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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

Abbreviations: CI, Confidence interval; COMPASS 31, Composite autonomic symptom score 31; COVID-19, Coronavirus disease 2019; DLCO, Diffusing capacity for carbon monoxide; ECLIA, Electrochemiluminescence immunoassay; ELISA, Enzyme-linked immunosorbent assay; ICU, Intensive care unit; IQR, Interquartile range; NA, Not applicable/available; PCS, Post-COVID syndrome; POTS, Postural orthostatic tachycardia syndrome; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-analyses; RBD, Receptor binding domain; S/Co, Signal-to-cut-off; SARS-CoV-2, Severe acute respiratory syndrome coronavirus 2; TNF, Tumor necrosis factor.

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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 $\geq$ 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 $\geq$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.,

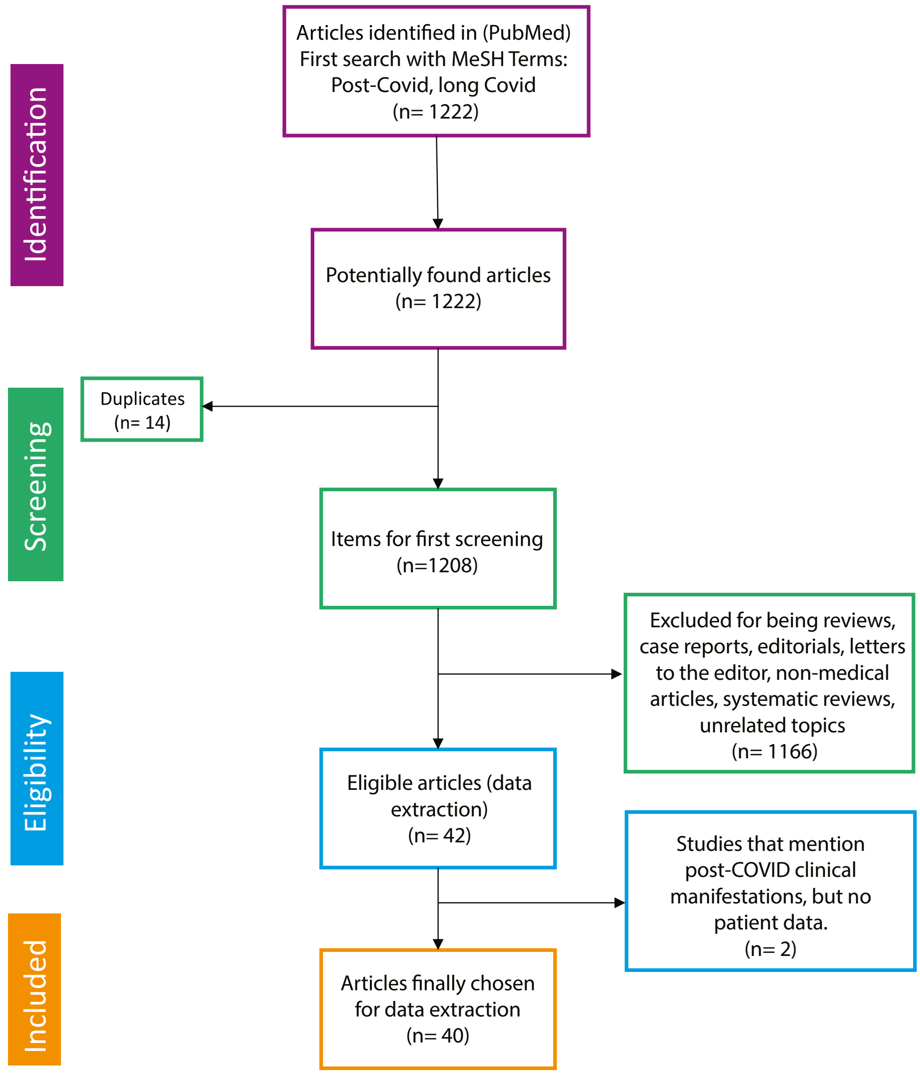

Fig. 1. Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) flow chart.

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%)
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 $\geq$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, $P < 0.0001$).

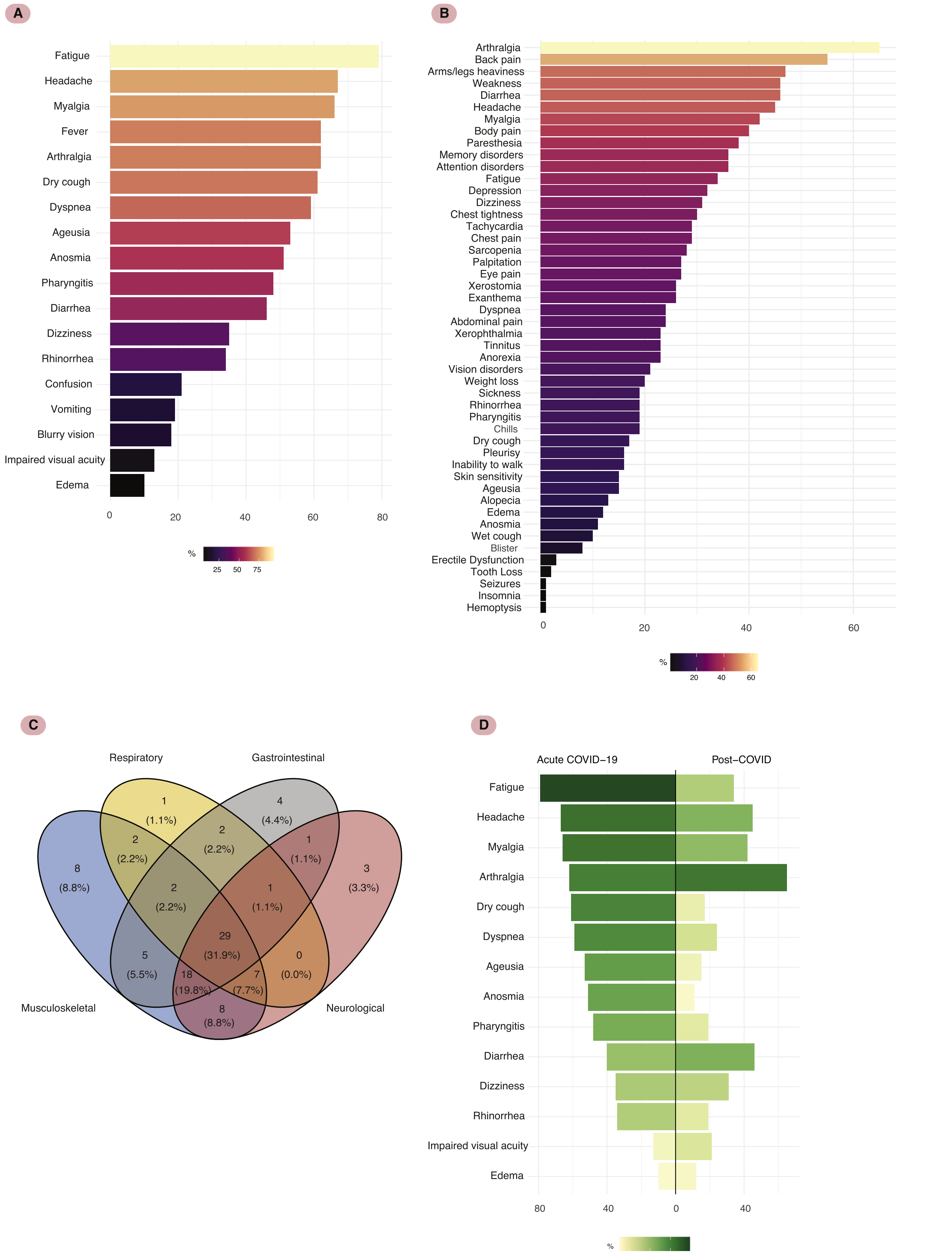

Fig. 2. Acute and post-COVID symptoms. A. Frequency bar plot for clinical manifestations on acute COVID-19. B. Frequency bar plot for post-COVID clinical manifestations. Frequency of depression was estimated by Zung scale. C. Venn diagram with the superposition of the main PCS symptoms. Analysis included 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.

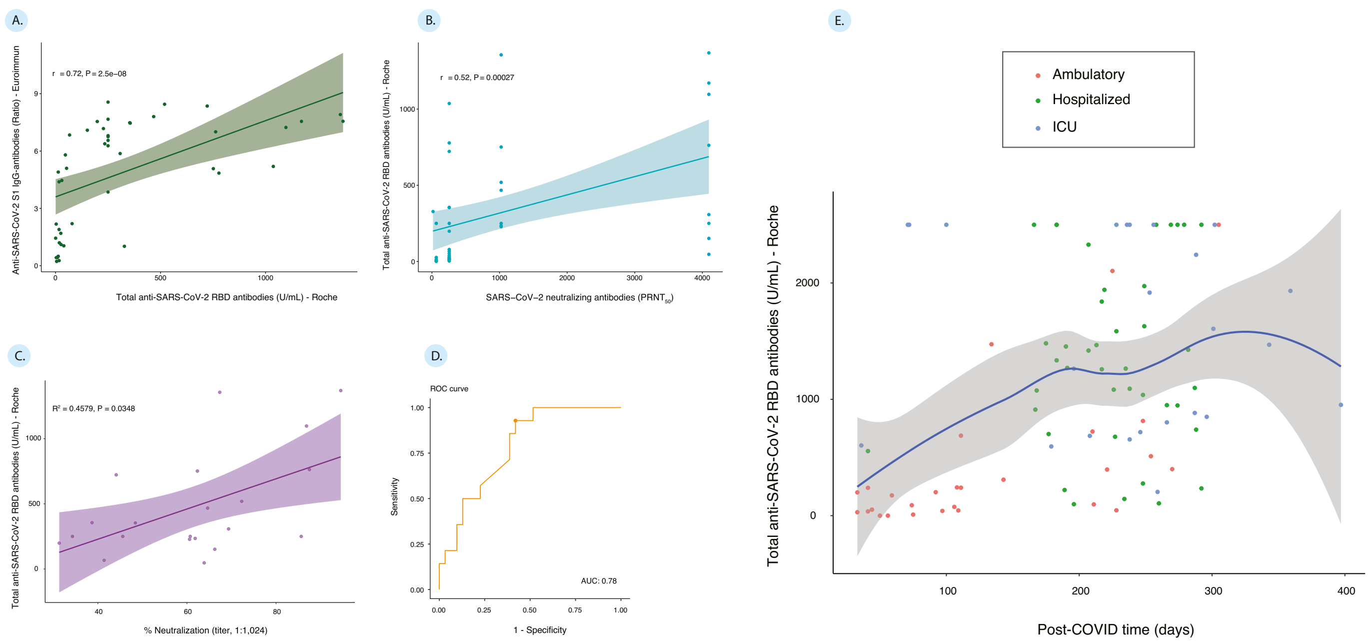

Fig. 3. Anti RBD SARS-CoV-2 antibodies (see Supplementary Material 1 for details). A. Correlation between IgG anti-SARS-CoV-2 by ELISA (Euroimmun) and total anti-SARS-CoV-2 antibodies by ECLIA (Roche). B. Correlation between neutralizing anti-SARS-CoV-2 antibodies ($PRNT_{50}$) and total anti-SARS-CoV-2 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
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 (Tau^2, I^2)
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 (Tau^2, I^2)
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

(*continued on next page*)

Table 3 (*continued*)

Signs and symptoms	Number of articles[a]	Cases/COVID-19 (% - mean, 95% CI)[b]	Q (*Tau*^{2}, I^2)
		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

Tau^2 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). I^2 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

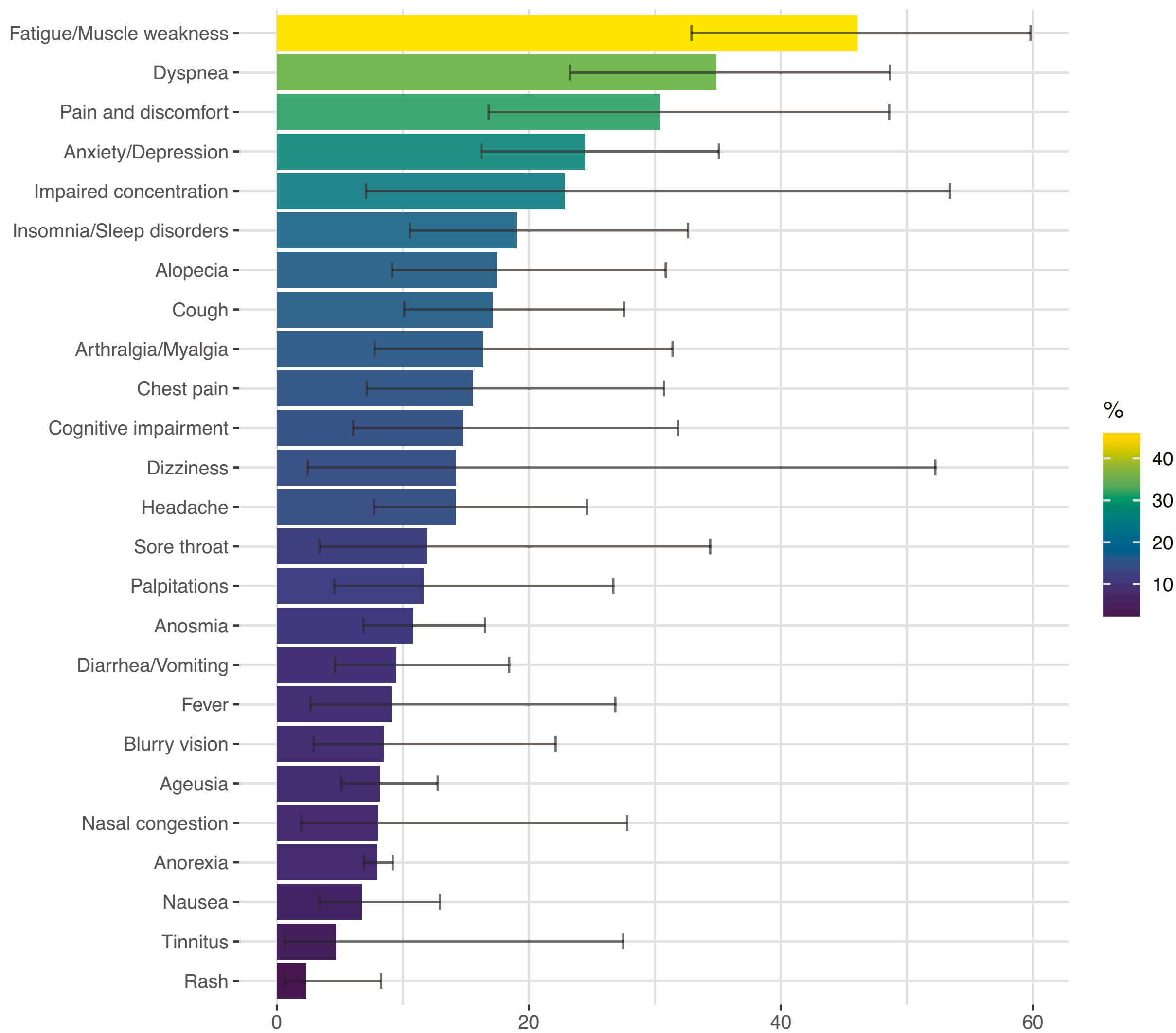

Fig. 4. Frequency bar plot for pooled prevalence of post-COVID manifestations in meta-analysis. Error bar represents the estimated 95% confidence interval. Only those clinical manifestations reported in more than 4 articles were included in this graph.

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 hyper-immune 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
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.

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Declaration of competing interest

None.

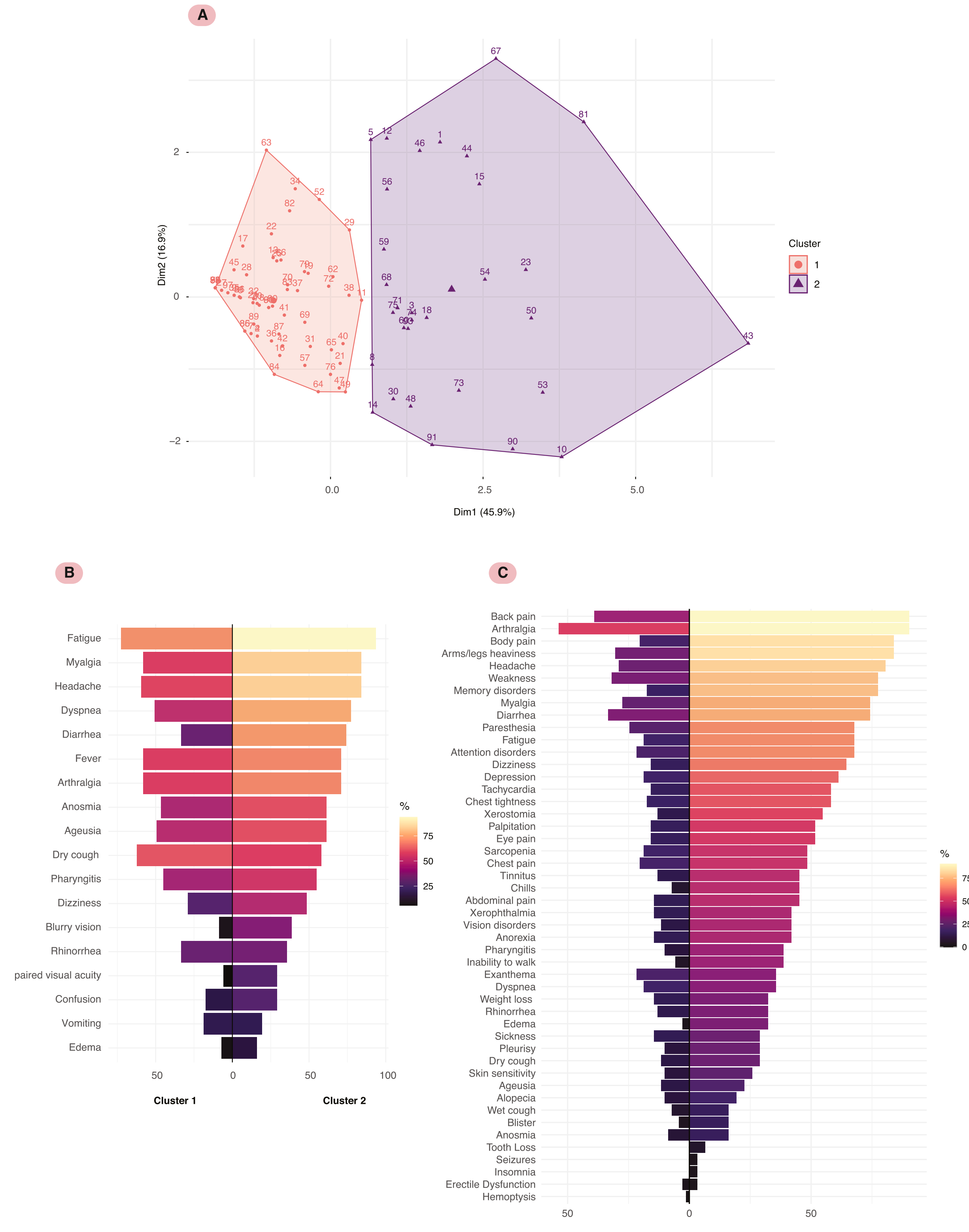

Fig. 5. Autonomic clusters in post-COVID syndrome. A. Principal components of *K*-means clustering for weighted COMPASS 31 domains. COMPASS 31: composite autonomic symptom score 31. B. Mirrored bar plot for acute COVID-19 symptoms on cluster 1 and 2. C. Mirrored bar plot for post-COVID clinical manifestations on cluster 1 and 2.

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Appendix A. Supplementary data

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