

Original Article

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Post-acute sequelae of SARS-CoV-2 infection: relationship of central nervous system manifestations with physical disability and systemic inflammation

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Abstract

Background. Despite the multitude of clinical manifestations of post-acute sequelae of SARS-CoV-2 infection (PASC), studies applying statistical methods to directly investigate patterns of symptom co-occurrence and their biological correlates are scarce.

Methods. We assessed 30 symptoms pertaining to different organ systems in 749 adults (age = 55 ± 14 years; 47% female) during in-person visits conducted at 6–11 months after hospitalization due to coronavirus disease 2019 (COVID-19), including six psychiatric and cognitive manifestations. Symptom co-occurrence was initially investigated using exploratory factor analysis (EFA), and latent variable modeling was then conducted using Item Response Theory (IRT). We investigated associations of latent variable severity with objective indices of persistent physical disability, pulmonary and kidney dysfunction, and C-reactive protein and D-dimer blood levels, measured at the same follow-up assessment.

Results. The EFA extracted one factor, explaining 64.8% of variance; loadings were positive for all symptoms, and above 0.35 for 16 of them. The latent trait generated using IRT placed fatigue, psychiatric, and cognitive manifestations as the most discriminative symptoms (coefficients > 1.5, $p < 0.001$). Latent trait severity was associated with decreased body weight and poorer physical performance (coefficients > 0.240; $p \leq 0.003$), and elevated blood levels of C-reactive protein (coefficient = 0.378; 95% CI 0.215–0.541; $p < 0.001$) and D-dimer (coefficient = 0.412; 95% CI 0.123–0.702; $p = 0.005$). Results were similar after excluding subjects with pro-inflammatory comorbidities.

Conclusions. Different symptoms that persist for several months after moderate or severe COVID-19 may unite within one latent trait of PASC. This trait is dominated by fatigue and psychiatric symptoms, and is associated with objective signs of physical disability and persistent systemic inflammation.

Introduction

Symptoms and signs of dysfunction of multiple organ systems may be present during both the acute and post-viral stages of coronavirus disease 2019 (COVID-19) (Al-Aly, Xie, & Bowe, 2021; Bell *et al.*, 2021; Blomberg *et al.*, 2021; Davis *et al.*, 2021; Huang *et al.*, 2021a, 2021b; Lopez-Leon *et al.*, 2021; Menges *et al.*, 2021; Nasserie, Hittle, & Goodman, 2021; Sudre *et al.*, 2021; Writing Committee for the COMEBAC Study Group *et al.*, 2021). Cognitive deficits, anxiety, depression, sleep disturbances, and post-traumatic stress disorder (PTSD) have been frequently shown to persist for weeks to several months after COVID-19 (Abel *et al.*, 2021; Becker *et al.*, 2021; Bourmistrova, Solomon, Braude, Strawbridge, & Carter, 2021; Damiano *et al.*, 2022; Hampshire *et al.*, 2021; Ismael *et al.*, 2021; Mazza *et al.*, 2020, 2021; Søråas *et al.*, 2021; Taquet, Geddes, Husain, Luciano, & Harrison, 2021), highlighting the relevance of central nervous system (CNS) manifestations in the long COVID syndrome (or post-acute sequelae of SARS-CoV-2 infection, PASC).

As in many disorders that present multiple clinical manifestations (Ahmad *et al.*, 2014; Aktas, Walsh, & Rybicki, 2010; Manca, De Marco, Ince, & Venneri, 2021), the detection of specific patterns of symptom clustering may help to elucidate the pathophysiology of PASC, which remains largely unknown. The identification of patterns of co-occurrence of psychiatric and cognitive symptoms with manifestations pertaining to other organ systems could guide hypotheses as to whether CNS symptoms in PASC may emerge under the influence of unifying pathological mechanisms, such as persistent systemic inflammatory and prothrombotic states (Bornstein *et al.*, 2021; Mackay, 2021; Perrin *et al.*, 2020; Phillips & Williams, 2021), or chronic dysfunction of the lungs (Sasannejad, Ely, & Lahiri, 2019) or kidneys (Desmond *et al.*, 2021).

Based on online surveys applied to 3762 subjects with confirmed or suspected COVID-19, one investigation of temporal profiles of PASC symptoms highlighted a cluster combining CNS manifestations with multiple other organ system symptoms, which shared patterns of persistence up to 7 months after acute disease (Davis *et al.*, 2021). Another study applied statistical methods to directly assess patterns of clustering of different PASC manifestations in subjects with moderate or severe COVID-19, based on data from a large sample of adults ($n = 1077$) evaluated during in-person visits between 2 and 7 months after in-hospital discharge (Evans *et al.*, 2021). The authors of the latter study described four clusters reflecting different levels of PASC severity, and in all clusters there was a close co-occurrence of three CNS symptoms (i.e. depression, anxiety, and PTSD) with manifestations pertaining to other organ systems (i.e. dyspnea, fatigue, and poor physical performance). Cluster severity was directly associated with blood levels of C-reactive protein measured at the same timepoint, possibly reflecting persistent systemic inflammation (Mackay, 2021; Perrin *et al.*, 2020). However, this investigation was limited by the inclusion of only three non-CNS manifestations in the cluster analysis design. Moreover, no analyses were conducted to directly account for the association found between C-reactive protein levels and increased body weight (Evans *et al.*, 2021), or the potentially confounding effects of other pro-inflammatory comorbidities.

In this study, we investigated the patterns of co-occurrence of 30 multi-organ system symptoms (including six psychiatric manifestations and cognitive complaints) in a relatively large sample of adults ($n = 749$) assessed by multidisciplinary teams at approximately 6–11 months after hospitalization due to COVID-19. We initially conducted an exploratory factor analysis (EFA) on the ratings of all symptoms, with the prediction that one factor would emerge combining cognitive and psychiatric complaints with multiple symptoms pertaining to other organ systems (Davis *et al.*, 2021; Evans *et al.*, 2021). Subsequently, we generated a latent variable combining symptoms of PASC using Item Response Theory (IRT), a statistical approach suitable for scaling multiple health outcomes along one single continuum of severity (latent trait modeling) (Hays, Morales, & Reise, 2000; Krueger *et al.*, 2004). This latent trait of PASC symptoms was used to investigate associations with objective signs of persistent physical disability, pulmonary dysfunction, and kidney function impairment. Finally, we investigated whether latent trait severity would be directly related to levels of blood markers of persistent inflammatory and prothrombotic states measured at the same follow-up assessment (C-reactive protein and D-dimer), accounting for the influence of obesity and other pro-inflammatory comorbidities.

Methods

Study design, participants, and procedures

We consecutively invited for a follow-up visit all adult (≥ 18 years) patients that had been admitted for at least 24 h as inpatients to *Hospital das Clínicas, Faculdade de Medicina, Universidade de São Paulo* (HCFMUSP), Brazil, due to laboratory-confirmed COVID-19, over a period of 5 months (between March and August 2020). Follow-up data collection occurred from October 2020 to April 2021.

Comorbid conditions prior to COVID-19 were identified using a database of information for all cases with suspected COVID-19 during their admission as inpatients at HCFMUSP (Busatto *et al.*, 2021), and we excluded patients with a previous diagnosis of dementia or end-stage cancer. Additional exclusion criteria were nosocomial COVID-19 infection, subjects living in nursing homes or long-term care facilities, and insufficient physical mobility to leave home. Finally, as re-infection by SARS-CoV-2 is possible, we enquired subjects about the emergence of symptoms and signs of infection (e.g. fever) during telephone calls on the day before the follow-up visit and again upon their arrival for the assessments. Any subjects with suspected re-infection had their research visit postponed, and they were referred to the infectious disease outpatient clinic at HCFMUSP dedicated to the diagnosis and management of acute COVID-19.

Online Supplementary material 1 (Methods S1) provides further details on the study period, procedures, and laboratory confirmation of COVID-19. A full description of general procedures for invitations and assessments was provided elsewhere (Busatto *et al.*, 2021).

Data from interviews, scales, and complementary examinations were captured and stored at real-time using web-based case report forms developed on a Research Electronic Data Capture (REDCap) system hosted at HCFMUSP (Harris *et al.*, 2009).

Protocols were approved by the local ethics committee (numbers 4.270.242, 4.502.334, 4.524.031, 4.302.745, and 4.391.560). Informed consent was obtained from all participants or their proxy prior to study procedures.

Evaluation of psychiatric and cognitive symptoms at the follow-up

To assess symptoms of PTSD (Weathers, Litz, Herman, Huska, & Keane, 1993), anxiety and depression (Zigmond & Snalth, 1983), insomnia (Bastien, Vallières, & Morin, 2001), and subjective memory impairment (Vale, Balieiro, & Silva-Filho, 2012), multi-item scales were applied by specialized teams (Busatto *et al.*, 2021). Validated cutoffs were used to generate categorical 'yes-no' variables (see online Supplementary Methods S2 and Table S1 for details). Complaints of impaired concentration were documented using the Clinical Interview Schedule-Revised (CIS-R) (Lewis, Pelosi, Araya, & Dunn, 1992). To identify potentially incident cases, we estimated the date of onset of symptoms using structured questions from the CIS-R; 'no' ratings were applied when symptoms were reported by patients as already present prior to SARS-CoV-2 infection.

Other self-reported symptoms at the follow-up

Additional symptoms previously highlighted as relevant to PASC (Lopez-Leon *et al.*, 2021; Nasserie *et al.*, 2021) (i.e. fatigue, dyspnea, muscle/joint pain, and taste and/or olfaction changes) were also assessed using standardized scales (Bestall *et al.*, 1999; Boonstra, Preuper, Balk, & Stewart, 2014; Brandão Neto *et al.*,

2021; Webster, Cella, & Yost, et al., 2003) (see online Supplementary Table S1 for details). An adaptation of the WHO screening tool for neuroepidemiology investigations in low-and-middle-income countries (WHO, 1982) was applied by a team of neurologists (Busatto et al., 2021) to assess neurological manifestations including headache, weakness, gait problems, episodes of loss of consciousness, and paresthesia. Finally, subjects were inquired about the presence of 14 persistent post-COVID symptoms covering additional organ-system domains (Busatto et al., 2021) (see full list in online Supplementary Table S1).

The symptoms above, added to those cited in item 2.2, comprised a total of 30 items (online Supplementary Table S1).

Objective assessments of functioning and blood laboratory indices at the follow-up

Objective indices of organ system dysfunction were generated from the following assessments conducted during the same in-person visit (Busatto et al., 2021): anthropometric measurements (including body mass index; BMI); 1 min sit-to-stand and handgrip strength tests (to measure physical disability) (Bohannon, 2015; Litmanovich, Chung, Kirkbride, Kicska, & Kanne, 2020; Strassmann et al., 2013; Vianna, Oliveira, & Araújo, 2007); measurements of resting oxygen saturation, decreased oxygen saturation during the sit-to-stand test, a chest X-ray (Litmanovich et al., 2020), and a spirometry test (Pereira, Sato, & Rodrigues, 2007) (all addressing pulmonary dysfunction); and blood creatinine levels (to estimate glomerular filtration rate, as a measure of kidney function impairment) (Levey et al., 2009).

Details regarding the criteria for rating objective indices of dysfunction as present are provided in online Methods S2 and Table S2 (Supplementary material 1). BMI values were used to detect the presence of clinically relevant weight change after COVID-19 (online Supplementary Table S2), and also to classify study subjects as obese (≥ 30 kg/m²) or non-obese (≤ 30 kg/m²) (Table 1).

Missing values for objective signs of dysfunction are provided in online Supplementary Table S3; most of the missing data were due to the fact that some of the assessment protocols were not ready for use at the starting date of data collection.

Methods for measuring C-reactive protein and D-dimer serum levels and information regarding missing data are provided in online Supplementary Methods S3.

Statistical analyses

Identifying symptom dimensions through exploratory factor analysis

Using the binary ratings for the 30 self-reported PASC symptoms outlined in items 2.2 and 2.3 above, we conducted an initial EFA including all symptoms. A total of 203 patients had to be excluded from this analysis (27.1% of the total sample) due to missing values for at least one symptom (see online Supplementary Table S4). Further methodological details and information on missing values are provided in online Methods S4 (Supplementary material 1).

Generation of a unidimensional latent variable through item response theory

Based on previous literature findings (Davis et al., 2021; Evans et al., 2021), we expected that the initial EFA could indicate symptom data to fit a unidimensional latent trait space. Based on this prediction, we chose to generate a latent variable of PASC

Table 1. Baseline and hospitalization characteristics of the sample

Variable	N = 749
Age – mean \pm s.d., years	55 \pm 14
Age groups	
18–39	119 (15.8%)
40–49	156 (20.8%)
50–59	173 (23%)
60–69	190 (25.3%)
≥ 70	111 (14.8%)
Sex	
Female	352 (47%)
Male	397 (53%)
Body mass index – median kg/m ² (IQR)	31.1 (27.5–36.6)
Socioeconomic status ^a	
A	19 (2.5%)
B1	40 (5.4%)
B2	137 (18.5%)
C1	243 (32.8%)
C2	227 (30.7%)
D + E	73 (10%)
Educational level	
<4 years	265 (35.6%)
4–8 years	142 (19%)
8–12 years	202 (27%)
>12 years	134 (18%)
Ethnicity	
White	342 (46.5%)
Asian	10 (1%)
Mixed ^b	273 (37%)
Black	102 (14%)
Indigenous	7 (1%)
Comorbidities	
Hypertension	425 (56.7%)
Diabetes	261 (34.8%)
Obesity ^c	429 (57.5%)
Chronic cardiovascular disease	136 (18.2%)
Chronic respiratory disease	58 (7.7%)
Chronic kidney disease (non-dialytic/dialytic)	49 (6.5%)/35 (4.7%)
Cerebrovascular disease	40 (5.3%)
Cancer	35 (4.7%)
Organ transplantation	35 (4.7%)
Rheumatological disease	31 (4.1%)
Chronic liver disease	26 (3.5%)
HIV	4 (0.5%)
Charlson comorbidity score – mean \pm s.d.	3.0 \pm 1.8

(Continued)

Table 1. (Continued.)

Variable	N = 749
Smoking	284 (38%)
Duration of COVID-19 symptoms in days – mean ± s.d.	9.0 ± 6.5
Events during hospitalization	
Hospital stay, duration in days – mean ± s.d.	18.6 ± 19.2
Days after hospitalization for the follow-up – median [IQR]	212 [201–254]
Days after hospital discharge for the follow-up – median [IQR]	200 [185–235]
WHO clinical progression scale ^d – frequency in different categories	
3–4	85 (11.3%)
5	327 (43.6%)
6	32 (4.3%)
7–8–9	305 (40.7%)
Renal replacement therapy (yes/no)	96 (12.8%)
ICU stay (yes/no)	445 (59.4%)
Intubation (yes/no)	305 (40.7%)

s.d., standard deviation; IQR, interquartile range; ICU, intensive care unit.

^aSix categories assessed in accordance to current criteria of the *Associação Brasileira de Empresas de Pesquisa* (ABEP, 2020).

^bBased on self-reported mixed black and white races.

^cRated as present if the body mass index of individuals was equal or higher than 30 kg/m², based on self-reported estimates of body weight prior to COVID-19 given by study subjects at the time of the follow-up assessments.

^dWHO scale categories: 3–4, no continuous supplemental oxygen needed; 5, continuous supplemental oxygen only; 6, continuous positive airway pressure ventilation, bi-level positive airway pressure or high flow nasal oxygen; 7–9, invasive mechanical ventilation and/or extra-corporeal membrane oxygenation (ECMO). WHO Working Group on the Clinical Characterisation and Management of COVID-19 infection (2020).

symptoms using two-parameter logistic IRT modeling (Hays et al., 2000; Krueger et al., 2004), scaling the 30 symptoms of PASC along one single continuum. The IRT approach is suitable for scaling multiple items related to health outcomes along a uni-dimensional continuum of severity, and it has the additional advantage of being highly flexible for handling missing values (Krueger et al., 2004). In order to classify the 30 multi-organ symptoms included in the latent trait of PASC, we used the property of discrimination as our parameter of interest, referring to the increment in the probability a given symptom to be scored as present as the latent dimension score increased. Further information about the calculation of discrimination indices and IRT details is provided in online Supplementary Methods S5.

We run a sensitivity analysis assessing the properties of all symptoms included in the IRT model after leaving out subjects with comorbidities known to be themselves associated with CNS manifestations (see online Supplementary Methods S6). We also run additional sensitivity analyses including only one psychiatric or cognitive symptom at a time, to test the unique role of each self-reported psychiatric or cognitive symptom within the latent variable (see online Supplementary Methods S6).

Relationships between the latent variable of PASC symptoms, objective signs of organ system dysfunction and laboratory test results

Using two-parameter logistic regression models, we investigated significant associations between the latent variable described

above and eight objective signs of organ system dysfunction (see online Supplementary Methods S7).

Additionally, we used a Differential Item Functioning (DIF) analysis approach to investigate relationships between elevated levels of blood tests (C-reactive protein and D-dimer) and the latent variable of PASC symptoms. The DIF approach allowed us to test whether significant relationships between abnormal test results and the latent dimension of PASC were due to different probabilities of endorsing any of the symptoms included in the latent variable (Saha et al., 2010; Penfield & Camilli, 2007). Initially, we investigated the relationship between blood test results and the latent dimension of symptoms under investigation (i.e. syndrome level), with statistical significance assessed using logistic coefficients and 95% confidence intervals. If any significant relationship with the severity of a latent PASC trait was detected, we then tested differential effects at the level of the individual PASC symptoms (i.e. manifestation level) through Mantel-Haenszel tests (see details in online Supplementary Methods S7).

We also conducted sensitivity analyses (logistic regressions) investigating relationships between the latent variable of PASC and blood test results after leaving out subgroups of subjects stratified by sex, age, race, and socio-economic status, in order to verify if the above associations were substantially affected by the influence of any demographic variables on levels of C-reactive protein or D-dimer (see details in online Methods S8, Supplementary material 1). Finally, to take account of the influence of confounding comorbidities on blood laboratory markers, we conducted additional sensitivity analyses after stratifying the sample by the presence of the following diagnoses: obesity; diabetes; chronic lung or heart disease; and additional comorbidities known to affect the blood indices investigated (rheumatic disease, chronic liver or kidney disease, hematological disease; active cancer; and organ transplantation).

Results

Demographics and baseline characteristics

Figure 1 provides the flowchart of potential participants and patient selection (including data on refusals and exclusions). A total of 749 eligible individuals attended the in-person follow-up assessments. Table 1 provides their details regarding demographics, comorbidities, hospitalization events, and time between symptom onset and hospital admission. The mean duration of symptoms characterizing acute COVID-19 prior to hospitalization (as referred by patients and/or relatives upon admission) equaled 9.0 ± 6.5 days (Table 1).

Online Supplementary Table S5 provides results of comparisons between the patients who attended the in-person assessments *v.* the remaining surviving individuals who did not participate (see details also in online Results S1, Supplementary material 1).

Exploratory factor analysis and latent variable modeling

The frequencies of each of the 30 symptoms in the overall sample are provided in online Supplementary Table S4.

One single factor was extracted in the initial EFA (eigenvalue = 4.65), explaining 64.8% of variance. All symptoms presented positive loadings for this factor; loadings >0.35 were found for 16 symptoms, with fatigue, insomnia, psychiatric, and cognitive complaints presenting the highest loadings (>0.5) (see online Supplementary Table S6). One additional factor approached the eigenvalue of one (0.99) and explained an additional amount of 13.8% of data

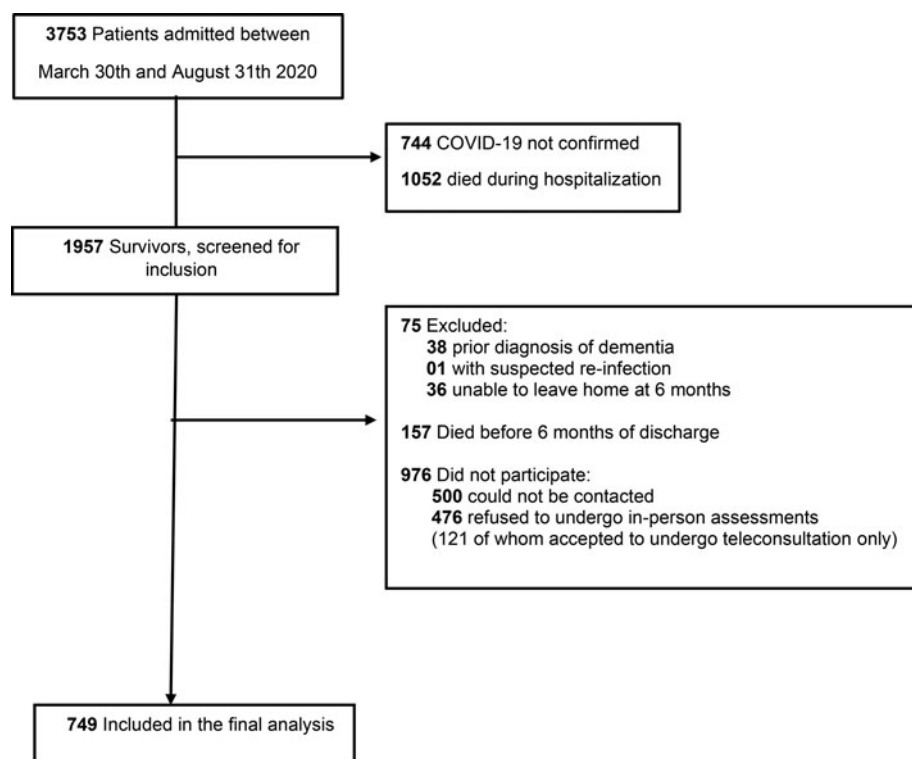


Fig. 1. Potentially eligible subjects and final sample included in the follow-up investigation.

variance, including the symptoms of weakness, gait impairment, and paresthesia, all with loadings above 0.45. Further details related to the EFA results are provided in online Results S2 (Supplementary material 1).

The unidimensional nature of the PASC symptom data, demonstrated by the above EFA, confirmed the validity of using the IRT approach to generate one single latent dimension of PASC. This analysis was conducted with all 749 subjects, taking advantage of the flexibility of the IRT approach for handling missing values. Discrimination properties for each of the 30 manifestations are displayed in Table 2. All 30 symptoms displayed discrimination coefficients from 0.2 to 2.3 ($p \leq 0.005$), with highest values for fatigue (2.3) and the six psychiatric and cognitive symptoms (1.5–2.1) (Table 2).

The sensitivity analysis assessing the properties of all symptoms included in the IRT model after leaving out subjects with comorbidities known to be themselves associated with CNS manifestations showed that all psychiatric and cognitive manifestations retained a high degree of discrimination (see online Supplementary Table S7).

In the six IRT analyses including only one psychiatric or cognitive symptom at a time, each of those variables persisted as highly discriminative within the resulting latent variable (see online Supplementary Table S8).

Significant associations between the latent variable of PASC symptoms, objective signs of organ system dysfunction, and laboratory test results

The three following objective signs of organ system dysfunction were significantly associated with the IRT-based latent variable of PASC symptoms: reduced BMI, abnormal sit-to-stand performance, and decreased handgrip strength (Table 3).

Blood levels of C-reactive protein and D-dimer at the follow-up evaluation showed significant direct relationships with the latent PASC dimension, with highest significance for the former (Table 4). There were no differential effects on any of the individual manifestations included in the PASC trait either for C-reactive protein or D-dimer levels (Table 4).

Results of the sensitivity analyses investigating relationships between the latent variable of PASC and blood test results after exclusion of each subgroup stratified by demographic variables are detailed in online Supplementary Results S3; statistical significance was retained in all analyses involving levels of C-reactive protein levels, but not D-dimer. Associations between the latent trait of PASC symptoms and blood biomarkers in each subgroup stratified by demographic variables are detailed in online Supplementary Table S9.

Finally, the sensitivity analyses conducted after excluding subjects with obesity or other comorbidities known to affect values of C-reactive protein and D-dimer showed that associations of the latent variable of PASC remained statistically significant with those two blood biomarkers (online Supplementary Table S10).

Discussion

In this study, we applied statistical methods to document patterns of co-occurrence of several PASC symptoms in a relatively large sample of patients with moderate or severe COVID-19 evaluated 6–11 months after hospitalization, investigating how such symptom co-occurrence was associated with signs of physical disability and persistent inflammation.

We demonstrated that fatigue, insomnia, psychiatric, and cognitive complaints were the symptoms with highest loadings (>0.5) in the single factor extracted by EFA, which explained a large proportion of data variance (64.8%). Several other symptoms presented meaningful loadings in the same EFA factor, and

Table 2. Latent variable modeling of post-acute sequelae of SARS-CoV-2 infection (PASC) using Item Response Theory

	Discrimination		
	Coefficient	<i>p</i>	95% CI
Psychiatric/cognitive symptoms			
Post-traumatic stress	2.110		1.618 2.602
Depression	2.052		1.603 2.502
Memory loss	2.036		1.626 2.445
Anxiety	1.961	<0.001	1.548 2.373
Lack of concentration	1.675		1.328 2.023
Insomnia	1.530		1.225 1.834
Other symptoms			
Fatigue	2.294		1.842 2.745
Nausea/vomiting	1.397		0.838 1.957
Loss of appetite	1.346		0.998 1.694
Dyspnea	1.300		1.024 1.575
Body pain	1.128		0.881 1.374
Hearing loss	1.102		0.804 1.400
Muscle/joint pain	1.085		0.849 1.321
Diarrhea	1.062		0.665 1.458
Loss of smell	1.063		0.795 1.331
Loss of taste	1.033	<0.001	0.773 1.293
Tinnitus	0.971		0.692 1.250
Abdominal pain	0.951		0.668 1.234
Weakness	0.862		0.582 1.143
Nocturia	0.769		0.545 0.993
Nasal obstruction	0.760		0.507 1.012
Gait impairment	0.742		0.460 1.025
Headache	0.704		0.422 0.986
Dizziness	0.695		0.495 0.894
Chest pain	0.680		0.449 0.911
Edema	0.675		0.438 0.918
Paresthesia	0.674		0.428 0.920
Skin problems	0.594	<0.001	0.352 0.835
Cough	0.509		0.289 0.729
Episodes of loss of consciousness	0.664	0.003	0.218 1.109

CI, confidence intervals.

each of them also showed significant discrimination ($p \leq 0.005$) along the latent variable of PASC generated using IRT (which allowed the recovery of cases with missing values). These findings confirm the notion that there is a significant degree of co-occurrence of multiple clinical manifestations in COVID-19 patients evaluated several months after hospitalization, suggesting that common underlying pathological mechanisms might influence on the persistence of different organ system symptoms in PASC.

The discriminative role of psychiatric and cognitive symptoms on the IRT-based latent variable of PASC remained high after the exclusion of cases with comorbid conditions themselves known to be associated with psychiatric and cognitive manifestations independently of COVID-19. Moreover, each of those CNS symptoms retained the same level of high discrimination when evaluated in isolation within the IRT model, together with fatigue. The fact that all other symptoms also displayed significant discrimination values in the same latent variable of PASC symptoms indicates that the likelihood of those additional symptoms to be referred by patients was higher in proportion to the presence of fatigue and psychiatric/cognitive complaints. These findings are consistent with the results of previous investigations that traced the trajectory of multiple individual symptoms of PASC over time, as these have indicated an incremental number of symptoms affecting multiple organ systems from approximately 10 weeks after acute COVID-19 onwards, with a prominence of CNS manifestations (Davis *et al.*, 2021).

The latent variable of PASC symptoms was directly related to three objective signs of persistent physical disability, namely low performance on the sit-to-stand test, impaired handgrip strength, and reduced BMI. Conversely, all other indices generated from objective tests of organ system functioning were unrelated to the latent trait of PASC symptoms, including the four signs of persistent respiratory dysfunction. The latter negative findings are consistent with previous observations that fatigue and ill health may be reported by patients several months after acute COVID-19 independently of whether objective signs of respiratory dysfunction are detected at the same timepoint (Townsend *et al.*, 2021a 2021b). The pattern of high discrimination of fatigue, psychiatric, and cognitive symptoms in our latent trait of PASC symptoms, together with its specific association with physical disability, is consistent with the proposed similarity of PASC with myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) (Bornstein *et al.*, 2021; Mackay, 2021; Perrin *et al.*, 2020; Phillips & Williams, 2021), a disorder thought to be often triggered by viral disease (Morris, Anderson, Galecki, Berk, & Maes, 2013). Cognitive complaints are listed in the diagnostic criteria for ME/CFS (Committee on the Diagnostic Criteria for Myalgic Encephalomyelitis/Chronic Fatigue Syndrome, Board on the Health of Select Populations, & Institute of Medicine, 2015). The diagnosis of ME/CFS is also commonly associated with anxiety, depression, and weight loss (Afari & Buchwald, 2003; Committee on the Diagnostic Criteria for Myalgic Encephalomyelitis/Chronic Fatigue Syndrome, Board on the Health of Select Populations, & Institute of Medicine, 2015).

The latent variable of PASC symptoms described herein was directly associated with persistently elevated blood levels of C-reactive protein at the follow-up assessment, supporting the proposed role for dysregulated inflammatory/immune mechanisms in the pathophysiology of PASC (Mackay, 2021; Perrin *et al.*, 2020). The latent trait of PASC symptoms was also significantly associated with elevated D-dimer levels, suggesting the persistence of a pro-thrombotic state possibly related to inflammatory mechanisms (Nalbandian *et al.*, 2021; Pasini *et al.*, 2021; Townsend *et al.*, 2021a, 2021b). These results extend the findings of Evans *et al.* (2021), who reported elevated blood levels of C-reactive protein in proportion to the severity of a symptom cluster combining persistent psychiatric manifestations, dyspnea, fatigue, and poor physical performance in COVID-19 patients evaluated between 2 and 7 months after hospital discharge (Evans *et al.*, 2021). Differently from that study, we

Table 3. Associations between the latent variable of PASC symptoms and objective signs of organ system dysfunction

Objective signs of dysfunction	Latent variable of PASC symptoms			
	Coefficient	<i>p</i>	95% CI	
Weight loss ($\leq 5\%$ of BMI value prior to COVID-19) ^a	0.258	0.003	0.090	0.426
Reduced resting oxygen saturation ($\leq 92\%$)	0.200	0.211	-0.113	0.513
Decreased oxygen saturation during effort ^b	0.029	0.985	-0.303	0.309
Reduced number of repetitions during sit-to-stand test	0.577	<0.001	0.382	0.772
Reduced handgrip strength	0.243	0.007	0.065	0.420
COVID-related abnormalities at X-ray	-0.031	0.727	-0.208	0.145
FVC <80% of predicted at spirometry test	-0.27	0.760	-0.202	0.147
eGFR lower than 60 ml/min/1.73 m ² (in subjects with no previous history of kidney disease) ^c	0.141	0.277	-0.113	0.394

CI, confidence intervals; BMI, body mass index; FVC, forced vital capacity; eGFR, estimated glomerular filtration rate.

^aDifference between current BMI measurement and calculated BMI based on self-reported estimates of body weight prior to COVID-19.

^bOxygen saturation reduction of ≥ 4 points during sit-to-stand test (not undertaken in subjects presenting resting pulse oximetry ratings lower than 90%).

^cEstimated glomerular filtration rate calculated according to CKD EPI³⁰.

conducted a set of sensitivity analyses which demonstrated that the association between PASC symptom severity and blood levels of either C-reactive protein or D-dimer remained significant in subgroups excluding patients with conditions known to affect levels of these biomarkers, including obesity, diabetes, and other pro-inflammatory comorbidities. Moreover, findings of the sensitivity analyses using subgroups stratified by demographic variables showed that the significant association between C-reactive protein levels and the latent trait of PASC symptoms was not determined by the influence of these factors (see details in online Discussion S1, Supplementary material 1).

The DIF analyses in our study showed no differential effects of either C-reactive protein or D-dimer levels on the individual symptoms included in the latent variable of PASC symptoms, suggesting that these biomarkers exert a uniform influence on psychiatric, cognitive, and all other symptoms along the overall PASC trait. Persistently elevated levels of these two indices and other inflammatory biomarkers were described in other studies that assessed subjects at variable time points after the onset of acute COVID-19 (Huang et al., 2021b; Mandal et al., 2021; Pasini et al., 2021; Townsend et al., 2021a, 2021b). However, associations with the severity of persistent clinical manifestations were inconsistently reported in those investigations, possibly due to modest sample sizes and the assessment of isolated PASC symptoms, rather than using a unifying latent variable as reported herein.

Peripheral biomarker findings suggestive of systemic inflammation were previously reported in association with symptoms of PTSD (Sankowski, Mader, & Valdés-Ferrer, 2015), mood disorders (Pariante, 2017), anxiety disorders (Michopoulos, Powers, Gillespie, Ressler, & Jovanovic, 2017), and ME/CFS (Montoya et al., 2017). A persistent state of systemic inflammation in PASC may lead to prominent psychiatric, cognitive, and physical dysfunctional manifestations via pro-inflammatory agents entering the CNS by circumventricular organs that have incomplete blood-brain barrier, or via abnormally permeable portions of blood-brain barrier damaged by cytokines (Mackay, 2021; Perrin et al., 2020; Sankowski et al., 2015). Through those pathways, pro-inflammatory agents may affect limbic regions and the hypothalamus, reduce monoamine neurotransmission, and trigger microglia activation and neurotoxicity (Boldrini, Canoll, & Klein, 2021; Mackay, 2021; Perrin et al., 2020).

The findings of this study highlight a multi-symptom dimension of PASC that is dominated by psychiatric manifestations and physical disability, and which may be related to persistent systemic inflammation. However, these results do not rule out the possible existence of additional clinical dimensions of relevance in PASC, combining other symptoms and objective signs of dysfunction. For instance, objectively assessed cognitive deficits (which were not addressed in the present study) may persist after COVID-19 (Becker et al., 2021; Evans et al., 2021; Hampshire et al., 2021) and have been suggested to be independent of psychiatric symptoms and physical disability (Evans et al., 2021); such objective cognitive deficits might be specifically associated with signs of pulmonary dysfunction (Sasanejad et al., 2019) or chemosensory symptoms (Pirker-Kees, Platho-Elwischger, Hafner, Redlich, & Baumgartner, 2021), both of which were prevalent in our sample (online Supplementary Tables S3 and S4). It is also worth noting that our EFA analysis detected an additional trend pattern of symptom co-occurrence involving three neurological manifestations (weakness, gait impairment, and paresthesia) (WHO, 1982). This suggests that there may be different patterns of symptom co-occurrence in PASC involving neurological, psychiatric, and cognitive manifestations, which could emerge under the influence of separate risk factors and underlying brain mechanisms (Boldrini et al., 2021; Taquet et al., 2021). These issues warrant further investigations in large samples of PASC sufferers.

One strength of the present study regards to the use of multi-item scales with validated cutoffs for the assessment of psychiatric manifestations and other key symptoms (Zigmond & Snalth, 1983), rather than simpler 'yes-no' questions (Blomberg et al., 2021; Huang et al., 2021a, 2021b; Søråas et al., 2021; Sudre et al., 2021; Writing Committee for the COMEBAC Study Group et al., 2021). A study limitation is that subjects were asked at the time of the follow-up assessments about the presence of symptoms before COVID-19, which is prone to recall bias. Therefore, we could not confirm that the onset of symptoms occurred after COVID-19, since subjects did not undergo similar assessments prior to the SARS-CoV-2 infection. Other limitations include: the lack of a control group (Abel et al., 2021); the lack of chest computed tomography imaging and diffusion capacity testing to detect pulmonary involvement in COVID-19 with greater accuracy (Huang et al.,

Table 4. Significant findings from the differential item functioning analysis investigating blood laboratorial predictors of post-acute sequelae of SARS-CoV-2 infection (PASC)

Latent dimension of PASC	C-reactive protein > 3.0 mg/l				D-dimer > 2000 ng/ml			
	Coefficient	<i>p</i>	95% CI		Coefficient	<i>p</i>	95% CI	
	0.378	<0.001	0.215	0.541	0.412	0.005	0.123	0.702
Clinical manifestations	aOR		95% CI		aOR		95% CI	
Psychiatric/cognitive symptoms								
Loss of memory	0.898	0.75	0.556	1.450	0.950	0.81	0.246	3.662
Anxiety	1.329	0.33	0.798	2.214	0.826	0.99	0.247	2.756
Lack of concentration	0.773	0.34	0.482	1.239	0.681	0.75	0.203	2.276
Post-traumatic stress	1.023	0.93	0.544	1.922	0.454	0.60	0.067	3.051
Insomnia	0.849	0.55	0.538	1.340	0.531	0.47	0.152	1.851
Depression	0.827	0.57	0.490	1.397	2.053	0.33	0.667	6.324
Other symptoms								
Gait impairment	1.795	0.10	0.931	3.461	3.110	0.14	0.960	10.079
Nocturia	1.298	0.33	0.814	2.070	0.645	0.66	0.188	2.221
Dyspnea	1.003	0.92	0.635	1.584	0.674	0.71	0.207	2.199
Fatigue	1.337	0.32	0.807	2.214	0.599	0.44	0.204	1.759
Loss of taste	1.126	0.74	0.685	1.851	0.670	0.78	0.177	2.541
Hearing loss	1.153	0.72	0.658	2.021	2.433	0.21	0.787	7.520
Edema	1.251	0.46	0.751	2.082	0.421	0.41	0.092	1.928
Body pain	1.057	0.88	0.688	1.625	1.351	0.78	0.471	3.874
Loss of appetite	1.353	0.47	0.695	2.635	0.428	0.72	0.049	3.731
Muscle/joint pain	1.117	0.68	0.736	1.696	1.504	0.59	0.542	4.177
Paresthesia	1.114	0.80	0.647	1.917	2.088	0.30	0.705	6.190
Skin problems	0.775	0.41	0.462	1.301	2.412	0.18	0.786	7.404
Weakness	1.060	0.97	0.575	1.956	3.644	0.08	1.106	12.004
Abdominal pain	1.071	0.68	0.736	1.696	1.575	0.69	0.477	5.210
Dizziness	0.927	0.83	0.585	1.467	0.548	0.48	0.172	1.750
Cough	1.222	0.49	0.751	1.990	2.012	0.27	0.746	5.424
Chest pain	1.018	0.96	0.619	1.675	0.249	0.21	0.036	1.745
Episodes of loss of consciousness	1.056	0.87	0.379	2.938	0.820	0.76	0.115	5.826
Loss of smell	0.771	0.40	0.455	1.304	npc	npc	npc	npc
Nasal obstruction	0.857	0.68	0.497	1.475	1.317	0.93	0.376	4.616
Headache	0.724	0.36	0.397	1.320	0.564	0.44	0.204	1.759
Tinnitus	0.652	0.26	0.342	1.243	1.310	0.96	0.358	4.796
Diarrhea	0.558	0.27	0.241	1.295	1.986	0.91	0.303	13.023
Nausea/vomiting	0.495	0.32	0.161	1.519	1.222	0.60	0.074	20.170

CI, confidence interval; aOR, odds ratio adjusted for the relationship between the latent trait score and the other PASC symptoms; npc, not possible to calculate odds ratio and 95%CI.

2020, 2021a); the successful recruitment of only 43% of all patients potentially eligible for in-person visits; and the inclusion of a single hospital site, which may limit the generalizability of our findings. However, it should be noted that the size of our single-site sample was larger than that of most unicentric studies of COVID-19 patients that undertook in-person follow-up assessments to date (Mandal *et al.*, 2021; Mazza *et al.*, 2020; Menges *et al.*, 2021; Sonnweber

et al., 2020; Townsend *et al.*, 2020; Writing Committee for the COMEBAC Study Group *et al.*, 2021).

Conclusions and implications

The unidimensional profile of symptom clustering described in this study indicates that multiple persistent manifestations

following moderate or severe COVID-19 may be united within one latent trait of PASC. This latent trait is dominated by fatigue, psychiatric, and cognitive symptoms, and is significantly associated with objective signs of physical disability and persistent systemic inflammation. Further longitudinal studies are needed to evaluate whether these PASC manifestations persist over longer follow-up periods. If confirmed in such additional investigations, our findings would reinforce the need for the development of healthcare services providing focused diagnostic assessments and evaluating the usefulness of tailored treatment programs for PASC sufferers (David, 2021; Heightman et al., 2021). These services could identify patients that do not present long-term, organ-specific sequelae of COVID-19, but who may benefit from multidisciplinary interventions emphasizing physical rehabilitation and mental health-promoting strategies. The present findings also warrant investigations using panels of specific pro-inflammatory and anti-inflammatory markers in large-sized samples of PASC sufferers, in order to ascertain which inflammatory pathways may be most distinctly related to the symptom dimension highlighted herein; the identification of key biomarkers in such investigations may guide randomized clinical trials testing the efficacy of pharmacological interventions to reduce the burden of co-occurring physical disability and neuropsychiatric features of PASC. Finally, the findings of the present study highlight the relevance of full vaccination schemes against SARS-Cov-2, as these have been found to reduce not only the severity of acute COVID-19 but also the risk of PASC manifestations (Antonelli et al., 2022).

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