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Review

Post-COVID syndrome. A case series and comprehensive review

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ABSTRACT

The existence of a variety of symptoms with a duration beyond the acute phase of COVID-19, is referred to as post-COVID syndrome (PCS). We aimed to report a series of patients with PCS attending a Post-COVID Unit and offer a comprehensive review on the topic. Adult patients with previously confirmed SARS-CoV-2 infection and PCS were systematically assessed through a semi-structured and validated survey. Total IgG, IgA and IgM serum antibodies to SARS-CoV-2 were evaluated by an electrochemiluminescence immunoassay. A systematic review of the literature and meta-analysis were conducted, following PRISMA guidelines. Univariate and multivariate methods were used to analyze data. Out of a total of 100 consecutive patients, 53 were women, the median of age was 49 years (IQR: 37.8–55.3), the median of post-COVID time after the first symptoms was 219 days (IQR: 143–258), and 65 patients were hospitalized during acute COVID-19. Musculoskeletal, digestive (i.e., diarrhea) and neurological symptoms including depression (by Zung scale) were the most frequent observed in PCS patients. A previous hospitalization was not associated with PCS manifestation. Arthralgia and diarrhea persisted in more than 40% of PCS patients. The median of anti-SARS-CoV-2 antibodies was 866.2 U/mL (IQR: 238.2–1681). Despite this variability, 98 patients were seropositive. Based on autonomic symptoms (by COMPASS 31) two clusters were obtained with different clinical characteristics. Levels of anti-SARS-CoV-2 antibodies were not different between clusters. A total of 40 articles (11,196 patients) were included in the meta-analysis. Fatigue/ muscle weakness, dyspnea, pain and discomfort, anxiety/depression and impaired concentration were presented in more than 20% of patients reported. In conclusion, PCS is mainly characterized by musculoskeletal, pulmonary, digestive and neurological involvement including depression. PCS is independent of severity of acute illness and humoral response. Long-term antibody responses to SARS-CoV-2 infection and a high inter-individual variability were confirmed. Future studies should evaluate the mechanisms by which SARS-CoV-2 may cause PCS and the best therapeutic options.

1. Introduction

During acute infection of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), responsible of the coronavirus disease 2019 (COVID-19), symptoms vary from mild forms to critical and more severe cases [1–3]. Symptoms in the mildest forms include dry cough, fatigue, anosmia, and fever. On the other hand, in the most severe forms, the symptoms can progress to respiratory failure requiring invasive

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mechanical ventilation [2,4,5]. Although most of the COVID-19 patients recover completely, without sequelae, many patients may continue experiencing COVID-19 symptoms after infection recovery and others may even develop new symptoms [6]. Altogether, this clinical spectrum occurring after acute infection is called post-COVID syndrome (PCS) [7]. Some authors have defined PCS as the presence of signs and symptoms after acute COVID-19 infection for more than 4 weeks [8,9].

Among the most frequently reported PCS symptoms are fatigue, headache, attention deficit, hair loss, dyspnea, myalgia, and arthralgia [10]. However, a wide variety of symptoms have been reported within the PCS involving multiple organs and systems demanding long-term follow-up [8,9], and even rehospitalization due to severity of PCS. In addition, most of these patients have comorbidities such as cardiovascular diseases, diabetes mellitus, obesity, cancer, and chronic kidney diseases [8,9]. Therefore, it is crucial to understand the heterogeneity of PCS. The objective of this work was to describe the clinical and serological characteristics (i.e., antibodies anti-SARS-CoV-2) of the first 100 consecutive post-COVID patients attending a post-COVID Unit in Bogota, Colombia. In addition, we conducted a systematic review and meta-analysis on the topic.

2. Methods

2.1. Study design

A cross-sectional study was conducted from March 18th to May 20th, 2021, at the post-COVID Unit lead by the Center for Autoimmune Diseases Research (CREA) at the Clínica del Occidente in Bogotá, Colombia. Patients older than 18 and previously confirmed SARS-CoV-2 by PCR in swab or sputum were invited to voluntary attend the post-COVID unit. The first 116 consecutive patients attending the post-COVID unit were assessed. Then, patients with history of vaccination against SARS-CoV-2 (n: 10), autoimmune diseases prior acute COVID-19 (n: 2), and patients without confirmed COVID-19 (n: 4) were excluded. A final sample size of 100 patients was included in the analyses. Of these patients, seven were asymptomatic during acute COVID-19.

Patients were systematically evaluated for post-COVID manifestations (see below), including depression and autonomic symptoms by validated scales, as well as for clinical characteristics during the acute COVID-19. All patients were tested for total anti-SARS-CoV-2 antibodies (see below for details). This study was done in compliance with Act 008430/1993 of the Ministry of Health of the Republic of Colombia, which classified it as minimal-risk research. All the patients were asked for their consent and were informed about the Colombian data protection law (1581 of 2012).

2.2. Survey validation

A semi-structured survey was constructed based on internationally validated questionnaires that sought information during and after COVID-19 acute infection [11–15]. It was validated by a consensus of expert physicians. Once validation and approval were obtained, a pilot test was done in a group of 30 volunteers. The pilot phase allowed to identify additional questions to assess systemic compromise, to organize queries, and adapt them to guarantee its interpretability by the respondent.

2.3. Survey and data collection

A total of 177 questions were included in the semi-structured survey, and distributed in the following areas: identification and consent, 6; sociodemographic and epidemiological characteristics, 12; past medical history, 15; diagnosis and clinical presentation of acute COVID-19, 29; current general state of health, 4; constitutional symptoms, 4; neuropsychological (including the composite autonomic symptom score 31 [COMPASS 31] and Zung scales), 58; sense organs, 10; cardiovascular,

6; pulmonary, 8; musculoskeletal, 11; dermatological, 4; gastrointestinal, 3; and COVID-19 vaccination information, 7 (https://forms.gle/QeD96DY6NZz53hAy7). All data were collected in an electronic and secure database as described elsewhere [16]. Depression was assessed by the Zung scale. This feature was categorized as follows: Zung score < 40 absence of depression, and Zung score ≥ 40 depression [17]. Autonomic symptoms were evaluated by COMPASS 31 [14,18].

2.4. Antibodies anti-SARS-CoV2

Total IgG, IgA and IgM antibodies to SARS-CoV-2 were evaluated in serum samples through the Elecsys Anti-SARS-CoV-2 electrochemiluminescence immunoassay "ECLIA" (Roche Diagnostics International AG, Rotkreuz, Switzerland). The Elecsys anti-SARS-CoV-2 S assay detects antibodies to SARS-CoV-2 Receptor Binding Domain (RBD) in a double-antigen sandwich assay format. The protocol was followed according to manufacturer instructions. Positive results by the ECLIA require a signal-to-cut-off (S/Co) value of ≥0.80 U/mL. Serum samples were initially analyzed directly without dilution, in case of results >250 U/mL, the serum sample was diluted 1:10, according to manufacturer's recommendations. An internal validation procedure was performed, that included samples previously tested by enzyme-linked immunosorbent assay (ELISA, Euroimmun, Luebeck, Germany), and a neutralizing antibody assay (Supplementary Material 1).

2.5. Information sources and search strategy for systematic review

A systematic review of the literature was done following the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guideline [19]. PubMed was systematically searched for published and unpublished studies. Additional manual searches of the references cited in the articles were done. The search included articles up to May 8th, 2021. No restrictions were placed on study period or sample size. Other information sources such as personal communications and author's repositories were included. Terms used for this search were: ("Post-COVID" OR "Long COVID") AND ("COVID-19"). Articles in Spanish and English were included.

2.6. Eligibility criteria

Studies meeting the following criteria were included: (a) studies describing clinical manifestations after acute COVID-19, (b) studies evaluating patients in clinical settings, (c) case series, cross-sectional, case-control, cohort, or clinical trial studies were also included, (d) studies including data from national registries or unaudited databases were excluded.

2.7. Study selection

Study selection was done independently by three reviewers (i.e., GR, ML, JMA) who evaluated studies for eligibility in a two-step procedure. In the first phase, all identified titles and abstracts were evaluated to ensure the relationship with PCS. The potentially relevant articles were subsequently selected and evaluated again in the second phase. Here, a full-text review was done to determine whether the studies effectively reported the data about the clinical features of PCS. Retrieved articles were rejected if the eligibility criteria were not meet, and a fourth reviewer (i.e., MRJ) was consulted in cases in which the eligibility criteria were not clear.

2.8. Data extraction and quality assessment

Data were extracted using a standardized form to include the following variables: author, country, region, age, gender, post-COVID time, and clinical features as specified for our clinical study. A single author (i.e., GR) extracted the information, and a second reviewer (i.e.,
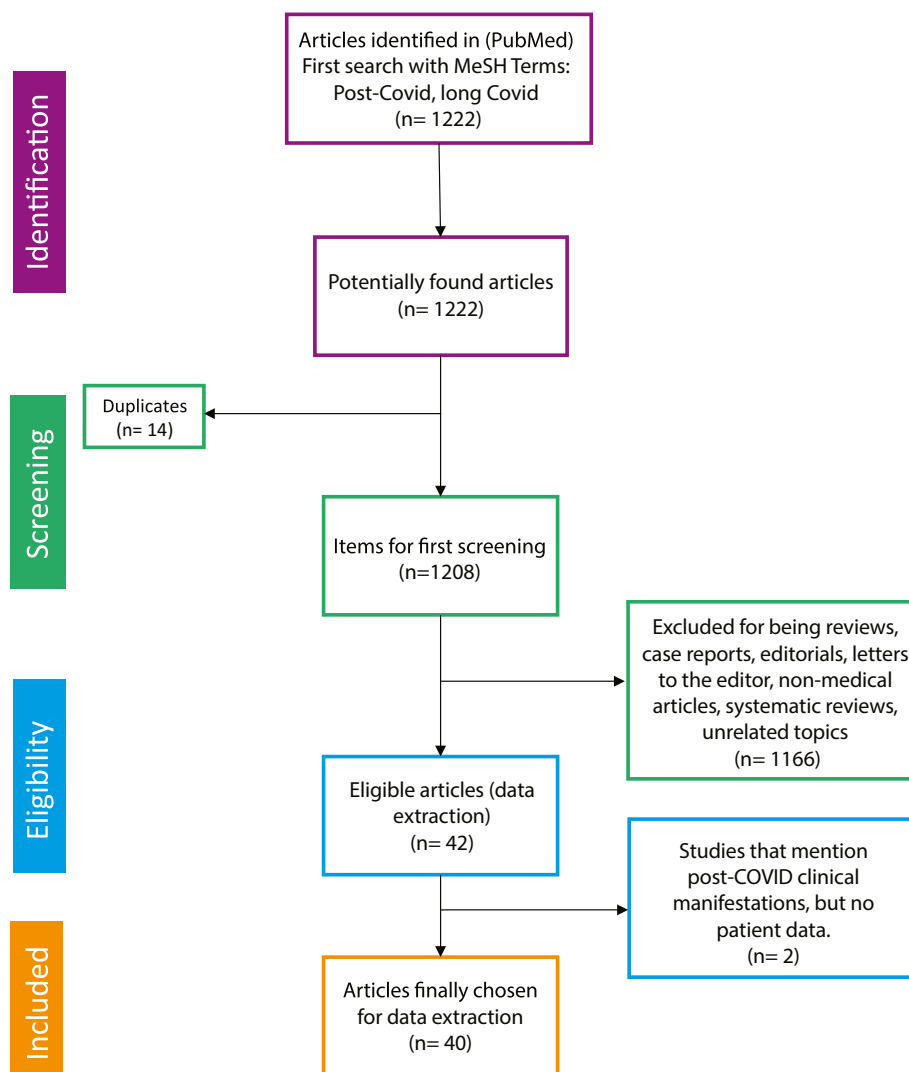
Fig. 1. Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) flow chart.

ML) verified the extracted information. Any discrepancies or missing information were resolved by consensus.

Given the discrepancies across the studies regarding the reporting of clinical manifestations, several clinical features were gathered to improve the reliability and interpretability of meta-analysis. These clinical manifestations included: impaired concentration, cognitive impairment, asthenia, dementia, polyneuropathy, heat intolerance/flushing, dizziness, headache, dysautonomia, blurry vision, xerophthalmia/sicca symptoms, nasal congestion, sneezing/coryza, palpitations, diarrhea/vomiting, dyspepsia, fatigue, arthralgia/myalgia, dyspnea, pleuritic pain, myocarditis, anxiety/depression, burning feet pain, fever, insomnia/sleep disorders. Evaluation of quality of the eligible studies was not performed. The PRISMA flowchart for systematic reviews is presented in Fig. 1.

2.9. Statistical analysis

Univariate descriptive statistics were performed. Categorical variables were analyzed using frequencies, and quantitative continuous variables were expressed the median and interquartile range (IQR). The Kruskal–Wallis, Mann–Whitney *U* test, or Fisher exact tests were used based on the results. In addition, Bonferroni correction was used for multiple testing on acute and post-COVID clinical manifestations.

To summarize the diverse information of frequencies of post-COVID manifestations, a meta-analysis approach was employed using Metafor R package (http://www.jstatsoft.org/v36/i03/). The logit transformed proportion was used to derive the weighted proportion. The overall pooled prevalence and 95% confidence intervals (CIs) were obtained using a random effect model for each clinical manifestation. Statistical heterogeneity between studies was evaluated by Cochran's Q-statistic, as well as Tau^2 and I^2 statistics. A P value >0.10 in Q-statistics or < 50% in I^2 statistic indicated a lack of heterogeneity.

Next, we aimed to evaluate the likely influence of autonomic symptoms in severity of PCS, and their association with clinical phenotypes. Thus, a K-means clustering analysis based on the algorithm of Hartigan and Wong on weighted COMPASS 31 domains was conducted [20]. Shortly, the K-means method, aims to partition the points into *k* groups such that the sum of squares from points to the assigned cluster centers is minimized. For this analysis, 25 random sets were used, and a final optimal number of clusters were obtained based on the average silhouette width. In addition, patients were evaluated based on their clinical status during acute COVID-19. The significance level of the study was set to 0.05. Statistical analyses were done using R software version 4.0.2.

Table 1
General characteristics of 100 post-COVID patients.

Variable	Post-COVID
	n: 100
Sex	
Female	53 (53.0%)
Male	47 (47.0%)
Age (Median -IQR)	49 (37.8–55.3)
Body mass index (Median -IQR)	28.1 (25.1–30.4)
Post-COVID time (days, Median -IQR)	219 days (143–258)
Comorbidities (Prior COVID-19)	
Hypertension	17 (17.0%)
Type 2 diabetes	15 (15.0%)
COPD	1 (1.0%)
Cancer	1 (1.0%)
Dyslipidemia	12 (12.0%)
Kidney disease	3 (3.0%)
Hypothyroidism	12 (12.0%)
Asthma	0 (0.0%)
Coronary artery disease	0 (0.0%)
Clinical management	
Hospitalization	65 (65.0%)
Days of hospitalization (Median -IQR)	11 (7.5–16.5)
ICU	24/65 (36.9%)
Days of ICU (Median -IQR)	10 (6.5–14)
Acute COVID-19 symptoms	
Fatigue	79 (79.0%)
Headache	67 (67.0%)
Myalgia	66 (66.0%)
Arthralgia	62 (62.0%)
Fever	62 (62.0%)
Dry cough	61 (61.0%)
Dyspnea	59 (59.0%)
Ageusia	53 (53.0%)
Anosmia	51 (51.0%)
Pharyngitis	48 (48.0%)
Diarrhea	40 (40.0%)
Dizziness	35 (35.0%)
Rhinorrhea	34 (34.0%)
Confusion	21 (21.0%)
Vomiting	19 (19.0%)
Blurry vision	18 (18.0%)
Impaired visual acuity	13 (13.0%)
Edema	10 (10.0%)
Post-COVID manifestations	
Arthralgia	65 (65.0%)
Back pain	55 (55.0%)
Arms/legs heaviness	47 (47.0%)
Weakness	46 (46.0%)
Diarrhea	46 (46.0%)
Headache	45 (45.0%)
Myalgia	42 (42.0%)
Body pain	40 (40.0%)
Paresthesia	38 (38.0%)
Attention disorders	36 (36.0%)
Memory disorders	36 (36.0%)
Fatigue	34 (34.0%)
Depression	32 (32.0%)
Dizziness	31 (31.0%)
Chest tightness	30 (30.0%)
Tachycardia	29 (29.0%)
Chest pain	29 (29.0%)
Eye pain	27 (27.0%)
Anorexia	23 (23.0%)
Chills	19 (19.0%)
Weight loss	20 (20.0%)
Exanthema	26 (26.0%)
Blisters	8 (8.0%)
Skin sensitivity	15 (15.0%)
Sarcopenia	28 (28.0%)
Palpitations	27 (27.0%)
Xerostomia	26 (26.0%)
Abdominal pain	24 (24.0%)
Dyspnea	24 (24.0%)
Tinnitus	23 (23.0%)
Xerophthalmia	23 (23.0%)
Vision disorders	21 (21.0%)

Table 1 (*continued*)

Variable	Post-COVID
	n: 100
Pharyngitis	19 (19.0%)
Rhinorrhea	19 (19.0%)
Sickness	19 (19.0%)
Dry cough	17 (17.0%)
Inability to walk	16 (16.0%)
Pleurisy	16 (16.0%)
Ageusia	15 (15.0%)
Alopecia	13 (13.0%)
Edema	12 (12.0%)
Anosmia	11 (11.0%)
Wet cough	10 (10.0%)
Erectile dysfunction	3 (3.0%)
Tooth Loss	2 (2.0%)
New onset AD	2 (2.0%)
Hemoptysis	1 (1.0%)
Seizures	1 (1.0%)
Insomnia	1 (1.0%)
COMPASS 31 score (Median -IQR)	9 (4–17)
Zung score (Median -IQR)	35.5 (30–41.5)
Thyroid stimulating hormone (µIU/mL) (Median -IQR)	2.2 (1.5–3.3)
Total anti-SARS-CoV-2 antibodies (U/mL) (Median -IQR)	866.2 (238.2–1681)

IQR: Interquartile range; ICU: Intensive care unit; COPD: Chronic pulmonary obstructive disease; AD: Autoimmune disease; COMPASS 31: Composite Autonomic Symptom Score 31; COVID-19: Coronavirus disease 2019; SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2. Thyroid stimulating hormone, by electroquimioluminiscence using the following thresholds: 0.3–4.5 µIU/mL.

3. Results

3.1. General characteristics

General characteristics of patients are shown in Table 1. Out of a total of 100 patients, 53 were women, the median age was 49 years (IQR: 37.8–55.3), the median of post-COVID time was 219 days (IQR: 143–258), and 65 patients were hospitalized during the acute COVID-19. Constitutional symptoms, musculoskeletal and respiratory symptoms, ageusia and anosmia were the most frequent clinical manifestations registered during the acute illness (Table 1).

3.2. Post-COVID manifestations

Musculoskeletal, digestive (i.e., diarrhea) and neurological symptoms including depression (35%) were the most frequent observed during PCS (Table 1, Fig. 2A–B). One-third of PCS patients presented with at least one musculoskeletal, respiratory, gastrointestinal and neurological symptoms simultaneously (Fig. 2C). Interestingly, there were a reduction in the frequency of some acute symptoms reported by patients. However, arthralgia and diarrhea persisted in more than 40% of the patients during PCS (Fig. 2D).

A median of anti-SARS-CoV-2 antibodies of 866.2 U/mL (IQR: 238.2–1681) was observed, indicating large inter-individual variability (Table 1). Despite this variability, almost all patients (98.0%) presented positivity for anti-SARS-CoV-2 antibodies (value of ≥0.80 U/mL, Fig. 3), of whom 88 patients disclosed titles above 151.4 U/mL.

Evaluation of PCS based on severity of acute illness showed that hospitalized and critically ill patients were older, more likely to exhibit elevated body mass index, higher frequency of hypertension, fatigue, and fever on admission that ambulatory patients (Table 2). Noteworthy, during the PCS a previous hospitalization was not associated with any clinical manifestation. The levels of antibodies anti-SARS-CoV-2 were lower in patients who were not previously hospitalized (Table 2). However, ambulatory patients were evaluated in earlier phases of PCS than hospitalized and critically ill patients (Kruskal–Wallis test, P < 0.0001).
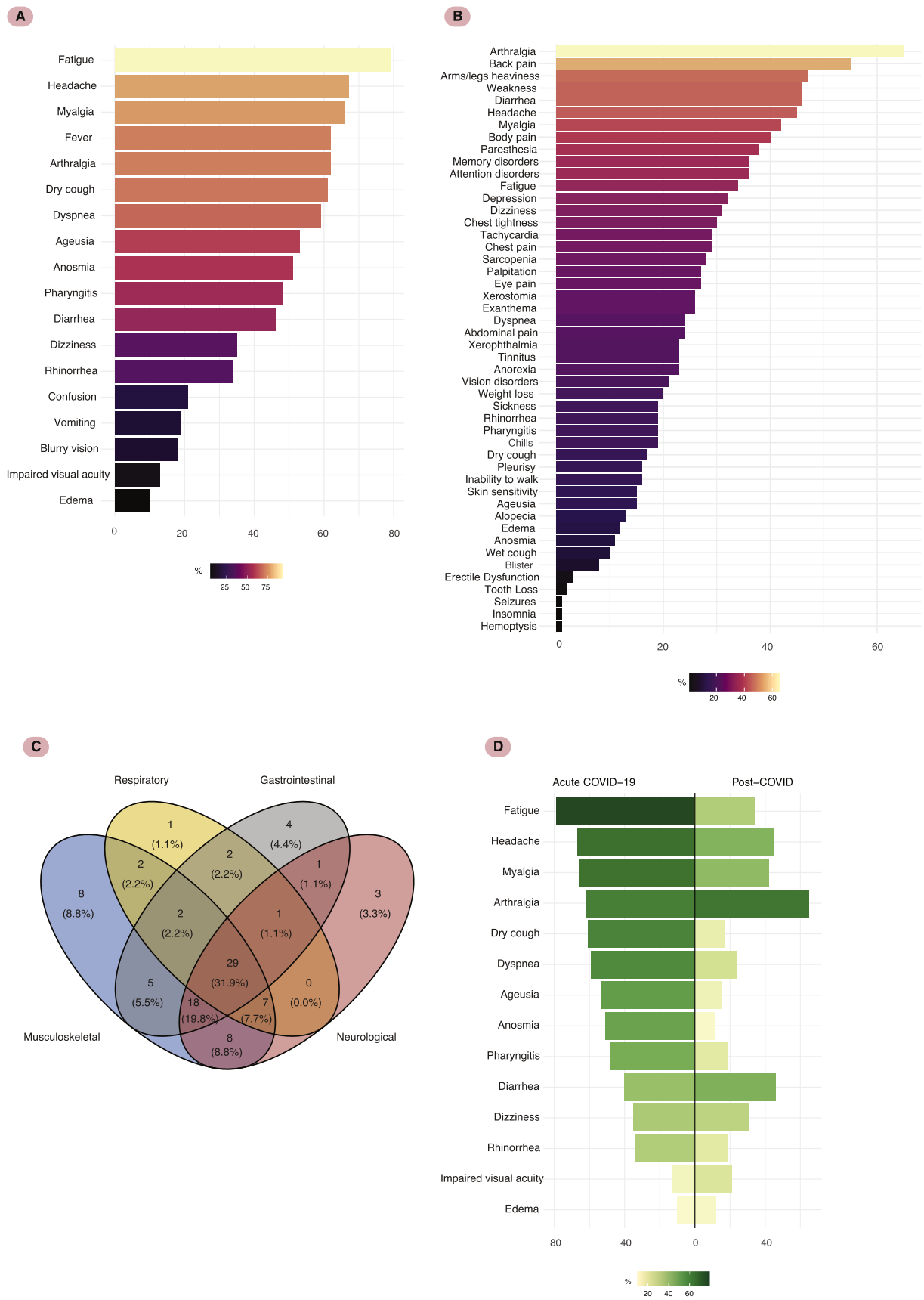
Fig. 2. Acute and post-COVID symptoms. A. Frequency bar plot for clinical manifestations on acute COVID-19. B. Frequency bar plot for post-COVID clinical manifestations. Frequency of depression was estimated by Zung scale. C. Venn diagram with the superposition of the main PCS symptoms. Analysis included 91

patients, because 9 out of 100 patients did not exhibit any of the four main symptoms. D. Mirrored bar plot for symptoms on acute COVID-19 and post-COVID syndrome.
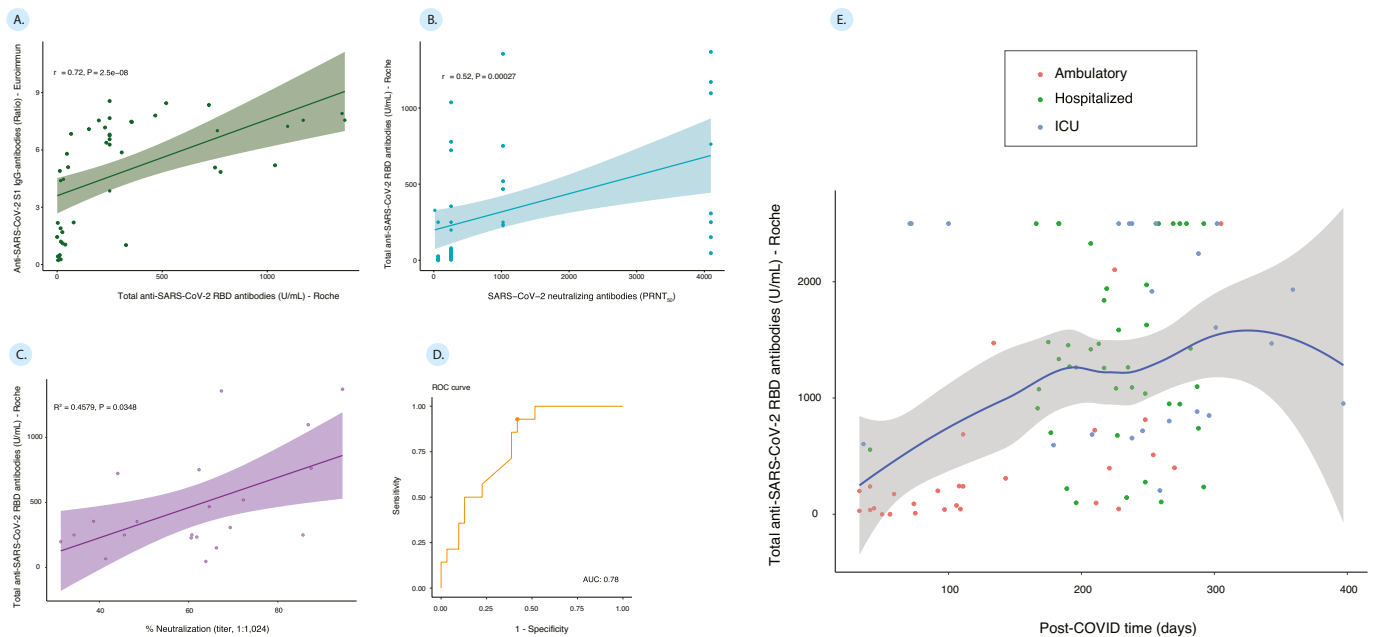

Fig. 3. Anti RBD SARS-CoV-2 antibodies (see Supplementary Material 1 for details). A. Correlation between IgG anti-SARS-CoV-2 by ELISA (Euroimmun) and total anti-SARS-CoV-2 antibodies by ECLIA (Roche). B. Correlation between neutralizing anti-SARS-CoV-2 antibodies ($PRNT_{50}$) and total anti-SARS-CoV-2 antibodies by ECLIA (Roche). C. Linear model for neutralizing antibodies based on ECLIA. D. ROC curve for the estimated cut-off value. The AUC represents the discrimination capacity of this threshold. E. Scatter plot for total anti-SARS-CoV-2 antibodies (by ECLIA, Roche) and post-COVID time. Line represents the locally estimated scatterplot smoothing with 95% confidence intervals.

3.3. Post-COVID systematic review

Initially, 1222 records were found through the database search. After duplicate studies were excluded, a total of 1208 studies were obtained. After the first records were screened by title and abstract, 42 articles were fully assessed for eligibility. Of these, 2 articles were excluded, since they reported PCS clinical manifestations but not patient data. This procedure left 40 articles (11,196 patients) that fulfilled the inclusion criteria, and they were included in the quantitative and qualitative synthesis (Fig. 1 and Supplementary Material 2).

3.4. Studies characteristics

Out of 40 studies included in the systematic review [7,10,21–58], 30 were cohort studies, 5 cross-sectional, 3 case series, and 2 case-control studies. No clinical trials were included in the systematic review and meta-analysis.

3.5. Post-COVID meta-analysis

Pooled prevalence of PCS manifestations is summarized in Table 3. Fatigue/muscle weakness, dyspnea, pain and discomfort, anxiety/depression and impaired concentration were presented in more than 20% of patients included in the meta-analysis (Fig. 4). These symptoms were reported in more than five manuscripts in the literature review. In addition, high methodological and statistical heterogeneity was found in this analysis, accounting for most of the imprecision detected by the Q and I^2 statistics.

3.6. Autonomic clusters in post-COVID syndrome

Based on autonomic symptoms (by COMPASS 31) two clusters were

obtained (Table 4, Fig. 5A). Impaired visual acuity and blurry vision were more frequently registered during the acute phase in patients belonging to cluster 2 that cluster 1 (Fig. 5B), while depression, chills, weakness, diarrhea, musculoskeletal, palpitations/tachycardia, dryness, cognitive involvement, headache, dizziness, and tinnitus were more frequently observed in the post-COVID cluster 2 (Fig. 5C). As expected, COMPASS 31 score was higher in cluster 2 than in cluster 1, as were the median Zung scores. Levels of antibodies were not different between clusters (Table 4).

4. Discussion

This study indicates that a significant number of patients present with a clinical spectrum after SARS-CoV-2 infection recovery, affecting the quality of life and requiring interdisciplinary approach. Although the cases series do not evaluate incidence nor prevalence, musculoskeletal, digestive (i.e., diarrhea) and neurological symptoms including depression were the most frequent observed in our PCS patients. Arthralgia and diarrhea were the two more frequent acute clinical manifestations persisting during the PCS. Our results were consistent with the meta-analysis in which fatigue/muscle weakness, dyspnea, pain and discomfort, anxiety/depression and impaired concentration were presented in more than 20% of patients. Noteworthy, PCS was independent of severity of acute illness and the humoral response to RBD SARS-CoV-2.

The causes of PCS are under study, however the main hypotheses include a persisting chronic inflammatory process, an autoimmune phenomenon or even a hormonal imbalance as a consequence of an alteration in the hypothalamic-pituitary-adrenal axis [59]. In this line, a study on COVID-19 patients at 3–6 months of convalescence showed that patients with PCS exhibit high levels of CD27^{−} IgD^{−} B cells (which have been associated with autoimmune diseases such as multiple sclerosis [60]), CD8+ T cells, as well as elevated production of Th1 and

Table 2

General characteristics of post-COVID patients based on severity of acute disease.

Variable	Ambulatory	Severe disease	Critical disease	P value[a]
	n: 35	n: 41	n: 24	
Sex				<0.0001
Female	30 (85.7%)	15 (36.6%)	8 (33.3%)	
Male	5 (14.3%)	26 (63.4%)	16 (66.7%)	
Age (Median -IQR)	41 (95.5–49.5)	51 (44–55)	52.5 (41.3–59.5)	0.0020
Body mass index (Median -IQR)	25.4 (23.6–28.4)	28.8 (26–32)	28.3 (25.7–30.3)	0.0006
Post-COVID time (days, Median -IQR)	108.5 (58.3–213.5)	277 (190–260)	250 (205–290)	<0.0001
Comorbidities (Prior COVID-19)				
Hypertension	2 (5.7%)	8 (19.5%)	7 (29.2%)	0.0361
Type 2 diabetes	2 (5.7%)	7 (17.1%)	6 (25.0%)	0.0943
COPD	0 (0.0%)	1 (2.4%)	0 (0.0%)	1.0000
Cancer	1 (2.9%)	0 (0.0%)	0 (0.0%)	0.5900
Dyslipidemia	1 (2.9%)	6 (14.6%)	5 (20.8%)	0.0733
Kidney disease	1 (2.9%)	1 (2.4%)	1 (4.2%)	1.0000
Hypothyroidism	2 (5.7%)	8 (19.5%)	2 (8.3%)	0.1824
Asthma	0 (0.0%)	0 (0.0%)	0 (0.0%)	–
Coronary artery disease	0 (0.0%)	0 (0.0%)	0 (0.0%)	–
Acute COVID-19 symptoms				
Anosmia	20 (57.1%)	22 (53.7%)	9 (37.5%)	0.3156
Ageusia	22 (62.9%)	22 (53.7%)	9 (37.5%)	0.1764
Fatigue	19 (54.3%)	38 (92.7%)	22 (91.7%)	<0.0001*
Headache	25 (71.4%)	28 (68.3%)	14 (58.3%)	0.5896
Dry cough	16 (45.7%)	27 (65.9%)	18 (75.0%)	0.0580
Rhinorrhea	12 (34.3%)	15 (36.6%)	7 (29.2%)	0.8301
Pharyngitis	17 (48.6%)	20 (48.8%)	11 (45.8%)	1.0000
Dizziness	11 (31.4%)	14 (34.1%)	10 (41.7%)	0.7186
Confusion	5 (14.3%)	7 (17.1%)	9 (37.5%)	0.0916
Impaired visual acuity	3 (8.6%)	8 (19.5%)	2 (8.3%)	0.3112
Blurry vision	5 (14.3%)	11 (26.8%)	2 (8.3%)	0.1586
Dyspnea	15 (42.9%)	27 (65.9%)	17 (70.8%)	0.0599
Diarrhea	9 (25.7%)	23 (56.1%)	8 (33.3%)	0.0203
Vomiting	4 (11.4%)	12 (29.3%)	3 (12.5%)	0.1161
Myalgia	20 (57.1%)	32 (78.0%)	14 (58.3%)	0.1071
Arthralgia	21 (60.0%)	27 (65.9%)	14 (58.3%)	0.7796
Edema	5 (14.3%)	4 (9.8%)	1 (4.2%)	0.5328
Fever	13 (37.1%)	30 (73.2%)	19 (79.2%)	0.0010*
Post-COVID symptoms				
Depression	13 (37.1%)	8 (19.5%)	11 (45.8%)	0.0661
New onset AD	2 (5.7%)	0 (0.0%)	0 (0.0%)	0.1760
Anorexia	9 (25.7%)	8 (19.5%)	6 (25.0%)	0.8272
Chills	7 (20.0%)	8 (19.5%)	4 (16.7%)	1.0000
Weight Loss	8 (22.9%)	6 (14.6%)	6 (25.0%)	0.5092
Exanthema	9 (25.7%)	12 (29.3%)	5 (20.8%)	0.7705
Blisters	4 (11.4%)	3 (7.3%)	1 (4.2%)	0.7217
Skin sensitivity	8 (22.9%)	7 (17.1%)	0 (0.0%)	0.0347
Sarcopenia	6 (17.1%)	11 (26.8%)	11 (45.8%)	0.0601
Weakness	14 (40.0%)	15 (36.6%)	17 (70.8%)	0.0221
Myalgia	14 (40.0%)	17 (41.5%)	11 (45.8%)	0.9333
Back pain	15 (42.9%)	24 (58.5%)	16 (66.7%)	0.1752
Arms/legs heaviness	12 (34.3%)	22 (53.7%)	13 (54.2%)	0.1825
Inability to walk	3 (8.6%)	7 (17.1%)	6 (25.0%)	0.2323
Body pain	10 (28.6%)	17 (41.5%)	13 (54.2%)	0.1420
Arthralgia	20 (57.1%)	28 (68.3%)	17 (70.8%)	0.4965
Fatigue	9 (25.7%)	15 (36.6%)	10 (41.7%)	0.4078
Palpitations	9 (25.7%)	11 (26.8%)	7 (29.2%)	0.9593
Xerostomia	9 (25.7%)	8 (19.5%)	9 (37.5%)	0.2800
Chest tightness	9 (25.7%)	14 (34.1%)	7 (29.2%)	0.6980
Tachycardia	10 (28.6%)	12 (29.3%)	7 (29.2%)	1.0000
Edema	5 (14.3%)	6 (14.6%)	1 (4.2%)	0.4584
Chest pain	11 (31.4%)	11 (26.8%)	7 (29.2%)	0.9596
Hemoptysis	1 (2.9%)	0 (0.0%)	0 (0.0%)	0.5900

Table 2 (*continued*)

Variable	Ambulatory	Severe disease	Critical disease	P value[a]
	n: 35	n: 41	n: 24	
Dyspnea	11 (31.4%)	8 (19.5%)	5 (20.8%)	0.4587
Wet cough	3 (8.6%)	4 (9.8%)	3 (12.5%)	0.8373
Dry cough	4 (11.4%)	10 (24.4%)	3 (12.5%)	0.3186
Pleurisy	7 (20.0%)	6 (14.6%)	3 (12.5%)	0.7371
Rhinorrhea	3 (8.6%)	9 (22.0%)	7 (29.2%)	0.1036
Sickness	7 (20.0%)	10 (24.4%)	2 (8.3%)	0.2869
Abdominal pain	8 (22.9%)	11 (26.8%)	5 (20.8%)	0.8716
Paresthesia	11 (31.4%)	16 (39.0%)	11 (45.8%)	0.5271
Attention disorders	13 (37.1%)	9 (22.0%)	14 (58.3%)	0.0140
Memory disorders	12 (34.3%)	9 (22.0%)	15 (62.5%)	0.0047
Seizures	1 (2.9%)	0 (0.0%)	0 (0.0%)	0.5900
Headache	15 (42.9%)	18 (43.9%)	12 (50.0%)	0.8734
Dizziness	11 (31.4%)	12 (29.3%)	8 (33.3%)	0.9616
Xerophthalmia	6 (17.1%)	11 (26.8%)	6 (25.0%)	0.5947
Tooth Loss	1 (2.9%)	1 (2.4%)	0 (0.0%)	1.0000
Tinnitus	10 (28.6%)	7 (17.1%)	6 (25.0%)	0.4914
Anosmia	7 (20.0%)	3 (7.3%)	1 (4.2%)	0.1589
Ageusia	10 (28.6%)	3 (7.3%)	2 (8.3%)	0.0368
Vision disorders	4 (11.4%)	10 (24.4%)	7 (29.2%)	0.1985
Eye pain	7 (20.0%)	13 (31.7%)	7 (29.2%)	0.5483
Pharyngitis	4 (11.4%)	7 (17.1%)	8 (33.3%)	0.1227
Alopecia	5 (14.3%)	5 (12.2%)	3 (12.5%)	1.0000
Erectile dysfunction	0 (0.0%)	0 (0.0%)	3 (12.5%)	0.0125
Insomnia	1 (2.9%)	0 (0.0%)	0 (0.0%)	0.5900
COMPASS-31 score (Median -IQR)	7 (2.5–16)	9 (5–17)	13 (6.5–17.5)	0.3221
Zung score (Median -IQR)	36 (29.5–45)	32 (29–38)	38.5 (32.8–44.3)	0.1506
Thyroid stimulating hormone (μIU/mL) (Median -IQR)	1.90 (1.1–2.5)	2.66 (2.0–4.0)	2.06 (1.3–3.5)	0.0130
Total anti-SARS-CoV-2 antibodies (U/mL) (Median -IQR)[b]	200.2 (52.1–398.2)	1270 (911.5–1941)	1537.5 (780.9–2500)	<0.0001

IQR: Interquartile range; ICU: Intensive care unit; COPD: Chronic pulmonary obstructive disease; AD: Autoimmune disease; COMPASS 31: Composite Autonomic Symptom Score 31; COVID-19: Coronavirus disease 2019; SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2; Thyroid stimulating hormone, by electroquimioluminiscence using the following thresholds: 0.3–4.5 μIU/mL.

[a] P values for categorical variables were obtained by Fisher's exact test. Quantitative variables were analyzed by Kruskal–Wallis test.

[b] A linear regression model including total SARS-CoV-2 antibodies as dependent variable was conducted. Sex, age, body mass index, clinical management, and post-COVID time were included as covariates. Linear model confirmed that post-COVID time was a confounding factor for the difference of total SARS-CoV-2 antibodies among groups ($\beta = 4.36$, P = 0.0126). In addition, significant interactions for ICU management confirmed this result ($\beta = -5.65$, P = 0.0221).

* Statistically significant after Bonferroni correction. P value threshold for acute COVID-19 symptoms: 0.05/18 = 0.0028; P value threshold for post-COVID symptoms: 0.05/47 = 0.0011.

Th17 cytokines, thus favoring a hyperinflammatory milieu. In addition, patients showed B cell impaired response given by IL-6/IL-10 imbalance [61]. In a similar study, convalescent patients yielded high levels of tumor necrosis factor (TNF) and IL-1β [62]. Recovered patients showed high levels of endothelial activation markers and pro-inflammatory mediators such as growth factors platelet-derived growth factor, vascular endothelial growth factor, MIP-1β, eotaxin, IL-12p70, and IL-17A [63]. Thus, suggesting that clinical manifestations in PCS could be associated to persistence of a pro-inflammatory profile induced by

Table 3

Clinical features of post-COVID-19 patients (systematic review and meta-analysis).

Signs and symptoms	Number of articles[a]	Cases/COVID-19 (% - mean, 95% CI)[b]	Q (Tau², I²)
Demographics			
Male	40	5087/11196 (50.0%, 44.5–55.6)	< 0.01 (0.5, 96.3%)
Age (years)	34	10,081 (50.2 years, 47.0–53.5)	< 0.01 (90.0, 99.4%)
Time to follow-up (days)	7	2849 (105.9 days, 89.1–122.7)	< 0.01 (512.1, 99.8%)
Constitutional symptoms			
Fever	8	269/3064 (9.1%, 2.7–26.9)	< 0.01 (3.3, 98.1%)
Anorexia	5	173/2183 (8.0%, 6.9–9.2)	0.77 (0, 0.0%)
Weight loss	3	82/2414 (4.1%, 2.8–5.9)	0.01 (0.1, 41.5%)
Night sweats	3	49/774 (5.10%, 0.8–26.6)	< 0.01 (2.7, 96.4%)
Asthenia	2	49/126 (20.9%, 2.1–76.8)	0.01 (2.9, 83.9%)
Heat intolerance/ Flushing	2	276/2140 (10.0%, 3.6–25.1)	0.18 (0.4, 43.5%)
Neurological			
Headache	16	1365/7018 (14.2%, 7.7–24.6)	< 0.01 (1.8, 98.5%)
Cognitive impairment	14	464/2991 (14.8%, 6.1–31.8)	< 0.01 (3.4, 98.4%)
Dizziness	6	722/4912 (14.2%, 2.5–52.3)	< 0.01 (5.4, 99.5%)
Dementia	3	89/405 (12.4%, 4.3–30.9)	< 0.01 (0.8, 82.0%)
Polyneuropathy	3	5/69 (8.3%, 3.5–18.5)	0.5 (0, 0.0%)
Dysautonomia	2	11/58 (16.9%, 4.0–49.8)	0.1 (1.0, 73.8%)
Inability to walk	2	105/359 (26.3%, 9.4–55)	< 0.01 (0.8, 95.7%)
Stroke	2	9/445 (1.8%, 0.5–6.6)	0.16 (0.6, 49.9%)
Anomic aphasia	2	7/49 (14.9%, 3.2–48.5)	0.06 (1.1, 72.5%)
Tremor	2	7/305 (3.8%, 0.2–48.9)	< 0.01 (5.0, 93.0%)
Syncope	1	3/27 (11.1%, 3.6–29.3)	NA
Restless leg syndrome	1	2/355 (0.56%, 0.1–2.2)	NA
Ataxia	1	1/48 (2.1%, 0.3–13.4)	NA
Orthostatic headache	1	6/27 (22.2%, 10.3–41.5)	NA
Paresthesia	1	13/49 (26.5%, 16.1–40.5)	NA
Delirium	1	2/27 (7.4%, 1.9–25.3)	NA
Ophthalmological			
Blurry vision	4	86/746 (8.5%, 2.9–22.1)	< 0.01 (1.1, 93.5%)
Xeropthalmia/Sicca symptoms	3	42/171 (14.1%, 2.7–49.1)	< 0.01 (2.1, 90.4%)
Impaired visual acuity	2	41/802 (10.0%, 1.0–56.3)	< 0.01 (3.1, 98.0%)
Conjunctivitis	1	2/102 (2.0%, 0.5–7.5)	NA
Eye tearing	1	2/64 (3.1%, 0.8–11.7)	NA
Macular detachment	1	55/87 (63.2%, 52.6–72.7)	NA
Ocular burning sensation	1	15/64 (23.4%, 14.7–35.3)	NA
Red eye	1	2/64 (3.1%, 0.8–11.7)	NA

Table 3 (*continued*)

Signs and symptoms	Number of articles[a]	Cases/COVID-19 (% - mean, 95% CI)[b]	Q (Tau², I²)
Retinal cotton wool spots	1	9/70 (12.9%, 6.8–22.9)	NA
Vitreous fibrillary degeneration	1	10/70 (14.3%, 7.9–24.6)	NA
Otorhinolaryngological			
Ageusia	13	707/6628 (8.2%, 5.1–12.8)	< 0.01 (0.7, 96.4%)
Anosmia	17	926/7302 (10.8%, 6.9–16.5)	< 0.01 (1.0, 97.4%)
Sore throat	6	781/4504 (11.9%, 3.4–34.4)	< 0.01 (2.8, 99.2%)
Nasal congestion	5	490/3373 (8.0%, 1.9–27.8)	< 0.01 (2.7, 99.0%)
Tinnitus	4	80/848 (4.7%, 0.6–27.5)	< 0.01 (3.9, 97.7%)
Sneezing/Coryza	2	290/2768 (8.29%, 3.8–17.3)	< 0.01 (0.4, 95.4%)
Vertigo	2	11/629 (1.8%, 0.9–3.4)	0.28 (0.0, 13.6%)
Otalgia	1	169/2113 (8.0%, 6.9–9.2)	NA
Epistaxis	1	4/655 (0.6%, 0.2–1.6)	NA
Hypoacusia	1	1/48 (2.1%, 0.3–13.4)	NA
Laryngeal sensitivity	1	17/100 (17.0%, 10.8–25.7)	NA
Nasal itching	1	30/655 (4.6%, 3.2–6.5)	NA
Cold nose	1	380/2113 (18.0%, 16.4–19.7)	NA
Phonophobia	1	1/18 (5.6%, 0.8–30.7)	NA
Dysphagia	1	8/100 (8.0%, 4.1–15.2)	NA
Voice changes	1	20/100 (20.0%, 13.3–29.0)	NA
Respiratory			
Dyspnea	23	2829/6275 (34.9%, 23.3–48.6)	< 0.01 (1.9, 98.8%)
Cough	17	1166/5113 (17.1%, 10.1–27.5)	< 0.01 (1.5, 98.0%)
Pleuritic pain	2	521/2228 (18.0%, 9.0–32.8)	< 0.01 (0.5, 87.6%)
Pulmonary fibrosis	2	20/455 (4.5%, 2.9–6.9)	0.6 (0, 0.0%)
Xerotrachea	1	423/2113 (20.0%, 18.4–21.8)	NA
Expectoration	1	6/49 (12.3%, 5.6–24.7)	NA
Wheezing	1	98/201 (48.8%, 41.9–55.6)	NA
Cardiovascular			
Chest pain	13	1391/5576 (15.6%, 7.1–30.7)	< 0.01 (2.5, 98.9%)
Palpitations	7	943/5352 (11.7%, 4.6–26.7)	< 0.01 (1.8, 99.1%)
Myocarditis	3	21/344 (10.1%, 0.8–60.8)	< 0.01 (2.3, 94.9%)
Arrhythmia	2	3/318 (1.7%, 0.1–23.7)	0.02 (3.7, 82.7%)
Bradycardia	2	4/386 (1.9%, 0.2–18.5)	0.01 (2.6, 83.4%)
Pericardial effusion	1	7/26 (26.9%, 13.4–46.7)	NA
Gastrointestinal			
Diarrhea/Vomiting	9	641/6363 (9.5%, 4.6–18.4)	< 0.01 (1.3, 98.5%)
Nausea	4	266/2463 (6.7%, 3.4–12.9)	< 0.01 (0.4, 72.5%)
Dyspepsia	3	23/731 (2.7%, 1.0–7.0)	< 0.01 (0.5, 71.3%)
Abdominal pain	1	5/49 (10.2%, 4.3–22.3)	NA
Early satiety	1		NA

Table 3 (*continued*)

Signs and symptoms	Number of articles[a]	Cases/COVID-19 (% - mean, 95% CI)[b]	Q (*Tau²*, *I²*)
		1/27 (3.7%, 0.5–22.1)	
Genitourinary			
Urinary urgency	1	1/27 (3.7%, 0.5–22.1)	NA
Urinary hesitancy	1	1/27 (3.7%, 0.5–22.1)	NA
Musculoskeletal			
Fatigue/Muscle weakness	25	4872/8520 (46.1%, 32.9–59.8)	< 0.01 (1.9, 99.0%)
Arthralgia/Myalgia	13	1297/6279 (16.4%, 7.75–31.4)	< 0.01 (2.3, 99.2%)
Pain and discomfort	5	384/1179 (30.4%, 16.8–48.6)	< 0.01 (0.8, 95.9%)
Burning feet pain	2	4/382 (2.0%, 0.1–45.5%)	< 0.01 (6.5, 90.4%)
Numbness	1	1/27 (3.7%, 0.5–22.1)	NA
Back pain	1	689/2113 (30.0%, 31.1–35.7)	NA
Sarcopenia	1	11/11 (95.8%, 57.5–99.7)	NA
Dermatological			
Alopecia	7	685/3622 (17.5%, 9.1–30.9)	< 0.01 (0.93, 98.2%)
Rash	4	129/2690 (2.3%, 0.6–8.3)	NA
Allodynia	1	1/27 (3.7%, 0.5–22.1)	NA
Eczema	1	1/31 (3.2%, 0.5–19.6)	NA
Hyperhidrosis	1	3/27 (11.1%, 3.6–29.3)	NA
Hypohidrosis	1	1/27 (3.7%, 0.5–22.1)	NA
Red spots on toes	1	42/2113 (2.0%, 1.5–2.7)	NA
Psychiatric			
Insomnia/Sleep disorders	13	1367/5666 (19%, 10.6–32.6)	< 0.01 (1.6, 99.0%)
Anxiety/Depression	12	835/3861 (24.5%, 16.2–35.1)	< 0.01 (0.8, 97.3%)
Impaired concentration	5	252/1029 (22.8%, 7.1–53.4)	< 0.01 (2.2, 97.5%)
Attention deficit	3	26/183 (22.2%, 5.99–56.0)	< 0.01 (1.6, 90.6%)
Post-traumatic stress	3	133/307 (42.5%, 30.0–56.1)	< 0.01 (0.2, 82.0%)
Adjustment disorder	1	5/355 (1.4%, 0.6–0.3)	NA
Obsessive compulsive disorder	1	14/287 (4.9%, 2.9–8.1)	NA
Panic attack	1	98/734 (13.4%, 11.1–16.0)	NA
Severe mood swings	1	2/18 (11.1%, 2.8–35.2)	NA

Tau² is the variance of the effect size parameters across the population of studies, and it reflects the variance of the true effect size (i.e., heterogeneity among studies). *I²* refers to the percentage of heterogenetic among the included studies. NA: Not applicable/available; Estimation was done assuming a random effects model.

[a] Results were ordered according to the number of articles included in each meta-analysis.

[b] COVID-19 represents the total of patients reported in selected articles.

COVID-19 during acute illness. In addition, this may suggest therapeutic targets for the specific management of PCS, including TNF blockade or immunomodulatory drugs.

Based on autonomic symptoms (by COMPASS 31) two clusters were obtained with different clinical characteristics. Cluster 2 exhibited high scores of COMPASS 31. This accounted for the 31% of all patients included (median COMPASS 31 score 22), suggesting that one-third of patients with PCS may yield higher scores when compared with the general population [64]. Interestingly, patients with higher scores exhibited more clinical manifestations and depression. These clusters may have therapeutic implications since clinicians should be aware of particular manifestations during the follow-up, and early psychosocial intervention may reduce the burden of PCS.

Persistence of symptoms has been evaluated in PCS. Moreno-Perez et al. [65], reported that up to 50.9% of the patients considered "recovered" persisted with symptoms similar to those experienced during the acute phase. Moreover, other studies showed that the reported duration of musculoskeletal symptoms varies widely depending on duration of patients follow-up [35,66–68]. Different protocols and populations as well as the preexistence of musculoskeletal symptoms, which were not evaluated in all the studies, preclude a comparative analysis. Nevertheless, early identification would allow to focus the therapeutic management of these patients [69].

Persistent elevation of IL-6 levels, an increase of the angiotensin-converting enzyme 2 in the peripheral nervous system and mast cell participation have been considered to explain the musculoskeletal symptoms in PCS [70–72]. Similarly, over-activation of nociceptive neurons, secondary to neurotropism of the virus, may cause prolongation of symptoms [73]. It is possible that most of the inflammatory response caused by the virus affects the integrity of the central and peripheral nervous system, which promotes the perpetuation of pain after the acute illness [74]. On the other hand, inflammatory damage, triggered by acute infection, would cause psychiatric disorders in predisposed individuals. These symptoms include depression, anxiety and, in worse situations, suicidal behavior [75].

Autonomic dysfunction was confirmed in our study. Orthostatic symptoms and hyperhidrosis have been described [56]. To date, it is unknown if a pre-existing history of minor autonomic symptoms may have some type of relation with autonomic disorders in PCS [76]. These results are relevant since disorders such as postural orthostatic tachycardia syndrome (POTS) and other autonomic dysfunctions may emerge after infectious triggers such as SARS-CoV-2 [77–81].

The mechanisms behind autonomic dysfunction are not clear. However, autoimmune phenomena could be associated with its appearance [82]. Production of autoantibodies against α1, β1 and β2 receptors, angiotensin II receptor type 1, opioids 1, acetylcholine, M2 and M4S receptors are associated with development of POTS [36,83–85]. This immune mechanism, secondary to SARS-CoV2, could be triggered through molecular mimicry between antigens of autonomic nerve fibers, autonomic ganglia, and SARS-CoV2 antigens, as described in some autoimmune conditions.

Respiratory symptoms in PCS are common. The meta-analysis indicated that up to 48% of patients with PCS persisted with respiratory symptoms. Some studies have shown the persistence of pulmonary radiological and functional changes after acute infection [53]. Among the main respiratory functional changes, alteration in gas transfer measured by diffusing capacity for carbon monoxide (DLCO) has been documented up to 12 weeks of follow-up [13,86–88]. DLCO alteration could be associated with interstitial and vascular damage, secondary to acute infection [89,90]. These features may depend on the severity of the disease during the acute COVID-19 [91–93]. Pulmonary radiological alterations have been documented after 12 months post-infection [53].

Some symptoms during acute COVID-19 have been reported to be predictors of PCS, including diarrhea, anosmia, dyspnea, pleurisy, skin sensitivity, and A blood type [15]. A lower SARS-CoV-2 IgG titer at the
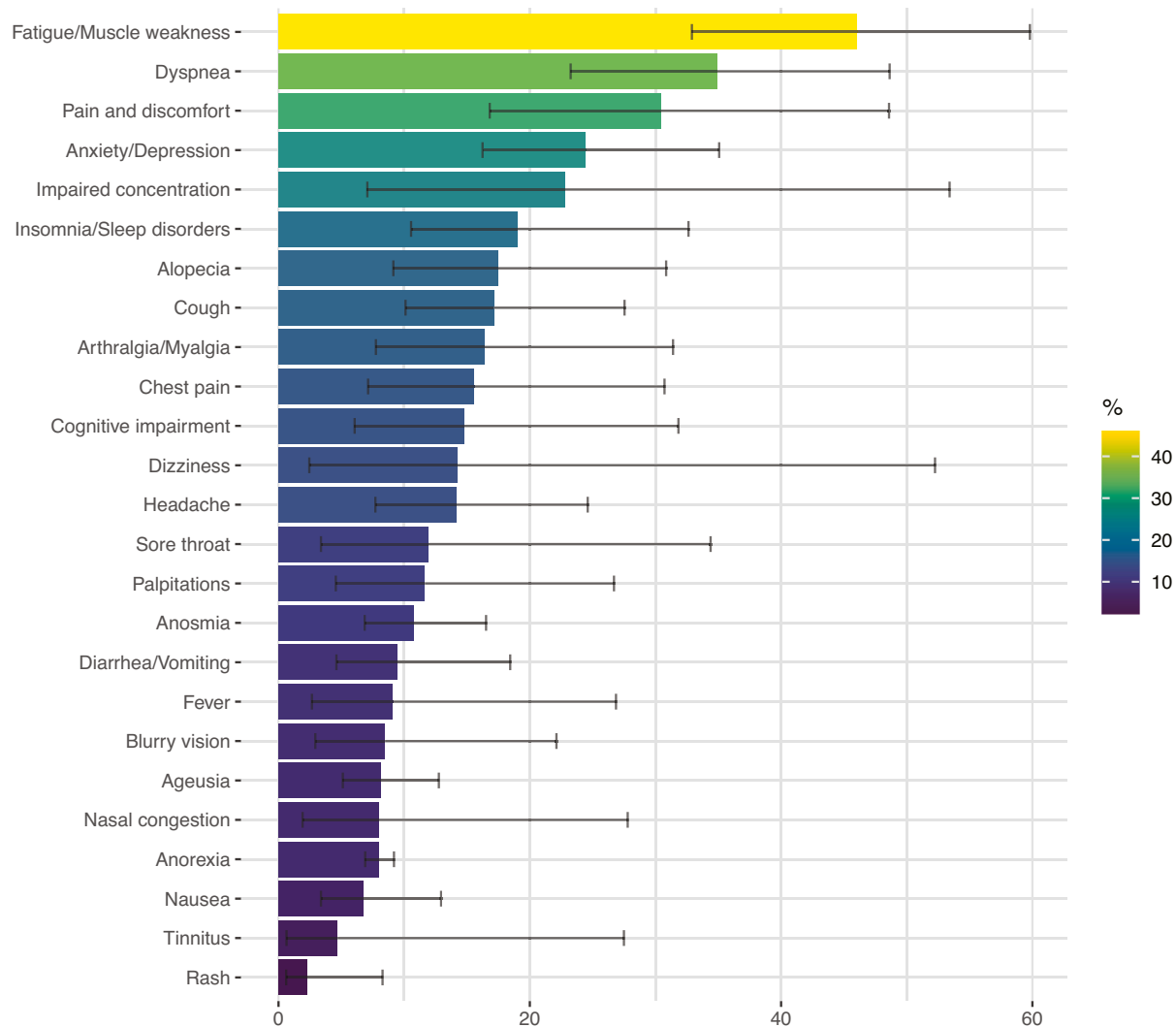
Fig. 4. Frequency bar plot for pooled prevalence of post-COVID manifestations in meta-analysis. Error bar represents the estimated 95% confidence interval. Only those clinical manifestations reported in more than 4 articles were included in this graph.

beginning of the observation period was associated with a higher frequency of PCS [94]. Severity of acute COVID-19 suggests that convalescent critically ill patients commonly experience long-lasting mental health illness. Anxiety, depression, post-traumatic stress disorder, memory and attention disorders are common [95]. However, in our case series severity of acute disease was not associated with PCS.

As expected, the levels of anti-SARS-CoV2 antibodies were lower in patients who were not previously hospitalized [96]. Our results confirm the heterogeneous but long-lasting humoral response to SARS-CoV-2 infection [97,98]. Other mechanisms beyond the humoral immune response can influence the persistence and/or triggering of PCS, such as viral shedding, therapy, clinical management, immune response, social isolation, comorbidities, age, sex, among others [54]. In terms of viral shedding, some studies have shown that persistent fragments of viral genes, including in feces though not infectious, could induce a hyperimmune response that explaining the persistence of symptoms in post-COVID patients [99,100]. Moreover, even if the virus is cleared, and

there are high neutralizing antibody titers, the immune system could continue to be overactive, thus inducing PCS [99].

5. Conclusions

PCS is mainly characterized by musculoskeletal, pulmonary, digestive and neurological involvement including depression. PCS is independent of severity of acute illness and humoral response. Our study confirms the long-term immunity for SARS-CoV-2 but also the inter-individual variability of the immune response. Future studies should evaluate the mechanisms by which SARS-CoV-2 may cause PCS and the best therapeutic options.

Post-COVID study group

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Table 4
Cluster analysis based on autonomic symptoms in post-COVID patients.

Variable	Cluster 1 (n: 69)	Cluster 2 (n: 31)	P value[a]
Sex			0.2873
Female	34 (49.3%)	19 (61.3%)	
Male	35 (50.7%)	12 (38.7%)	
Age (Median -IQR)	50 (41–55)	48 (37–55.5)	0.3748
Body mass index (Median -IQR)	28 (25.2–30.2)	28.1 (25–31.4)	0.9021
Post-COVID time (days, Median -IQR)	202 (111–257)	228 (207–257.5)	0.1177
Comorbidities (Prior COVID-19)			
Hypertension	12 (17.4%)	5 (16.1%)	1.0000
Diabetes type 2	10 (14.5%)	5 (16.1%)	1.0000
COPD	1 (1.4%)	0 (0.0%)	1.0000
Cancer	0 (0.0%)	1 (3.2%)	0.3100
Dyslipidemia	9 (13.0%)	3 (9.7%)	0.7495
Kidney disease	2 (2.9%)	1 (3.2%)	1.0000
Hypothyroidism	9 (13.0%)	3 (9.7%)	0.7495
Asthma	0 (0.0%)	0 (0.0%)	–
Coronary artery disease	0 (0.0%)	0 (0.0%)	–
Clinical management			
Hospitalization	43 (62.3%)	22 (71.0%)	0.4986
Days of hospitalization (Median -IQR)	11 (8–17)	12 (7.3–15.8)	0.8339
ICU	15 (34.9%)	9 (40.9%)	0.7866
Days of ICU (Median -IQR)	9.5 (4.5–13)	12 (7–15)	0.4678
Acute COVID-19 symptoms			
Anosmia	32 (46.4%)	19 (61.3%)	0.1981
Ageusia	34 (49.3%)	19 (61.3%)	0.2873
Fatigue	50 (72.5%)	29 (93.5%)	0.0173
Headache	41 (59.4%)	26 (83.9%)	0.0210
Dry cough	43 (62.3%)	18 (58.1%)	0.8249
Rhinorrhea	23 (33.3%)	11 (35.5%)	0.8239
Pharyngitis	31 (44.9%)	17 (54.8%)	0.3931
Dizziness	20 (29.0%)	15 (48.4%)	0.0722
Confusion	12 (17.4%)	9 (29.0%)	0.1960
Impaired visual acuity	4 (5.8%)	9 (29.0%)	0.0028*
Blurry vision	6 (8.7%)	12 (38.7%)	0.0006*
Dyspnea	35 (50.7%)	24 (77.4%)	0.0155
Diarrhea	22 (31.9%)	18 (58.1%)	0.0163
Vomiting	13 (18.8%)	6 (19.4%)	1.0000
Myalgia	40 (58.0%)	26 (83.9%)	0.0126
Arthralgia	40 (58.0%)	22 (71.0%)	0.2681
Edema	5 (7.2%)	5 (16.1%)	0.2773
Fever	40 (58.0%)	22 (71.0%)	0.2681
Post-COVID symptoms			
Depression	13 (18.8%)	19 (61.3%)	<0.0001*
New onset AD	0 (0.0%)	2 (6.5%)	0.0939
Anorexia	10 (14.5%)	13 (41.9%)	0.0043
Chills	5 (7.2%)	14 (45.2%)	<0.0001*
Weight Loss	10 (14.5%)	10 (32.3%)	0.0576
Exanthema	15 (21.7%)	11 (35.5%)	0.2170
Blisters	3 (4.3%)	5 (16.1%)	0.1031
Skin sensitivity	7 (10.1%)	8 (25.8%)	0.0666
Sarcopenia	13 (18.8%)	15 (48.4%)	0.0037
Weakness	22 (31.9%)	24 (77.4%)	<0.0001*
Diarrhea	23 (33.3%)	23 (74.2%)	0.0002*
Myalgia	19 (27.5%)	23 (74.2%)	<0.0001*
Back pain	27 (39.1%)	28 (90.3%)	<0.0001*
Arms/legs heaviness	21 (30.4%)	26 (83.9%)	<0.0001*
Inability to walk	4 (5.8%)	12 (38.7%)	<0.0001*
Fatigue	13 (18.8%)	21 (67.7%)	<0.0001*
Body pain	14 (20.3%)	26 (83.9%)	<0.0001*
Arthralgia	37 (53.6%)	28 (90.3%)	0.0003*
Palpitations	11 (15.9%)	16 (51.6%)	0.0005*
Xerostomia	9 (13.0%)	17 (54.8%)	<0.0001*
Chest tightness	12 (17.4%)	18 (58.1%)	<0.0001*
Tachycardia	11 (15.9%)	18 (58.1%)	<0.0001*
Edema	2 (2.9%)	10 (32.3%)	0.0001*
Chest pain	14 (20.3%)	15 (48.4%)	0.0079
Hemoptysis	1 (1.4%)	0 (0.0%)	1.0000
Dyspnea	13 (18.8%)	11 (35.5%)	0.0818
Wet cough	5 (7.2%)	5 (16.1%)	0.2773
Dry cough	8 (11.6%)	9 (29.0%)	0.0442
Pleurisy	7 (10.1%)	9 (29.0%)	0.0354

Table 4 (*continued*)

Variable	Cluster 1 (n: 69)	Cluster 2 (n: 31)	P value[a]
Rhinorrhea	9 (13.0%)	10 (32.3%)	0.0301
Sickness	10 (14.5%)	9 (29.0%)	0.1028
Abdominal pain	10 (14.5%)	14 (45.2%)	0.0019
Paresthesia	17 (24.6%)	21 (67.7%)	0.0001*
Attention disorders	15 (21.7%)	21 (67.7%)	<0.0001*
Memory disorders	12 (17.4%)	24 (77.4%)	<0.0001*
Seizures	0 (0.0%)	1 (3.2%)	0.3100
Headache	20 (29.0%)	25 (80.6%)	<0.0001*
Dizziness	11 (15.9%)	20 (64.5%)	<0.0001*
Xerophthalmia	10 (14.5%)	13 (41.9%)	0.0043
Tooth Loss	0 (0.0%)	2 (6.5%)	0.0939
Tinnitus	9 (13.0%)	14 (45.2%)	0.0008*
Anosmia	6 (8.7%)	5 (16.1%)	0.3089
Ageusia	8 (11.6%)	7 (22.6%)	0.2243
Vision disorders	8 (11.6%)	13 (41.9%)	0.0011*
Eye pain	11 (15.9%)	16 (51.6%)	0.0005*
Pharyngitis	7 (10.1%)	12 (38.7%)	0.0017
Alopecia	7 (10.1%)	6 (19.4%)	0.2152
Erectile dysfunction	2 (2.9%)	1 (3.2%)	1.0000
Insomnia	0 (0.0%)	1 (3.2%)	0.3100
COMPASS 31 score (Median -IQR)	6 (3–9)	22 (18–26)	<0.0001
Zung score (Median -IQR)	32 (26–37)	40 (36.5–47)	<0.0001
Thyroid stimulating hormone (μIU/mL) (Median -IQR)	2.14 (1.4–3.2)	2.4 (2.0–3.5)	0.2465
Total anti-SARS-CoV-2 antibodies (U/mL) (Median -IQR)	701.6 (220.7–1481)	1258 (336.5–1945)	0.2395

IQR: Interquartile range; ICU: Intensive care unit; COPD: Chronic pulmonary obstructive disease; AD: Autoimmune disease; COMPASS 31: Composite Autonomic Symptom Score 31; COVID-19: Coronavirus disease 2019; SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2. Thyroid stimulating hormone, by electroquimioluminiscence using the following thresholds: 0.3–4.5 μIU/mL.

[a] P values for categorical variables were obtained by Fisher's exact test. Quantitative variables were analyzed by Mann–Whitney U test.

* Statistically significant after Bonferroni correction. P value threshold for acute COVID-19 symptoms: 0.05/18 = 0.0028; P value threshold for post-COVID symptoms: 0.05/47 = 0.0011.
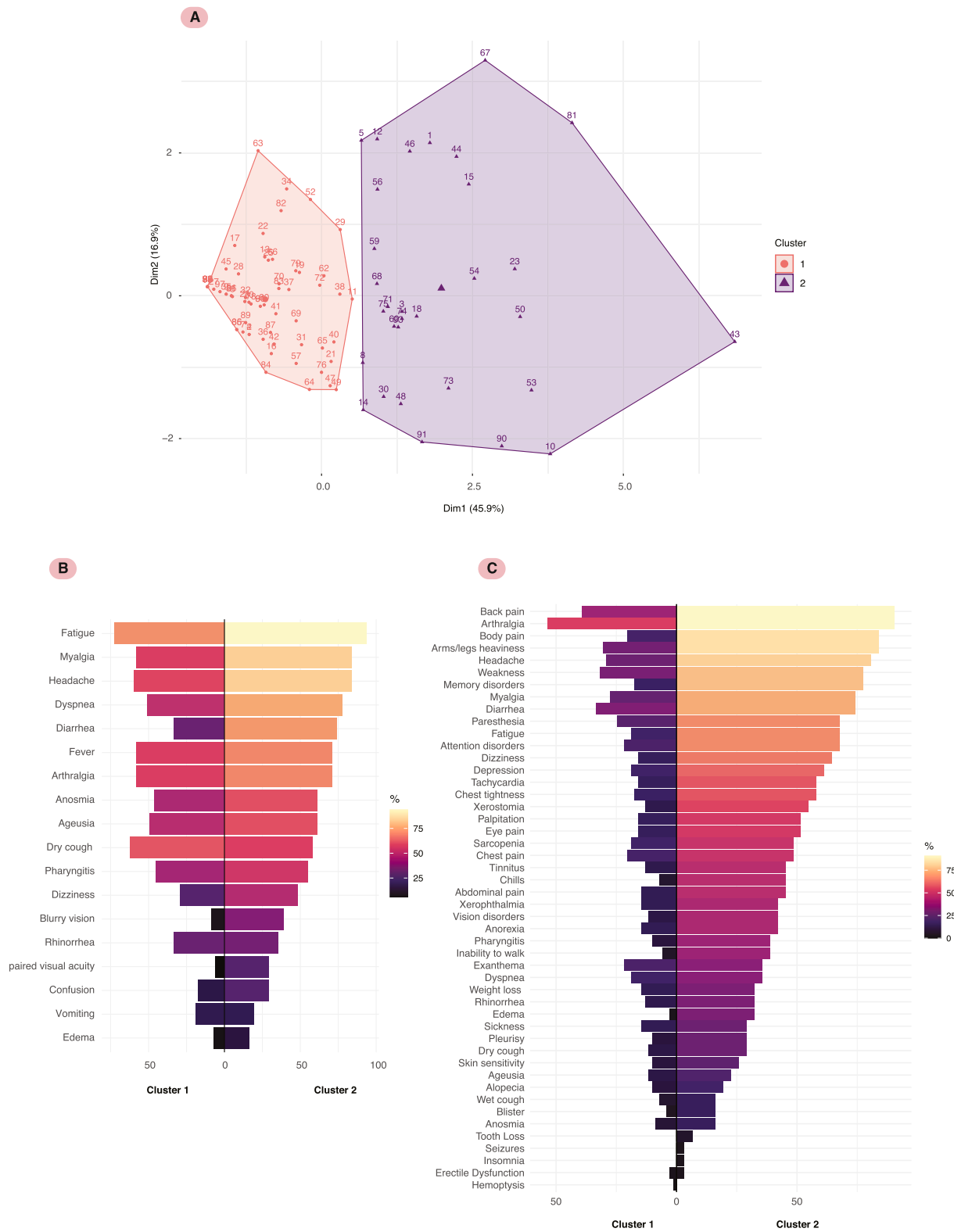
Fig. 5. Autonomic clusters in post-COVID syndrome. A. Principal components of *K*-means clustering for weighted COMPASS 31 domains. COMPASS 31: composite autonomic symptom score 31. B. Mirrored bar plot for acute COVID-19 symptoms on cluster 1 and 2. C. Mirrored bar plot for post-COVID clinical manifestations on cluster 1 and 2.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.autrev.2021.102947.

References

[1] National Institute for Health and Care Excellence. COVID-19 rapid guideline: Managing the long-term effects of COVID-19. In: NICE Guid; 2021.

[2] Acosta-Ampudia Y, Monsalve DM, Rojas M, Rodríguez Y, Gallo JE, Salazar-Uribe JC, et al. COVID-19 convalescent plasma composition and immunological effects in severe patients. J Autoimmun 2021;118:102598. https://doi.org/10.1016/j.jaut.2021.102598.

[3] Guan W, Ni Z, Hu Y, Liang W, Ou C, He J, et al. Clinical characteristics of coronavirus disease 2019 in China. N Engl J Med 2020;382:1708–20. https://doi.org/10.1056/NEJMoa2002032.

[4] Lopez-Leon Sandra, Wegman-Ostrosky Talia, Perelman Carol, Sepulveda Rosalinda, Rebolledo Paulina A, Angelica Cuapio SV. More than 50 long-term effects of COVID-19: a systematic review and meta-analysis. MedRxiv 2021. https://doi.org/10.1101/2021.01.27.21250617.

[5] Goyal P, Choi JJ, Pinheiro LC, Schenck EJ, Chen R, Jabri A, et al. Clinical characteristics of Covid-19 in New York City. N Engl J Med 2020;382:2372–4. https://doi.org/10.1056/NEJMc2010419.

[6] Sudre C, Murray B, Varsavsky T, Graham M, Penfold R, Bowyer R, et al. Attributes and predictors of Long-COVID: analysis of COVID cases and their symptoms collected by the Covid Symptoms Study App. BMJ 2020. https://doi.org/10.1101/2020.10.19.20214494. In press.

[7] Garrigues E, Janvier P, Kherabi Y, Le Bot A, Hamon A, Gouze H, et al. Post-discharge persistent symptoms and health-related quality of life after hospitalization for COVID-19. J Infect 2020;81:e4–6. https://doi.org/10.1016/j.jinf.2020.08.029.

[8] Ayoubkhani D, Khunti K, Nafilyan V, Maddox T, Humberstone B, Diamond I, et al. Post-covid syndrome in individuals admitted to hospital with covid-19: retrospective cohort study. BMJ 2021:n693. https://doi.org/10.1136/bmj.n693.

[9] Giannis D, Allen SL, Tsang J, Flint S, Pinhasov T, Williams S, et al. Postdischarge thromboembolic outcomes and mortality of hospitalized patients with COVID-19: the CORE-19 registry. Blood 2021;137:2838–47. https://doi.org/10.1182/blood.2020010529.

[10] Kamal M, Abo Omirah M, Hussein A, Saeed H. Assessment and characterisation of post-COVID-19 manifestations. Int J Clin Pract 2021;75. https://doi.org/10.1111/ijcp.13746.

[11] Vicente Herrero MT, Delgado Bueno S, Bandrés Moyá F, de la Torre MV Ramírez Iñiguez, Capdevila García L. Valoración del dolor. Revisión Comparativa de Escalas y Cuestionarios. Rev Soc Esp Dolor 2018. https://doi.org/10.20986/resed.2018.3632/2017.

[12] GeCo Group. Towards a cooperative construction of questionnaires for Covid-19 host genetics initiative. Italy: Politec Di Milan; 2020.

[13] Guler SA, Ebner L, Aubry-Beigelman C, Bridevaux P-O, Brutsche M, Clarenbach C, et al. Pulmonary function and radiological features 4 months after COVID-19: first results from the national prospective observational Swiss COVID-19 lung study. Eur Respir J 2021;57. https://doi.org/10.1183/13993003.03690-2020.

[14] Zung WWK. A self-rating depression scale. Arch Gen Psychiatry 1965;12:63. https://doi.org/10.1001/archpsyc.1965.01720310065008.

[15] Cirulli ET, Schiabor Barrett KM, Riffle S, Bolze A, Neveux I, Dabe S, et al. Long-term COVID-19 symptoms in a large unselected population. MedRxiv 2020. https://doi.org/10.1101/2020.10.07.20208702. 2020.10.07.20208702.

[16] Rojas M, Rodriguez Y, Pacheco Y, Zapata E, Monsalve DM, Mantilla RD, et al. Resilience in women with autoimmune rheumatic diseases. Jt Bone Spine 2018; 85:715–20. https://doi.org/10.1016/j.jbspin.2017.12.012.

[17] Campo-Arias A, Díaz-Martínez LA, Rueda-Jaimes GE, Barros-Bermúdez JA. Validación de la escala de Zung para depresión en universitarias de Bucaramanga, Colombia. Rev Colomb Psiquiatr 2005;34:54–62.

[18] Sletten DM, Suarez GA, Low PA, Mandrekar J, Singer W. COMPASS 31: a refined and abbreviated composite autonomic symptom score. Mayo Clin Proc 2012;87: 1196–201. https://doi.org/10.1016/j.mayocp.2012.10.013.

[19] Page MJ, Moher D, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. PRISMA 2020 explanation and elaboration: updated guidance and exemplars for reporting systematic reviews. BMJ 2021;372:n160. https://doi.org/10.1136/bmj.n160.

[20] Hartigan JA, Wong MA. Algorithm AS 136: a K-means clustering algorithm. Appl Stat 1979;28:100. https://doi.org/10.2307/2346830.

[21] Brandão Neto D, Fornazieri MA, Dib C, Di Francesco RC, Doty RL, Voegels RL, et al. Chemosensory dysfunction in COVID-19: prevalences, recovery rates, and clinical associations on a large Brazilian sample. Otolaryngol Neck Surg 2021; 164:512–8. https://doi.org/10.1177/0194599820954825.

[22] Santis LV-D, Sobrino B, González GE, Ruíz-Mesa JD, Plata A, Márquez-Gómez I, et al. Clinical and immunoserological status 12 weeks after infection with COVID-19: prospective observational study. MedRxiv 2020. https://doi.org/10.1101/2020.10.06.20206060.

[23] Akter F, Mannan A, Mehedi HMH, Rob MA, Ahmed S, Salauddin A, et al. Clinical characteristics and short term outcomes after recovery from COVID-19 in patients with and without diabetes in Bangladesh. Diabetes Metab Syndr Clin Res Rev 2020;14:2031–8. https://doi.org/10.1016/j.dsx.2020.10.016.

[24] Goel N, Goyal N, Kumar R. Clinico-radiological evaluation of post COVID-19 at a tertiary pulmonary care centre in Delhi. India Monaldi Arch Chest Dis 2021. https://doi.org/10.4081/monaldi.2021.1682.

[25] Alemanno F, Houdayer E, Parma A, Spina A, Del Forno A, Scatolini A, et al. COVID-19 cognitive deficits after respiratory assistance in the subacute phase: a COVID-rehabilitation unit experience. PLoS One 2021;16:e0246590. https://doi.org/10.1371/journal.pone.0246590.

[26] Ordinola Navarro A, Cervantes-Bojalil J, Cobos Quevedo O de J, Avila Martínez A, Hernández-Jiménez CA, Pérez Álvarez E, et al. Decreased quality of life and spirometric alterations even after mild-moderate COVID-19. Respir Med 2021;181:106391. https://doi.org/10.1016/j.rmed.2021.106391.

[27] Zhao Y, Shang Y, Song W, Li Q, Xie H, Xu Q, et al. Follow-up study of the pulmonary function and related physiological characteristics of COVID-19 survivors three months after recovery. EClinicalMedicine 2020;25:100463. https://doi.org/10.1016/j.eclinm.2020.100463.

[28] Woo MS, Malsy J, Pöttgen J, Seddiq Zai S, Ufer F, Hadjilaou A, et al. Frequent neurocognitive deficits after recovery from mild COVID-19. Brain Commun 2020; 2. https://doi.org/10.1093/braincomms/fcaa205.

[29] Wallukat G, Hohberger B, Wenzel K, Fürst J, Schulze-Rothe S, Wallukat A, et al. Functional autoantibodies against G-protein coupled receptors in patients with persistent long-COVID-19 symptoms. J Transl Autoimmun 2021;4:100100. https://doi.org/10.1016/j.jtauto.2021.100100.

[30] Skala M, Svoboda M, Kopecky M, Kocova E, Hyrsl M, Homolac M, et al. Heterogeneity of post-COVID impairment: interim analysis of a prospective study from Czechia. Virol J 2021;18:73. https://doi.org/10.1186/s12985-021-01546-8.

[31] Osikomaiya B, Erinoso O, Wright KO, Odusola AO, Thomas B, Adeyemi O, et al. 'Long COVID': persistent COVID-19 symptoms in survivors managed in Lagos State. Nigeria BMC Infect Dis 2021;21:304. https://doi.org/10.1186/s12879-020-05716-x.

[32] Arjmand P, Murtaza F, Eshtiaghi A, Popovic MM, Kertes PJ, Eng KT. Impact of the COVID-19 pandemic on characteristics of retinal detachments: the Canadian experience. Can J Ophthalmol 2021;56:88–95. https://doi.org/10.1016/j.jcjo.2020.12.008.

[33] Needham E, Newcombe V, Michell A, Thornton R, Grainger A, Anwar F, et al. Mononeuritis multiplex: an unexpectedly frequent feature of severe COVID-19. J Neurol 2020. https://doi.org/10.1007/s00415-020-10321-8. In press.

[34] Dennis A, Wamil M, Alberts J, Oben J, Cuthbertson DJ, Wootton D, et al. Multiorgan impairment in low-risk individuals with post-COVID-19 syndrome: a prospective, community-based study. BMJ 2021;11. https://doi.org/10.1136/bmjopen-2020-048391.

[35] Fernández-de-las-Peñas C, Rodríguez-Jiménez J, Fuensalida-Novo S, Palacios-Ceña M, Gómez-Mayordomo V, Florencio LL, et al. Myalgia as a symptom at hospital admission by severe acute respiratory syndrome coronavirus 2 infection is associated with persistent musculoskeletal pain as long-term post-COVID sequelae. Pain 2021. https://doi.org/10.1097/j.pain.0000000000002306. In press.

[36] Gambini G, Savastano MC, Savastano A, De Vico U, Crincoli E, Cozzupoli GM, et al. Ocular surface impairment after coronavirus disease 2019: a cohort study. Cornea 2021;40:477–83. https://doi.org/10.1097/ICO.0000000000002643.

[37] Klein H, Asseo K, Karni N, Benjamini Y, Nir-Paz R, Muszkat M, et al. Onset, duration and unresolved symptoms, including smell and taste changes, in mild COVID-19 infection: a cohort study in Israeli patients. Clin Microbiol Infect 2021; 27:769–74. https://doi.org/10.1016/j.cmi.2021.02.008.

[38] Leta V, Rodríguez-Violante M, Abundes A, Rukavina K, Teo JT, Falup-Pecurariu C, et al. Parkinson's disease and post–COVID-19 Syndrome: the Parkinson's long-COVID spectrum. Mov Disord 2021. https://doi.org/10.1002/mds.28622. mds.28622.

[39] Savastano A, Crincoli E, Savastano M, Younis S, Gambini G, De Vico U, et al. Peripapillary retinal vascular involvement in early post-COVID-19 patients. J Clin Med 2020;9:2895. https://doi.org/10.3390/jcm9092895.

[40] Townsend L, Dyer AH, Jones K, Dunne J, Mooney A, Gaffney F, et al. Persistent fatigue following SARS-CoV-2 infection is common and independent of severity of initial infection. PLoS One 2020;15:e0240784. https://doi.org/10.1371/journal.pone.0240784.

[41] Gaber TA-ZK, Ashish A, Unsworth A. Persistent post-covid symptoms in healthcare workers. Occup Med (Chic Ill) 2021. https://doi.org/10.1093/occmed/kqab043. In press.

[42] Mandal S, Barnett J, Brill SE, Brown JS, Denneny EK, Hare SS, et al. 'Long-COVID': a cross-sectional study of persisting symptoms, biomarker and imaging abnormalities following hospitalisation for COVID-19. Thorax 2021;76:396–8. https://doi.org/10.1136/thoraxjnl-2020-215818.

[43] Stavem K, Ghanima W, Olsen MK, Gilboe HM, Einvik G. Persistent symptoms 1.5–6 months after COVID-19 in non-hospitalised subjects: a population-based cohort study. Thorax 2021;76:405–7. https://doi.org/10.1136/thoraxjnl-2020-216377.

[44] Goërtz YMJ, Van Herck M, Delbressine JM, Vaes AW, Meys R, Machado FVC, et al. Persistent symptoms 3 months after a SARS-CoV-2 infection: the post-

COVID-19 syndrome? ERJ Open Res 2020;6:00542–2020. https://doi.org/
10.1183/23120541.00542-2020.

[45] Leth S, Gunst JD, Mathiasen V, Hansen K, Søgaard O, Østergaard L, et al.
Persistent symptoms in patients recovering from COVID-19 in Denmark. Open
Forum Infect Dis 2021;8. https://doi.org/10.1093/ofid/ofab042.

[46] Sykes DL, Holdsworth L, Jawad N, Gunasekera P, Morice AH, Crooks MG. Post-
COVID-19 symptom burden: what is long-COVID and how should we manage it?
Lung 2021;199:113–9. https://doi.org/10.1007/s00408-021-00423-z.

[47] Mahmud R, Rahman MM, Rassel MA, Monayem FB, Sayeed SKJB, Islam MS, et al.
Post-COVID-19 syndrome among symptomatic COVID-19 patients: a prospective
cohort study in a tertiary care center of Bangladesh. PLoS One 2021;16:
e0249644. https://doi.org/10.1371/journal.pone.0249644.

[48] Halpin SJ, McIvor C, Whyatt G, Adams A, Harvey O, McLean L, et al.
Postdischarge symptoms and rehabilitation needs in survivors of COVID-19
infection: a cross-sectional evaluation. J Med Virol 2021;93:1013–22. https://doi.
org/10.1002/jmv.26368.

[49] Simani L, Ramezani M, Darazam IA, Sagharichi M, Aalipour MA, Ghorbani F,
et al. Prevalence and correlates of chronic fatigue syndrome and post-traumatic
stress disorder after the outbreak of the COVID-19. J Neurovirol 2021;27:154–9.
https://doi.org/10.1007/s13365-021-00949-1.

[50] Savastano MC, Gambini G, Cozzupoli GM, Crincoli E, Savastano A, De Vico U,
et al. Retinal capillary involvement in early post-COVID-19 patients: a healthy
controlled study. Graefes Arch Clin Exp Ophthalmol 2021. https://doi.org/
10.1007/s00417-020-05070-3. In press.

[51] Iqbal A, Iqbal K, Arshad Ali S, Azim D, Farid E, Baig MD, et al. The COVID-19
sequelae: a cross-sectional evaluation of post-recovery symptoms and the need for
rehabilitation of COVID-19 survivors. Cureus 2021. https://doi.org/10.7759/
cureus.13080. In press.

[52] Islam MS, Ferdous MZ, Islam US, Mosaddek ASM, Potenza MN, Pardhan S.
Treatment, persistent symptoms, and depression in people infected with COVID-
19 in Bangladesh. Int J Environ Res Public Health 2021;18:1453. https://doi.org/
10.3390/ijerph18041453.

[53] Wu X, Liu X, Zhou Y, Yu H, Li R, Zhan Q, et al. 3-month, 6-month, 9-month, and
12-month respiratory outcomes in patients following COVID-19-related
hospitalisation: a prospective study. Lancet Respir Med 2021. https://doi.org/
10.1016/S2213-2600(21)00174-0.

[54] Huang C, Huang L, Wang Y, Li X, Ren L, Gu X, et al. 6-month consequences of
COVID-19 in patients discharged from hospital: a cohort study. Lancet 2021;397:
220–32. https://doi.org/10.1016/S0140-6736(20)32656-8.

[55] Gallus R, Melis A, Rizzo D, Piras A, De Luca LM, Tramaloni P, et al.
Audiovestibular symptoms and sequelae in COVID-19 patients. J Vestib Res 2021:
1–7. https://doi.org/10.3233/VES-201505. In press.

[56] Shouman K, Vanichkachorn G, Cheshire WP, Suarez MD, Shelly S, Lamotte GJ,
et al. Autonomic dysfunction following COVID-19 infection: an early experience.
Clin Auton Res 2021. https://doi.org/10.1007/s10286-021-00803-8. In press.

[57] Huang L, Zhao P, Tang D, Zhu T, Han R, Zhan C, et al. Cardiac involvement in
patients recovered from COVID-2019 identified using magnetic resonance
imaging. JACC Cardiovasc Imaging 2020;13:2330–9. https://doi.org/10.1016/j.
jcmg.2020.05.004.

[58] Sonnweber T, Sahanic S, Pizzini A, Luger A, Schwabl C, Sonnweber B, et al.
Cardiopulmonary recovery after COVID-19: an observational prospective
multicentre trial. Eur Respir J 2021;57:2003481. https://doi.org/10.1183/
13993003.03481-2020.

[59] Klok FA, Kruip MJHA, van der Meer NJM, Arbous MS, Gommers DAMPJ,
Kant KM, et al. Incidence of thrombotic complications in critically ill ICU patients
with COVID-19. Thromb Res 2020;191:145–7. https://doi.org/10.1016/j.
thromres.2020.04.013.

[60] Fraussen J, Marquez S, Takata K, Beckers L, Montes Diaz G, Zografou C, et al.
Phenotypic and Ig repertoire analyses indicate a common origin of IgD − CD27 −
double negative B cells in healthy individuals and multiple sclerosis patients.
J Immunol 2019;203:1650–64. https://doi.org/10.4049/jimmunol.1801236.

[61] Shuwa HA, Shaw TN, Knight SB, Wemyss K, McClure FA, Pearmain L, et al.
Alterations in T and B cell function persist in convalescent COVID-19 patients.
Med 2021. https://doi.org/10.1016/j.medj.2021.03.013.

[62] Talla A, Vasaikar SV, Lemos MP, Moodie Z, Pebworth M-PL, Henderson KE, et al.
Longitudinal immune dynamics of mild COVID-19 define signatures of recovery
and persistence. BioRxiv 2021. https://doi.org/10.1101/2021.05.26.442666.

[63] Ong SWX, Fong S-W, Young BE, Chan Y-H, Lee B, Amrun SN, et al. Persistent
symptoms and association with inflammatory cytokine signatures in recovered
coronavirus disease 2019 patients. Open Forum Infect Dis 2021;8. https://doi.
org/10.1093/ofid/ofab156.

[64] Rodríguez Y, Rojas M, Ramírez-Santana C, Acosta-Ampudia Y, Monsalve DM,
Anaya J-M. Autonomic symptoms following Zika virus infection. Clin Auton Res
2018;28:211–4. https://doi.org/10.1007/s10286-018-0515-1.

[65] Moreno-Pérez O, Merino E, Leon-Ramirez J-M, Andres M, Ramos JM, Arenas-
Jiménez J, et al. Post-acute COVID-19 syndrome. Incidence and risk factors: a
Mediterranean cohort study. J Infect 2021;82:378–83. https://doi.org/10.1016/j.
jinf.2021.01.004.

[66] Arnold DT, Hamilton FW, Milne A, Morley AJ, Viner J, Attwood M, et al. Patient
outcomes after hospitalisation with COVID-19 and implications for follow-up:
results from a prospective UK cohort. Thorax 2020;76:399–401. https://doi.org/
10.1136/thoraxjnl-2020-216086.

[67] Carfì A, Bernabei R, Landi F. Persistent SYMPTOMS in patients after acute COVID-
19. JAMA 2020;324:603. https://doi.org/10.1001/jama.2020.12603.

[68] Jacobs LG, Gourna Paleoudis E, Lesky-Di Bari D, Nyirenda T, Friedman T,
Gupta A, et al. Persistence of symptoms and quality of life at 35 days after
hospitalization for COVID-19 infection. PLoS One 2020;15:e0243882. https://
doi.org/10.1371/journal.pone.0243882.

[69] Kemp HI, Corner E, Colvin LA. Chronic pain after COVID-19: implications for
rehabilitation. Br J Anaesth 2020;125:436–40. https://doi.org/10.1016/j.
bja.2020.05.021.

[70] Mulchandani R, Lyngdoh T, Kakkar AK. Deciphering the COVID-19 cytokine
storm: systematic review and meta-analysis. Eur J Clin Invest 2021;51:e13429.
https://doi.org/10.1111/eci.13429.

[71] Coomes EA, Haghbayan H. Interleukin-6 in Covid-19: a systematic review and
meta-analysis. Rev Med Virol 2020;30:1–9. https://doi.org/10.1002/rmv.2141.

[72] Shiers SI, Ray PR, Wangzhou A, Sankaranarayanan I, Tatsui CE, Rhines LD, et al.
ACE2 and SCARF expression in human dorsal root ganglion nociceptors:
implications for SARS-CoV-2 virus neurological effects. Pain 2020;161:2494–501.
https://doi.org/10.1097/j.pain.0000000000002051.

[73] McFarland AJ, Yousuf MS, Shiers S, Price TJ. Neurobiology of SARS-CoV-2
interactions with the peripheral nervous system: implications for COVID-19 and
pain. PAIN Reports 2021;6:e885. https://doi.org/10.1097/
PR9.0000000000000885.

[74] Cohen SP, Baber ZB, Buvanendran A, McLean BC, Chen Y, Hooten WM, et al. Pain
management best practices from multispecialty organizations during the COVID-
19 pandemic and public health crises. Pain Med 2020;21:1331–46. https://doi.
org/10.1093/pm/pnaa127.

[75] Sher L. Post-COVID syndrome and suicide risk. QJM 2021;114:95–8. https://doi.
org/10.1093/qjmed/hcab007.

[76] Blitshteyn S, Whitelaw S. Postural orthostatic tachycardia syndrome (POTS) and
other autonomic disorders after COVID-19 infection: a case series of 20 patients.
Immunol Res 2021;69:205–11. https://doi.org/10.1007/s12026-021-09185-5.

[77] Thieben MJ, Sandroni P, Sletten DM, Benrud-Larson LM, Fealey RD, Vernino S,
et al. Postural orthostatic tachycardia syndrome: the Mayo clinic experience.
Mayo Clin Proc 2007;82:308–13. https://doi.org/10.4065/82.3.308.

[78] Novak P. Post COVID-19 syndrome associated with orthostatic cerebral
hypoperfusion syndrome, small fiber neuropathy and benefit of immunotherapy:
a case report. ENeurologicalSci 2020;21:100276. https://doi.org/10.1016/j.
ensci.2020.100276.

[79] Dani M, Dirksen A, Taraborrelli P, Torocastro M, Panagopoulos D, Sutton R, et al.
Autonomic dysfunction in "long COVID": rationale, physiology and management
strategies. Clin Med (Northfield IL) 2021;21:e63–7. https://doi.org/10.7861/
clinmed.2020-0896.

[80] Miglis MG, Prieto T, Shaik R, Muppidi S, Sinn D-I, Jaradeh S. A case report of
postural tachycardia syndrome after COVID-19. Clin Auton Res 2020;30:449–51.
https://doi.org/10.1007/s10286-020-00727-9.

[81] Kanjwal K, Jamal S, Kichloo A, Grubb BP. New-onset postural orthostatic
tachycardia syndrome following coronavirus disease 2019 infection. J Innov Card
Rhythm Manag 2020;11:4302–4. https://doi.org/10.19102/icrm.2020.111102.

[82] Blitshteyn S. Autoimmune markers and autoimmune disorders in patients with
postural tachycardia syndrome (POTS). Lupus 2015;24:1364–9. https://doi.org/
10.1177/0961203315587566.

[83] Yu X, Li H, Murphy TA, Nuss Z, Liles J, Liles C, et al. Angiotensin II Type 1
receptor autoantibodies in postural tachycardia syndrome. J Am Heart Assoc
2018;7. https://doi.org/10.1161/JAHA.117.008351.

[84] Watari M, Nakane S, Mukaino A, Nakajima M, Mori Y, Maeda Y, et al.
Autoimmune postural orthostatic tachycardia syndrome. Ann Clin Transl Neurol
2018;5:486–92. https://doi.org/10.1002/acn3.524.

[85] Li H, Yu X, Liles C, Khan M, Vanderlinde-Wood M, Galloway A, et al.
Autoimmune basis for postural tachycardia syndrome. J Am Heart Assoc 2014;3:
e000755. https://doi.org/10.1161/JAHA.113.000755.

[86] Mo X, Jian W, Su Z, Chen M, Peng H, Peng P, et al. Abnormal pulmonary function
in COVID-19 patients at time of hospital discharge. Eur Respir J 2020;55. https://
doi.org/10.1183/13993003.01217-2020.

[87] Qin W, Chen S, Zhang Y, Dong F, Zhang Z, Hu B, et al. Diffusion capacity
abnormalities for carbon monoxide in patients with COVID-19 at three-month
follow-up. Eur Respir J 2021. https://doi.org/10.1183/13993003.03677-2020.

[88] Shah AS, Wong AW, Hague CJ, Murphy DT, Johnston JC, Ryerson CJ, et al.
A prospective study of 12-week respiratory outcomes in COVID-19-related
hospitalisations. Thorax 2020;76:402–4. https://doi.org/10.1136/thoraxjnl-
2020-216308.

[89] Patel BV, Arachchillage DJ, Ridge CA, Bianchi P, Doyle JF, Garfield B, et al.
Pulmonary angiopathy in severe COVID-19: physiologic, imaging, and
hematologic observations. Am J Respir Crit Care Med 2020;202:690–9. https://
doi.org/10.1164/rccm.202004-1412OC.

[90] Hanidziar D, Robson SC. Hyperoxia and modulation of pulmonary vascular and immune responses in COVID-19. Am J Physiol Lung Cell Mol Physiol 2021;320: L12–6. https://doi.org/10.1152/ajplung.00304.2020.

[91] Moldofsky H, Patcai J. Chronic widespread musculoskeletal pain, fatigue, depression and disordered sleep in chronic post-SARS syndrome; a case-controlled study. BMC Neurol 2011;11:37. https://doi.org/10.1186/1471-2377-11-37.

[92] Hui DS. Impact of severe acute respiratory syndrome (SARS) on pulmonary function, functional capacity and quality of life in a cohort of survivors. Thorax 2005;60:401–9. https://doi.org/10.1136/thx.2004.030205.

[93] Hui DS, Wong KT, Ko FW, Tam LS, Chan DP, Woo J, et al. The 1-year impact of severe acute respiratory syndrome on pulmonary function, exercise capacity, and quality of life in a cohort of survivors. Chest 2005;128:2247–61. https://doi.org/10.1378/chest.128.4.2247.

[94] Augustin M, Schommers P, Stecher M, Dewald F, Gieselmann L, Gruell H, et al. Post-COVID syndrome in non-hospitalised patients with COVID-19: a longitudinal prospective cohort study. Lancet Reg Heal Eur 2021;6:100122. https://doi.org/10.1016/j.lanepe.2021.100122.

[95] Hosey MM, Needham DM. Survivorship after COVID-19 ICU stay. Nat Rev Dis Primers 2020;6:60. https://doi.org/10.1038/s41572-020-0201-1.

[96] Okba NMA, Müller MA, Li W, Wang C, GeurtsvanKessel CH, Corman VM, et al. Severe acute respiratory syndrome coronavirus 2-specific antibody responses in coronavirus disease patients. Emerg Infect Dis 2020;26:1478–88. https://doi.org/10.3201/eid2607.200841.

[97] Dan JM, Mateus J, Kato Y, Hastie KM, Yu ED, Faliti CE, et al. Immunological memory to SARS-CoV-2 assessed for up to 8 months after infection. Science (80-) 2021;371. https://doi.org/10.1126/science.abf4063.

[98] Mazzoni A, Maggi L, Capone M, Vanni A, Spinicci M, Salvati L, et al. Heterogeneous magnitude of immunological memory to SARS-CoV-2 in recovered individuals. Clin Transl Immunol 2021;10:e1281. https://doi.org/10.1002/cti2.1281.

[99] Folgueira MD, Luczkowiak J, Lasala F, Pérez-Rivilla A, Delgado R. Prolonged SARS-CoV-2 cell culture replication in respiratory samples from patients with severe COVID-19. Clin Microbiol Infect 2021;27:886–91. https://doi.org/10.1016/j.cmi.2021.02.014.

[100] Salamanna F, Veronesi F, Martini L, Landini MP, Fini M. Post-COVID-19 syndrome: the persistent symptoms at the post-viral stage of the disease. A systematic review of the current data. Front Med 2021;8:653516. https://doi.org/10.3389/fmed.2021.653516.