13. van den Houdt SCM, Slurink IAL, Mertens G. Long COVID is not a uniform syndrome: Evidence from person-level symptom clusters using latent class analysis. J Infect Public Health. 2024;17(2):321–8 Available from: https://linkinghub.elsevier.com/retrieve/pii/S1876034123004616. Cited 26 Mar 2024.

14. Ito F, Terai H, Kondo M, Takemura R, Namkoong H, Asakura T, et al. Cluster analysis of long COVID in Japan and association of its trajectory of symptoms and quality of life. BMJ Open Respir Res. 2024;11(1):e002111. https://doi.org/10.1136/bmjresp-2023-002111.

15. Gerritzen I, Brus IM, Spronk I, Biere-Rafi S, Polinder S, Haagsma JA. Identification of post-COVID-19 condition phenotypes, and differences in health-related quality of life and healthcare use: a cluster analysis. Epidemiol Infect. 2023;151:e123. Available from: https://www.cambridge.org/core/journals/epidemiology-and-infection/article/identification-of-postcovid19-condition-phenotypes-and-differences-in-healthrelated-quality-of-life-and-healthcare-use-a-cluster-analysis/C41527998B05928DECB7B7440604A784. Cited 2024 Mar 27.

16. Kisiel MA, Lee S, Malmquist S, Rykatkin O, Holgert S, Janols H, et al. Clustering analysis identified three long covid phenotypes and their association with general health status and working ability. J Clin Med. 2023;12(11):3617 Available from: https://www.mdpi.com/2077-0383/12/11/3617/htm. Cited 2024 Mar 26.

17. Fischer A, Badier N, Zhang L, Elbéji A, Wilmes P, Oustric P, et al. Long COVID classification: findings from a clustering analysis in the predi-COVID cohort study. Int J Environ Res Public Health. 2022;19(23):16018 Available from: https://www.mdpi.com/1660-4601/19/23/16018/htm . Cited 27 Mar 2024.

18. Kavanagh KT, Cormier LE, Pontus C, Bergman A, Webley W. Long COVID's impact on patients, workers, & society: a review. Vol. 103, Medicine (United States). Wolters Kluwer Health; 2024. p. E37502. https://doi.org/10.1097/MD.0000000000037502. Cited 2024 Apr 1.

19. Tsuchida T, Yoshimura N, Ishizuka K, Katayama K, Inoue Y, Hirose M, et al. Five cluster classifications of long COVID and their background factors: a cross-sectional study in Japan. Clin Exp Med. 2023;23(7):3663–70. https://doi.org/10.1007/s10238-023-01057-6. Cited 2024 Mar 21.

20. Dinis Teixeira JP, Santos MJDS, Soares P, de Azevedo L, Barbosa P, Boas AV, et al. LOCUS (LOng Covid–Understanding Symptoms, events and use

of services in Portugal): A three-component study protocol. PLoS ONE. 2023;18(4 April):1–12.

21. World Health Organization. Noncommunicable diseases global monitoring framework: Indicator definitions and specifications. Geneva: World Health Organization; 2014.

22. R Core Team. R: A language and environment for statistical computing. Vienna, Austria; 2022. Available from: https://www.r-project.org/.

23. Maechler M, Rousseeuw P, Struyf A, Hubert M, Hornik K. cluster: cluster analysis basics and extensions. R Package Version. 2023;2:1.

24. Reese JT, Blau H, Casiraghi E, Bergquist T, Loomba JJ, Callahan TJ, et al. Generalisable long COVID subtypes: Findings from the NIH N3C and RECOVER programmes. EBioMedicine. 2023;87:104413 Available from: https://www.thelancet.com/article/S2352396422005953/fulltext. Cited 16 May 2024.

25. Blankestijn JM, Abdel-Aziz MI, Baalbaki N, Bazdar S, Beekers I, Beijers RJHCG, et al. Long COVID exhibits clinically distinct phenotypes at 3–6 months post-SARS-CoV-2 infection: results from the P4O2 consortium. BMJ Open Respir Res. 2024;11(1):e001907. Available from: https://bmjopenrespres.bmj.com/content/11/1/e001907.

26. Bello-Chavolla OY, Fermín-Martínez CA, Ramírez-García D, Vargas-Vázquez A, Fernández-Chirino L, Basile-Alvarez MR, et al. Prevalence and determinants of post-acute sequelae after SARS-CoV-2 infection (Long COVID) among adults in Mexico during 2022: a retrospective analysis of nationally representative data. Lancet Reg Health - Am. 2024;30:100688. https://doi.org/10.1016/j.lana.2024.100688.

27. Danesh V, Arroliga AC, Bourgeois JA, Boehm LM, McNeal MJ, Widmer AJ, et al. Symptom clusters seen in adult COVID-19 recovery clinic care seekers. J Gen Intern Med. 2023;38(2):442–9 Available from: https://link.springer.com/article/10.1007/s11606-022-07908-4 . Cited 12 Apr 2024.

28. Wong-Chew RM, Rodríguez Cabrera EX, Rodríguez Valdez CA, Lomelin-Gascon J, Morales-Juárez L, de la Cerda MLR, et al. Symptom cluster analysis of long COVID-19 in patients discharged from the Temporary COVID-19 hospital in Mexico City. Ther Adv Infect Dis. 2022;9:204993612110692. https://doi.org/10.1177/20499361211069264. Cited 2024 Apr 12.

29. Kenny G, McCann K, O'Brien C, O'Broin C, Tinago W, Yousif O, et al. Impact of vaccination and variants of concern on long COVID clinical phenotypes. BMC Infect Dis. 2023;23(1):804. https://doi.org/10.1186/s12879-023-08783-y. Cited 2024 Apr 12.

30. Instituto Nacional de Saúde Doutor Ricardo Jorge (INSA). Diversidade genética do novo coronavírus SARS-CoV-2 (COVID-19) em Portugal. Lisboa, Portugal ; 2022. Available from: https://insaflu.insa.pt/covid19. Cited 2024 May 22.

31. Kabir MF, Yin KN, Jeffree MS, Ahmedy FB, Zainudin MF, Htwe O, et al. Clinical presentation of post-COVID pain and its impact on quality of life in long COVID patients: a cross-sectional household survey of SARS-CoV-2 cases in Bangladesh. BMC Infect Dis. 2024;24(1):1–13 https://bmcinfectdis.biomedcentral.com/articles/10.1186/s12879-024-09267-3. Cited 2024 May 28.

32. Sunata K, Miyata J, Terai H, Matsuyama E, Watase M, Namkoong H, et al. Asthma is a risk factor for general fatigue of long COVID in Japanese nation-wide cohort study. Allergol Int. 2024;73(2):206–13 Available from: https://linkinghub.elsevier.com/retrieve/pii/S1323893023001156 . Cited 2 Apr 2024.

33. Zhang JJ, Dong X, Liu GH, Gao YD. Risk and protective factors for COVID-19 morbidity, severity, and mortality. Clin Rev Allergy Immunol. 2022;64(1):90–107 Available from: https://link.springer.com/article/10.1007/s12016-022-08921-5. Cited 2024 May 22.

34. Subramanian A, Nirantharakumar K, Hughes S, Myles P, Williams T, Gokhale KM, et al. Symptoms and risk factors for long COVID in non-hospitalized adults. Nat Med. 2022;28(8):1706–14 https://www.nature.com/articles/s41591-022-01909-w. Cited 2024 Apr 2.

35. Alkodaymi MS, Omrani OA, Fawzy NA, Shaar BA, Almamlouk R, Riaz M, et al. Prevalence of post-acute COVID-19 syndrome symptoms at different follow-up periods: a systematic review and meta-analysis. Clin Microbiol Infect. 2022;28(5):657–66.

36. Bamps L, Armenti JP, Bojan M, Grandbastien B, von Garnier C, Du Pasquier R, et al. Long-term consequences of COVID-19: A 1-year analysis. J Clin Med. 2023;12(7):2673.

37. Ling DQ, Gibney G, James F, Holmes NE, Chua KY. Post-COVID-19 condition symptoms 12 and 24 months after COVID-19 during the first month of the pandemic in Melbourne: a cohort study. Med J Aus.

2024;220(6):336–8. https://doi.org/10.5694/mja2.52260. Cited 2024 May 22.

38. Vernon SD, Hartle M, Sullivan K, Bell J, Abbaszadeh S, Unutmaz D, et al. Post-exertional malaise among people with long COVID compared to myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS). Work. 2023;74(4):1179–86.

39. Maffitt NJ, Germann M, Baker AME, Baker MR, Baker SN, Soteropoulos DS. Recovery of neurophysiological measures in post-COVID fatigue: a 12-month longitudinal follow-up study. Sci Rep. 2024;14(1):1–8 Available from: https://www.nature.com/articles/s41598-024-59232-y . Cited 24 May 2024.

40. Matias-Guiu JA, Herrera E, González-Nosti M, Krishnan K, Delgado-Alonso C, Díez-Cirarda M, et al. Development of criteria for cognitive dysfunction in post-COVID syndrome: the IC-CoDi-COVID approach. Psychiatry Res. 2023;319: 115006.

41. Herrera E, del Carmen Pérez-Sánchez M, San Miguel-Abella R, Barrenechea A, Blanco C, Solares L et al. Cognitive impairment in young adults with post COVID-19 syndrome. 123AD; https://doi.org/10.1038/s41598-023-32939-0. Cited 2024 May 28.

42. Fedorowski A, Sutton R. Autonomic dysfunction and postural orthostatic tachycardia syndrome in post-acute COVID-19 syndrome. Nat Rev Cardiol. 2023;20(5):281–2. https://www.nature.com/articles/s41569-023-00842-w.

43. Jennings S, Corrin T, Waddell L. A systematic review of the evidence on the associations and safety of COVID-19 vaccination and post COVID-19 condition. Epidemiol Infect. 2023;151:e145 Available from: https://www.cambridge.org/core/product/identifier/S0950268823001279/type/journal_article.

44. Byambasuren O, Stehlik P, Clark J, Alcorn K, Glasziou P. Effect of covid-19 vaccination on long covid: systematic review. BMJ Med. 2023;2(1):e000385.

45. Sigfrid L, Drake TM, Pauley E, Jesudason EC, Olliaro P, Lim WS, et al. Long covid in adults discharged from UK hospitals after Covid-19: a prospective, multicentre cohort study using the ISARIC WHO clinical characterisation protocol. Lancet Reg Health - Eur. 2021;8:100186. https://doi.org/10.1016/j.lanepe.2021.100186.

Publisher's Note