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ORIGINAL RESEARCH

Associations Between Inflammatory and Catecholamine Markers and Clinical Outcomes in People with Post-Acute SARS-CoV-2 Infection

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Purpose: The diagnosis of post-acute SARS-CoV-2 infection (PASC) is broad, referring to new or persistent health problems >four weeks after being infected with SARSCoV-2. The aim of this study was to determine whether cytokines, chemokines or catecholamine levels could specify the clinical condition.

Patients and Methods: Seventy-nine participants participated in person to study PASC. They were average 51 years (mean), 52% female, 62% Caucasian, 11% African American and 37% Hispanic with a mean BMI of 30.5. Most prevalent symptoms were fatigue, memory loss and shortness of breath. We extracted co-morbid conditions, length of hospital stay and course and laboratory values; medications, history of regular exercise (total of 150 minutes/week), measures of cognition (PCCOG), including Color Word Interference Test (CWIT), Coding, Arithmetic, Matrix Reasoning), clinical assessment of health behavior change, and several patient reported outcomes (PROs) (Edmonton Symptom Assessment System (ESAS), health-related quality of life instrument (EQ5D), anxiety and depression (GAD7, PHQ9) and fatigue (Functional Assessment of Chronic Illness Therapy – Fatigue (FACIT-F).

Results: These data suggest that people with PASC are more likely to report lower levels of physical well-being, emotional well-being and higher fatigue levels than the non-PASC population. Epinephrine levels correlate statistically significantly with PROs ($p<0.05$), for overall FACIT-F, as well as the physical and functional subscales. The fatigue severity self-report, PHQ9 and number of symptoms were also significantly correlated. Interleukin-1 beta (IL1b) was inversely correlated with the Physical Well Being (PWB) and Emotional Well Being (EWB) FACIT-F subscales, the GAD7 and the PCCOG scale ($p<0.05$).

Conclusion: Participants in this observational study of PASC report lower levels of emotional, physical well-being, more fatigue, anxiety and depression than are reported in population norms. Epinephrine and IL1b correlate with these findings and may offer a biological measurement, providing clinically useful information for tracking persistence or recovery. These findings may encourage further study to develop newer treatment approaches.

Keywords: post acute SARS-CoV-2, PASC, patient reported outcomes, cytokines, catecholamines, chemokines

Introduction

At present, the diagnosis of post-acute SARS-CoV-2 infection (PASC) also called long-COVID, as defined by Centers for Disease Control (CDC) is a wide range of new, returning, or ongoing health problems people can experience four or more weeks after first being infected with the virus that causes SARS-CoV-2.[1] Other definitions have been proposed and are used globally which makes uniformity of diagnosis difficult.[2,3] While there may be disagreements on the strict definition of PASC, there is widespread agreement that it is chronic, likely to have many organ-systems impacted, often difficult to treat and has global health and economic impact for as many at 400 million people.[4,5]

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The challenges of not having a universally accepted definition of PASC or long-COVID, coupled with the large number of reported symptoms and clinical findings, present difficulties for health care professionals to efficiently evaluate and treat people affected. While the number of publications about who is likely to develop PASC, and which symptoms are most persistent are increasing,[6–11] published data on risk factors for prolonged, unresolved symptoms are incomplete. A highly desirable initiative would be to identify a biosignature sensitive and specific for PASC. One that links objective and self-reported findings that could serve as a predictive model for whether there would be prolonged symptoms, have substantial negative impact of daily functioning or conversely, would have a high probability of resolution.

Data have been published linking some micro-analytes with persistence of anxiety/depression in people with chronic pain.[12] A recent publication provides detailed analyses for people with chronic fatigue.[13] Therefore, it is reasonable to pursue a similar approach to analyze these findings in people with PASC. A significant problem, however, is developing a panel of micro-analytes that are readily available from a serum sample, have a high likelihood of identifying the population and have sensitivity to change as symptoms improve.

Operating from the presupposition that sufferers of PASC may be heterogeneous regarding underlying systemic mechanism,[9] but that dysregulation of inflammation may be key to the development of long-term/chronic symptoms, a "wide net" approach to choosing biomarkers that offered some resolution with regard to inflammatory processes, but also some supportive/contradictory evidence regarding other, not directly inflammation-related mechanisms was chosen for this study. From this perspective, analytes were chosen based on consideration of several factors, including previous implication in relevant factors, such as fatigue or depression, pleiotropism (examples of high pleiotropism include Interleukin-6 (IL-6) and Brain-Derived Neurotrophic Factor (BDNF)), and availability of relatively inexpensive, high fidelity assays that can be performed in most laboratories. Regarding inflammation, Orosomucoid or alpha-1-acid glycoprotein (ORM), Interferon-alpha (IFNa), IFNa auto-antibodies (AAIFNA), C-C motif Chemokine ligand 2 (CCL2), IL1b, Interleukin-2 (IL2), Interleukin-4 (IL4), IL6, Interleukin-10 (IL10), Interleukin-12 (IL12), and Interleukin-17 (IL17) were measured to provide varying degrees of insight into associated mechanisms, such as auto-immunity, the "Th" paradigm, or extended "acute phase" signaling post-infection; additionally, some of these analytes, such as ORM are associated with fatigue and/or physical activity. Other measured analytes (BDNF, Epinephrine, fractalkine (Fract), Insulin-like growth factor (IGF), serotonin, and Vascular endothelial growth factor (VEGF)) were chosen for an ability to modulate inflammation (such as epinephrine), or for association with confounding factors, such as depression or metabolically associated fatigue. Although the use of biomarkers limits this study to observational science, analytes were chosen to aid further research from the community to inform future hypothesis generation. This paper does not suggest causal inference between the presence of microanalytes and clinical findings.

This paper was undertaken to explore the relationships among PASC symptoms and a select number of microanalytes. The aim was to determine whether research participants with confirmed acute SARS CoV-2 infection had concordance between most commonly reported symptoms; specifically, clinically significant fatigue, shortness of breath and "brain fog" and particular analytes or analytes grouped by class (eg, pro-inflammatory cytokines, growth factors, catecholamines etc).

Materials and Methods

Participants were self-selected from a larger research study aimed at assessing the natural history of PASC, described in previous papers.[14,15] Briefly, we recruited 323 participants who had been treated as inpatients or outpatients for SARS-CoV-2 in a large, metropolitan, community health system. They were invited to enroll in an IRB approved observational study. Some were asymptomatic at the time of enrollment. Data were collected at baseline and 6 months, and continuing annual follow-ups for up to 2 years only for those who continued to experience symptoms. Participants were given the choice as to whether they would be evaluated in person or virtually. Only those who chose to come in person are included in this report. Initially, each person was asked to list symptoms that developed after the onset of SARS-CoV-2, along with the symptom severity (eg, mild, moderate, severe). Initially, each person was asked to list symptoms that developed after the onset of SARS-CoV-2, along with the symptom severity (eg, mild, moderate, severe). All were asked to freely describe symptoms without being provided a list of common symptoms to choose from. Due to variability in responses,

symptoms were reviewed by investigators and categories were created based on the most commonly reported symptoms. Our study physician (LG) then reviewed the symptoms and placed them into appropriate categories by organ-systems (eg, neurological, cardiovascular etc). At subsequent visits, investigators reviewed each symptom with the study participants that had been mentioned at the initial visit and asked if symptoms were better, worse or unchanged.

The study was approved by Inova Health System's Institutional Review Board and complies with the Declaration of Helsinki.

Study Measures

We extracted information pertaining to co-morbid conditions as well as length of hospital stay, hospital course and laboratory values in those who had been hospitalized; and medications, sociodemographic status, history of regular exercise (30 minutes, 5x/week or a total of 150 minutes/week), measures of cognition (PCCOG), including Color Word interference Test (CWIT), Coding, Arithmetic, Matrix Reasoning), a clinical assessment of health behavior change, and a variety of PROs (eg, Edmonton Symptom Assessment System (ESAS), EuroQol-5 dimension health-related quality of life instrument (EQ5D, GAD7, PHQ9 et al). Full protocol and instrument descriptions can be found in prior publications as well as Appendix 1.[14,15]

Fatigue Symptoms

Detailed measures of fatigue included the responses on the Functional Assessment of Chronic Illness Therapy – Fatigue (FACIT-F).[16] The FACIT-F includes 4 subscales of well-being: physical (PWB, range 0–28), emotional (EWB, 0–24), social (SWB, 0–28) and functional (FWB, 0–28); and a fatigue subscale domain (FS, 0–52), which adds up to a total FACIT-F score (0–160). For all domains, greater values are designed to reflect better health status.[16] Using the general population norm and standard deviation (SD) for FS, we defined severe fatigue as FS lower than the norm by at least one SD, which yields the cutoff of 29.7 (population norm 40.1, SD 10.4). Symptom categorization for free responses can also be found in our previous publications.[14,15] FACIT-F score and Symptom Reporting were also analyzed using chi-square with odds ratio and confidence interval reporting.

Biological Measures

Blood and serum were collected from 79 of the 323 consented subjects during their initial in-person visit and stored at −80` C. Circulating BDNF (ThermoFisher), serotonin (Rocky Mountain Diagnostics), ORM (R&D Systems), IGF (ThermoFisher), fractalkine (ThermoFisher), and IFNa auto-antibodies (ThermoFisher) were measured from serum by ELISA. Circulating IFNa, Epinephrine, CCL2, IL6, EGF, IL1b, IL2, IL4, IL10, IL12, IL17, and VEGF were all measured in serum by ligation proximity assay (Human ProQuantum Immunoassays, ThermoFisher). All assays were performed as per manufacturer's protocol.

Data Analysis

This cross-sectional study presents post hoc analysis of prospectively collected data. All parameters were summarized as N (%) or mean ± SD and compared between groups of subjects using chi-square or Kruskal–Wallis non-parametric tests. The Spearman correlation coefficients were calculated to assess relationships between continuous variables. Free-text responses were categorized into pre-defined categories by the study personnel. Two-sided p-values <0.05 were considered statistically significant. SAS 9.4 (SAS Institute, Cary, NC) was used for all analyses. All study participants gave informed consent. Due to limited sample size, there was no additional adjustment for multiple testing.

Multiple heat maps were created using the data from the Spearman correlation to identify areas of signal intensity. Heat Map 3a was created using a two-tiered temperature index to visualize the R-values, the darkest green represents the highest negative R-values and the darkest blue represents the highest positive R-values. Bold font cells represent statistically significant associations with a $p<0.05$. Heat map 3b was created using a single tiered temperature index and was used to generate heatmaps for the p-values, where the darkest shade of red indicates the most statistically significant value (the lowest numerical value was set to the darkest shade of red eg P-value 0.0001) for any given micro-analyte correlation.

The conditional formatting function in Excel was used to generate a two-tiered temperature index to visualize the R-values, where the darkest green represents the highest negative R-values and the darkest blue represents the highest positive R-values. A single tiered temperature index was used to generate heatmaps for the p-values, where the darkest colors indicate the most statistically significant value (the lowest number was set to the darkest color eg P-value 0.0001) for any given micro-analyte correlation.

Results

The cohort demographics are presented in Table 1. The distribution between hospitalized vs. non-hospitalized participants was not different (48% were and 52% were not hospitalized). We used hospitalization as a clinical indicator of

Table 1 Cohort Descriptors at Baseline in Participants with In-Person Visits

Number	**79 (n)**
Age, years (mean)	51.1 ± 30.9
Number hospitalized (Y/N)	37/42
Number without symptoms	11
Number ≤ 3mo since dx	12
Male	38 (48.1%)
Race:	
Caucasian	62 (78.5%)
Asian	6 (7%)
Black	9 (11.3%)
>1 race	2 (3.2%)
Ethnicity:	
Hispanic	30 (37.9%)
Non-Hispanic	48 (60.7%)
Undetermined	1 (1.2%)
Anthropometrics:	
BMI (mean)	30.59 (18.7–54)
Body fat (mean)	33.6%
Habit of Exercise:	
Exercise ≥30 min ≥3/week (n)	37 (46.8%)
Less than 30 min/3X/week (n)	33 (41.7%)
Varies/unsure (n)	9 (11.3%)
Prior Medical History (%)	
Hospitalized for COVID (Y/N)	37/42
Anxiety	11 (13.9%)
Arthritis	8 (10%)
Asthma	11 (13.9%)
Coronary artery disease	2 (2.5%)
Cancer	11 (13.9%)
Chronic kidney disease	3 (3.0%)
Chronic liver disease	14 (17.7%)
Depression	9 (11.4%)
Diabetes	1 (1%)
Hypertension	26 (32.9%)
Hyperlipidemia	29 (36.7%)
Sleep apnea	10 (12.6%)
Major Symptoms **n (%)**	25 (31.6%)
Fatigue	27 (34.2%)
Memory Changes	19 (24.17%)
Shortness of Breath	

Table 2 Prevalence of Abnormal Patient Reported Outcomes for the Cohort

Sample Size: 79	
Means	
Number of Symptoms	2.85±2.38 (no normal data available)
PWB (score)	22.6±4.6 (above normal population)
EWB (score)	18.4±4.9 (below normal population)
SWB (score)	19.4±5.9 (below normal population)
FWB (score)	17.9±5.9 (below normal population)
FACIT-F (score)	114.9±26.3 (fatigued)
PHQ9 (score)	6.23±5.55 (mild depressive symptoms)
PCCOG (score)	3.6±0.84 (not standardized)
ESAS (Total)	2.58±1.94 (no normal data available)
GAD7	4.31±4.68 (mild anxiety)
EQ5D (Total)	0.808±0.126 (patient reported health acceptable)

severity of SARS-CoV-2 infection. Supplementary Table 1 shows key differences between hospitalized versus non-hospitalized in the full sample.

Table 2 summarizes the mean scores and standard deviations for the administered standardized PROs. Bolded numbers represent normal range scores for each PRO, when available. Specifically, there are no known normal ranges for the number of symptoms reported for the PCCOG.

Table 3 is a visual presentation of rank sum correlation for each PRO at baseline by analyte. Table 4 is a visual presentation of the p values of these relationships. Darker colors represent stronger correlations. Epinephrine correlations with PROs are most frequently identified as significant, followed by IL1b.

Figure 1 presents a graphical grouping of the PROs, and analytes. The number of symptoms is related to 3 domains of reports: fatigue, shortness of breath and memory loss. Shortness of breath has significant impact on ESAS scores (physical and emotional well-being and total score) and PWB subscale of the FACIT-F. PHQ9, cognition and number of symptoms impact memory, which are associated with circulating micro-analytes (VEGF, IGF and IL17).

Discussion

PASC remains a clinical challenge for a variety of reasons. As has been described by other investigators, people infected with SARS-CoV-2 suffer a variety of organ system involvements and have reported a large number of symptoms, as many as 200, temporally related to the post-infection state.[8–10,17–19] This large spectrum of patient reported symptoms and findings coupled with the many organ system that may be involved requires large cohorts to be able to identify necessary symptoms for diagnosis. What has evolved has been an understanding and acceptance that PASC diagnosis requires a layered series of events rather than organ-specific involvement or specific symptom complexes. It focuses on the documentation of infection, time since infection of emergence of symptoms and findings and the absence of a disease or syndrome that would explain the clinical presentation. This creates a situation in which decision making for treatment often relies upon patient self-reports, a frequent situation for chronic Lyme disease or myalgic encephalomyelitis/chronic fatigue syndrome. These self-reports may include symptoms and functional measures that reflect an individual's needs. Specific testing, for example for autonomic dysfunction, pulmonary mechanics or abnormalities of exercise testing, coupled with more general laboratory and imaging abnormalities are not required for diagnosing PASC, though they are often performed for people with postural hypotension and fatigue.[20] Using reliable measures, including both objective

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Table 3 Heat Map of Relationships Among PROs and Micro-Analytes (R Values)

Analyte	IL1b	IL2	IL4	IL6	IL10	IL12	IL17	CCL2	IFNa	AAIFNA	ORM	IGF	EGF	VEGF	BDNF	Fract	Epinephrine	Serotonin	Glucose
Clinical/PRO	R	R	R	R	R	R	R	R	R	R	R	R	R	R	R	R	R	R	R
EWB_BSLN	**−0.32**	−0.14	−0.04	−0.09	0.00	−0.04	0.20	0.04	**0.27**	−0.01	0.02	0.04	0.06	−0.09	−0.07	0.17	**0.40**	−0.05	0.00
PWB_BSLN	**−0.42**	−0.15	−0.13	−0.09	0.02	0.10	0.04	0.09	0.19	−0.08	0.07	0.08	0.11	−0.22	−0.07	0.05	**0.44**	−0.02	−0.03
FS_BSLN	−0.24	−0.06	−0.15	−0.09	−0.07	0.03	0.11	0.03	0.08	0.12	0.05	0.10	0.03	−0.05	**−0.27**	0.17	**0.36**	−0.09	0.19
GAD7_BSLN	**0.31**	0.16	0.07	0.09	0.27	0.18	−0.11	0.02	−0.17	−0.06	−0.05	−0.20	−0.14	0.16	0.13	−0.22	**−0.29**	0.02	−0.25
DISTHER_BSLN	0.22	**0.31**	−0.06	0.13	0.01	0.04	−0.26	−0.07	−0.20	−0.22	0.12	−0.09	**−0.34**	0.11	−0.04	−0.20	−0.23	0.16	−0.09
TMWD_BSLN	−0.08	−0.07	**0.32**	0.23	0.03	0.05	0.22	0.26	0.23	**−0.31**	−0.12	−0.05	0.05	0.00	0.04	0.07	−0.06	0.20	−0.02
SICK_DAYS	0.12	0.17	0.13	**0.28**	−0.09	0.21	0.07	−0.06	0.08	−0.08	0.06	0.01	−0.04	0.11	−0.03	0.03	−0.21	−0.04	0.08
NSYMPT_BSLN	0.20	0.11	0.18	0.03	0.11	0.18	0.17	0.04	−0.21	−0.16	−0.03	−0.15	−0.08	**0.28**	0.04	−0.09	0.02	0.08	−0.01
FACITF_BSLN	−0.21	−0.10	−0.03	−0.11	−0.08	−0.04	0.13	−0.02	0.16	0.10	0.00	0.08	0.07	−0.03	−0.20	0.16	**0.33**	−0.01	0.11
PHQ9_BSLN	0.20	−0.02	0.09	0.15	0.07	0.04	−0.06	−0.01	−0.05	−0.12	−0.07	−0.15	−0.10	0.05	0.09	−0.13	**−0.29**	0.14	−0.15
PCCOG_BSLN	**−0.30**	0.04	−0.19	−0.10	−0.05	−0.03	−0.07	−0.04	0.10	0.16	0.05	0.12	0.02	−0.16	−0.06	−0.08	0.13	0.01	0.14
ESASPHYS_BSLN	0.13	0.21	0.18	0.11	0.16	−0.22	0.10	−0.12	0.07	−0.09	−0.01	−0.12	−0.18	0.28	0.07	−0.14	**−0.35**	0.07	0.01
ESASEMO_BSLN	0.25	0.13	−0.02	0.12	0.22	−0.02	−0.11	−0.19	−0.17	−0.14	0.07	−0.25	−0.11	0.11	0.09	−0.18	**−0.39**	0.00	0.03
ESASTOTL_BSLN	0.19	0.19	0.11	0.07	0.20	−0.18	−0.01	−0.18	−0.05	−0.13	0.00	−0.20	−0.15	0.24	0.06	−0.18	**−0.37**	0.04	−0.04
EQ5Di_BSLN	−0.10	**−0.32**	−0.17	−0.11	−0.12	0.04	−0.05	0.06	0.15	−0.02	−0.16	0.02	0.22	−0.24	0.11	0.12	0.22	0.11	−0.15
SWB_BSLN	0.19	0.07	0.16	−0.15	0.02	0.06	0.09	−0.10	0.12	0.02	−0.23	−0.01	0.12	0.06	−0.10	0.12	0.06	0.16	0.05
FWB_BSLN	−0.17	−0.19	0.04	0.00	−0.13	−0.13	0.18	−0.02	0.12	0.17	−0.05	−0.01	0.15	0.04	−0.12	0.05	0.13	0.10	0.22
STIGMA_BSLN	0.07	−0.02	−0.01	−0.08	0.04	−0.10	0.09	−0.12	−0.06	−0.06	−0.19	−0.20	−0.13	0.23	−0.20	0.06	0.09	0.00	−0.08
GRIP_BSLN	0.07	0.00	−0.06	0.01	0.16	0.05	0.03	−0.17	−0.06	−0.17	−0.17	0.11	0.08	−0.10	0.05	−0.06	−0.19	0.02	0.10

Notes: A two tiered temperature index to visualize the R-values, the darkest green represents the highest negative R-values and the darkest blue represents the highest positive R-values. Bold font cells represents statistically significant associations with a $p<0.05$.

Abbreviations: BSLN, Baseline; DISTHER, Distress Thermometer; TMWD, Two-Minute Walk Distance; SICK_DAYS, Days sick with COVID; NSYMPT, Number of Post-COVID Symptoms; ESASPHYS, Physical domain of the ESAS; ESASEMO, Emotional domain of the ESAS; STIGMA, Stigma questionnaire; GRIP, Grip Strength.

Table 4 Heat Map of Relationships Among PROs and Micro-Analytes (p values)

Analyte	IL1b	IL2	IL4	IL6	IL10	IL12	IL17	CCL2	IFNa	AAIFNA	ORM	IGF	EGF	VEGF	BDNF	Fract	Epinephrine	Serotonin	Glucose
Clinical/PRO	p	p	p	p	p	p	p	p	p	p	p	p	p	p	p	p	p	p	p
EWB_BSLN	0.0110	0.29	0.77	0.51	0.98	0.77	0.12	0.77	0.0384	0.95	0.86	0.78	0.66	0.52	0.58	0.19	0.0013	0.73	0.97
PWB_BSLN	0.0007	0.23	0.31	0.52	0.88	0.44	0.76	0.50	0.14	0.52	0.60	0.52	0.41	0.08	0.62	0.72	0.0004	0.89	0.81
FS_BSLN	0.07	0.64	0.25	0.48	0.57	0.81	0.39	0.83	0.55	0.36	0.70	0.43	0.81	0.71	0.0346	0.19	0.0044	0.49	0.17
GAD7_BSLN	0.0304	0.27	0.65	0.53	0.06	0.22	0.47	0.91	0.23	0.70	0.72	0.18	0.33	0.29	0.36	0.13	0.0437	0.90	0.09
DISTHER_BSLN	0.12	0.0326	0.70	0.38	0.96	0.79	0.07	0.63	0.18	0.13	0.42	0.54	0.0158	0.44	0.80	0.17	0.11	0.29	0.53
TMWD_BSLN	0.56	0.63	0.0171	0.10	0.83	0.70	0.11	0.06	0.09	0.0206	0.38	0.75	0.74	1.00	0.79	0.62	0.65	0.14	0.91
SICK_DAYS	0.31	0.14	0.27	0.0167	0.44	0.08	0.54	0.60	0.50	0.51	0.60	0.91	0.75	0.37	0.81	0.79	0.07	0.77	0.48
NSYMPT_BSLN	0.08	0.36	0.11	0.81	0.32	0.11	0.13	0.75	0.06	0.16	0.82	0.20	0.47	0.0150	0.76	0.46	0.87	0.50	0.95
FACITF_BSLN	0.10	0.46	0.82	0.39	0.54	0.77	0.33	0.90	0.22	0.45	0.97	0.56	0.57	0.83	0.13	0.22	0.0089	0.94	0.41
PHQ9_BSLN	0.12	0.90	0.51	0.25	0.60	0.76	0.67	0.92	0.69	0.37	0.60	0.24	0.43	0.69	0.49	0.34	0.0210	0.28	0.27
PCCOG_BSLN	0.0203	0.78	0.14	0.47	0.71	0.81	0.58	0.76	0.46	0.21	0.71	0.36	0.91	0.23	0.64	0.55	0.32	0.91	0.31
ESASPHYS_BSLN	0.38	0.14	0.21	0.47	0.27	0.13	0.49	0.41	0.64	0.54	0.97	0.42	0.20	0.06	0.65	0.34	0.0136	0.63	0.95
ESASEMO_BSLN	0.09	0.38	0.88	0.42	0.12	0.87	0.47	0.19	0.25	0.33	0.66	0.08	0.44	0.48	0.53	0.21	0.0057	0.99	0.86
ESASTOTL_BSLN	0.19	0.20	0.45	0.62	0.16	0.21	0.96	0.23	0.74	0.38	0.98	0.17	0.31	0.10	0.68	0.22	0.0082	0.79	0.80
EQ5Di_BSLN	0.41	0.0096	0.19	0.40	0.34	0.78	0.71	0.62	0.23	0.88	0.20	0.86	0.08	0.06	0.39	0.33	0.08	0.39	0.26
SWB_BSLN	0.14	0.57	0.22	0.25	0.88	0.63	0.50	0.44	0.36	0.88	0.08	0.92	0.36	0.63	0.42	0.36	0.65	0.22	0.70
FWB_BSLN	0.20	0.14	0.77	0.99	0.33	0.32	0.16	0.86	0.34	0.20	0.72	0.91	0.26	0.78	0.35	0.68	0.33	0.43	0.10
STIGMA_BSLN	0.62	0.89	0.92	0.61	0.78	0.49	0.56	0.44	0.70	0.67	0.20	0.19	0.38	0.12	0.17	0.69	0.53	1.00	0.61
GRIP_BSLN	0.57	0.99	0.60	0.93	0.18	0.70	0.80	0.15	0.63	0.15	0.15	0.38	0.48	0.39	0.69	0.63	0.11	0.84	0.41

Notes: A single tiered temperature index was used to generate heatmaps for the p-values, where the darkest shade of red indicates the most statistically significant value (the lowest numerical value was set to the darkest shade of red eg p-value 0.0001) for any given micro-analyte correlation.

Abbreviations: BSLN, Baseline; DISTHER, Distress Thermometer; TMWD, Two-Minute Walk Distance; SICK_DAYS, Days sick with COVID; NSYMPT, Number of Post-COVID Symptoms; ESASPHYS, Physical domain of the ESAS; ESASEMO, Emotional domain of the ESAS; STIGMA, Stigma questionnaire; GRIP, Grip Strength.

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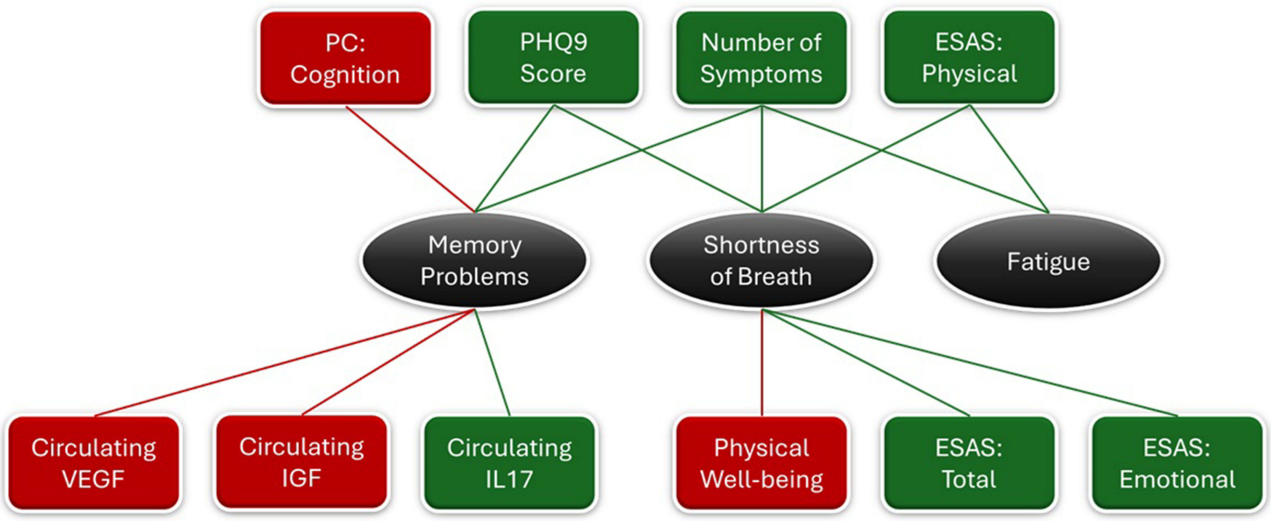

Figure 1 Graphic presentation of relationships among variables of interest. Relationships are represented by connecting lines. Red lines are inverse relationships and green lines are positive correlations.

evaluations and self-reports to determine patient experience and degree of disability is critical to managing this complex, challenging clinical syndrome.

Other challenges for successfully establishing the criteria for diagnosis of PASC include the varying impact each of the viral strains has had on the clinical PASC symptomatology. Each wave of SARS-CoV-2 variants had different symptoms and prevalences. This led to changes in the profile of patient experiences, changes in the phenotype with different strains. Often there was a modulation of symptoms following vaccination[21–23] Nonetheless, the efforts to describe the common features have resulted in general acceptance of the condition, which includes (CDC): Development of new or recurrent symptoms and conditions after the symptoms of initial acute COVID-19 illness have resolved; symptoms that can emerge, persist, resolve, and reemerge over varying lengths of time; A spectrum of physical, social, and psychological consequences and functional limitations that can affect patient wellness and quality of life and may cause disability.[1] With this acceptance, the health care community has accepted that PASC is prevalent, difficult to treat and negatively impacts the lives of millions worldwide.

The study reported here was designed to try to identify a possible biosignature that includes multiple domains of measurement. These domains included objective and standardized self-reported measures, as well as unscripted inquiry of symptoms. We expanded the objective measures to include serological assessments of chemokines, cytokines, catecholamines and growth factors as recent reports have identified potential serological profiles in people with PASC[13,18,22,24] and persistent indices of autonomic dysfunction.[25]

This manuscript describes a carefully studied small cohort of people who volunteered to participate in a natural history study of PASC infection and elected to participate on-site. Ongoing participation, hence follow-up, was interrupted by the vicissitudes of COVID prevalence and changing phenotype in the community as well as participants' comfort and ability to come to a clinic environment. Therefore, we chose to use baseline data, which was complete and available despite having only 79 participants, of whom only 14% had persistent symptoms when they entered the study.

We selected a battery of patient-reported measures to report here, which is a subset of all the data we had collected from the entire cohort. The decision about which ones to include for this submission was based on our prior work reporting the impact of SARS -Co-V-2 on individuals' symptoms and functioning,[14,15] what the literature has reported to be among the most common and/or disruptive experiences to individuals' lives.[26,27] We also used data we had gathered from our work assessing fatigue and function in people with chronic liver disease.[28,29] It is our view that measures of fatigue, cognitive function, physical activity, overall well-being, mood, and sleep should be included routinely, as part of evaluations of all with persistent symptoms following SARS-CoV-2 infection. These should be in addition to standard clinical, organ-system driven assessments and laboratory measures in the evaluation and treatment planning for people

with PASC. It is our firm commitment that this group of patients needs the combination of objective and self-reported measures in order to effectively treat and hopefully mitigate persistent symptoms to achieve functional improvement.

The findings of abnormal microanalyte concentrations, if confirmed by other investigators using larger sample sizes and their association with self-reports, suggest physiological abnormalities that may be contributors to symptoms. It has been reported that the strongest predictor of persistent PASC is low levels of cortisol, a stress hormone.[30,31] ACTH stimulates the adrenal cortex to produce cortisol as part of the stress response. The hypothalamus contains the paraventricular nucleus (PVN) which controls neuroendocrine and autonomic function and regulates the hypothalamic–pituitary–adrenal (HPA) axis through the release of corticotrophin-releasing hormone (CRH). This stimulates the pituitary to produce adrenocorticotropic hormone (ACTH).[30,32]

The PVN also exerts negative feedback control over the HPA axis via cortisol receptors. When cortisol production adequately responds to stress, it provides negative feedback to the PVN in the hypothalamus. If cortisol is low, the stress response is inadequate and may result in over production of catecholamines (epinephrine, norepinephrine).[33] Exploration of this association may help explain our findings. Investigators report low cortisol levels in people with PASC. It has been reported that treating hypocortisolemia may offer treatment options for those with these findings,[34] and lead to a better understanding of underlying mechanisms that result in effective treatment approaches. It is important to note that many authors report other important contributors to the regulation of stress. Chronic stress, which refers to a state in which stress continues over a protracted Not mentioned period of time, often leads to physiological stress.[35] Physiological stress refers to the body's response to internal or external stressors that disrupt homeostasis. Chronic infection is an example, which may activate physiological stress pathways and compromise health and well-being, promote systemic inflammation through the upregulation of inflammatory mediators, contributing to the pathogenesis of autoimmune diseases and chronic inflammatory disorders, also reported in some with PASC.[35]

There are limitations associated with the current paper. The sample size is small and we did not perform statistical adjustments for multiple analyses. Confirmation of the findings will require larger sample sizes to confirm these preliminary results. It is a heterogenous group of participants, some with and some without symptoms, hence the use of free text comments about symptoms may introduce inconsistencies in reporting. We believe the use of standardized testing provides some reliability and correction for this. Additionally, the necessary office visit for blood draw reasonably may have selected out some of those with the greatest symptom burden introducing selection bias. The recruitment effort was interrupted by intermittent surges in infection rates in our area and the SARS-CoV-2 variants changed over time. Finally, the amount of time elapsed since infection varied from 30 days to several months. Nonetheless, we are able to identify associations that are statistically significant and are consistent with findings of others who suggest a role for hypocortisolemia, increases in pro-inflammatory cytokines and catecholamines.[36–40]

Conclusion

This paper reports the experience of 79 people post SARS-CoV2 infection. The results of their self-reported outcomes suggest that various aspects of well-being, particularly emotional and functional well-being are lower than a previously uninfected population. Fatigue is more prevalent and more severe in the group, when compared to population norms, as is depression and anxiety. The assays of biofluids in this convenience sample show some strong correlations with the self-reports. Specifically, measures of well-being are positively correlated with levels of epinephrine, whereas they are inversely correlated with levels of IL1b, suggesting that catecholamines and inflammatory cytokines may contribute to patient reported symptoms and functioning. The correlations further suggest there is a role for the HPA axis and inflammatory pathways in people who have these persistent post-SARS-CoV-2 clinical findings.

Abbreviations

PWB, Physical well Being Subscale Score; EWB, Emotional Well Being Subscale Score; SWB, Social Well Being Subscale Score; FWB, Functional Well Being Subscale Score; FACIT-F, Functional Assessment of Chronic Illness Therapy-Fatigue; PHQ9, Patient Health Questionnaire 9; PCCOG, Post-Covid Cognitive Test; ESAS, Edmonton Symptom Assessment System (ESAS); GAD 7, General Anxiety Disorder 7; EQ5D, EuroQol-5 dimension health-related quality of life instrument; BDNF, Brain-Derived Neurotrophic Factor; IL-6, Interleukin-6; IL-1b, Interleukin-1

beta; IL-2, Interleukin-2; IL-4, Interleukin-4; IL-10, Interleukin-10; IL-12, Interleukin-12; IL-17. Interleukin-17; ORM, Orosomucoid or alpha-1-acid glycoprotein; IFNa, Interferon-alpha; AAIFNA, Interferon-alpha auto-antibodies; CCL2, C-C motif Chemokine ligand 2; IGF, Insulin-like growth factor; VEGF, Vascular endothelial growth factor; Fract, Fractalkine.

Disclosure

The authors report no conflicts of interest in this work.

References

1. CDC. Long COVID basics. COVID-19. 2025. Available from: https://www.cdc.gov/covid/long-term-effects/index.html. Accessed March 7, 2025.
2. Thaweethai T, Jolley SE, Karlson EW, et al. Development of a definition of postacute sequelae of SARS-CoV-2 infection. *JAMA*. 2023;329 (22):1934–1946. doi:10.1001/jama.2023.8823
3. WHO. Post COVID-19 condition (Long COVID). Available from: https://www.who.int/europe/news-room/fact-sheets/item/post-covid-19-condition. Accessed August 8, 2024.
4. Rodriguez-Morales AJ, Lopez-Echeverri MC, Perez-Raga MF, et al. The global challenges of the long COVID-19 in adults and children. *Travel Med Infect Dis*. 2023;54:102606. doi:10.1016/j.tmaid.2023.102606
5. Al-Aly Z, Davis H, McCorkell L, et al. Long COVID science, research and policy. *Nat Med*. 2024;30(8):2148–2164. doi:10.1038/s41591-024-03173-6
6. Huerne K, Filion KB, Grad R, Ernst P, Gershon AS, Eisenberg MJ. Epidemiological and clinical perspectives of long COVID syndrome. *Am J Med Open*. 2023;9:100033. doi:10.1016/j.ajmo.2023.100033
7. Price JK, de Avila L, Stepanova M, et al. Severe, persistent, disruptive fatigue post-SARS-CoV-2 disproportionately affects young women. *Int J Gen Med*. 2023;16:4393–4404. doi:10.2147/IJGM.S423910
8. Davis HE, Assaf GS, McCorkell L, et al. Characterizing long COVID in an international cohort: 7 months of symptoms and their impact. *EClinicalMedicine*. 2021;38:101019. doi:10.1016/j.eclinm.2021.101019
9. Davis HE, McCorkell L, Vogel JM, Topol EJ. Long COVID: major findings, mechanisms and recommendations. *Nat Rev Microbiol*. 2023;21 (3):133–146. doi:10.1038/s41579-022-00846-2
10. Lopez-Leon S, Wegman-Ostrosky T, Perelman C, et al. More than 50 long-term effects of COVID-19: a systematic review and meta-analysis. *Sci Rep*. 2021;11(1):16144. doi:10.1038/s41598-021-95565-8
11. Hu W, Tang R, Gong S, et al. The prevalence and associated factors of post-COVID-19 fatigue: a systematic review and meta-analysis. *Cureus*. 2024;16(7):e63656. doi:10.7759/cureus.63656
12. Pradeep A, Birerdinc A, Branigan T, et al. Evidence for an association of serum microanalytes and myofascial pain syndrome. *BMC Musculoskelet Disord*. 2023;24(1):624. doi:10.1186/s12891-023-06744-9
13. Walitt B, Singh K, LaMunion SR, et al. Deep phenotyping of post-infectious myalgic encephalomyelitis/chronic fatigue syndrome. *Nat Commun*. 2024;15(1):907. doi:10.1038/s41467-024-45107-3
14. de Avila L, Price JK, Stepanova M, et al. Regular exercise is associated with low fatigue levels and good functional outcomes after COVID-19: a prospective observational study. *Am J Phys Med Rehabil*. 2023;102(5):433–443. doi:10.1097/PHM.0000000000002197
15. Price JK, Gerber LH, Stepanova M, et al. Post-acute SARS-CoV-2 symptoms are fewer, less intense over time in people treated with mono-clonal antibodies for acute infection. *Int J Gen Med*. 2023;16:1479–1490. doi:10.2147/IJGM.S406571
16. Webster K, Cella D, Yost K. The functional assessment of chronic illness therapy (FACIT) measurement system: properties, applications, and interpretation. *Health Qual Life Outcomes*. 2003;1(1):79. doi:10.1186/1477-7525-1-79
17. Tan S, Pryor AJG, Melville GW, Fischer O, Hewitt L, Davis KJ. The lingering symptoms of post-COVID-19 condition (long-COVID): a prospective cohort study. *Internal Med J*. 2024;54(2):224–233. doi:10.1111/imj.16251
18. Tsilingiris D, Vallianou NG, Karampela I, et al. Laboratory findings and biomarkers in long COVID: what do we know so far? Insights into epidemiology, pathogenesis, therapeutic perspectives and challenges. *Int J Mol Sci*. 2023;24(13):10458. doi:10.3390/ijms241310458
19. Cornelissen MEB, Haarman MM, Twisk JWR, et al. The progression of symptoms in post COVID-19 patients: a multicentre, prospective, observational cohort study. *Biomedicines*. 2024;12(11):2493. doi:10.3390/biomedicines12112493
20. Goldstein DS, Mina Y, Walitt B, et al. Persistent autonomic and immunologic abnormalities in neurologic post-acute sequelae of SARS-CoV2 infection. *Neurology*. 2024;103(6):e209742. doi:10.1212/WNL.0000000000209742
21. Fernandez-de-Las-Peñas C, Notarte KI, Macasaet R, et al. Persistence of post-COVID symptoms in the general population two years after SARS-CoV-2 infection: a systematic review and meta-analysis. *J Infect*. 2024;88(2):77–88. doi:10.1016/j.jinf.2023.12.004
22. Stróż S, Kosiorek P, Stasiak-Barmuta A. The COVID-19 inflammation and high mortality mechanism trigger. *Immunogenetics*. 2024;76(1):15–25. doi:10.1007/s00251-023-01326-4
23. Hengkrawit K, Thananon J, Telapol K, Chiewchalermsri C. clinical characteristics and outcomes of hospitalized COVID-19 patients with different variants of SARS-CoV-2 in a tertiary care hospital, Thailand. *Trop Med Infect Dis*. 2024;9(11):266. doi:10.3390/tropicalmed9110266
24. Saito S, Shahbaz S, Osman M, et al. Diverse immunological dysregulation, chronic inflammation, and impaired erythropoiesis in long COVID patients with chronic fatigue syndrome. *J Autoimmun*. 2024;147:103267. doi:10.1016/j.jaut.2024.103267
25. Compeer B, Neijzen TR, van Lelyveld SFL, Martina BEE, Russell CA, Goeijenbier M. Uncovering the contrasts and connections in PASC: viral load and cytokine signatures in acute COVID-19 versus post-acute sequelae of SARS-CoV-2 (PASC). *Biomedicines*. 2024;12(9):1941. doi:10.3390/biomedicines12091941
26. Walvekar SS, Mohite VR. Tracking health beyond recovery: a study on identifying post-COVID syndrome symptoms. *Indian J Crit Care Med*. 2024;28(2):170–174. doi:10.5005/jp-journals-10071-24641

27. Lippi G, Sanchis-Gomar F, Henry BM. COVID-19 and its long-term sequelae: what do we know in 2023? *Pol Arch Intern Med*. 2023;133 (4):16402. doi:10.20452/pamw.16402
28. Gerber LH, Weinstein AA, Mehta R, Younossi ZM. Importance of fatigue and its measurement in chronic liver disease. *World J Gastroenterol*. 2019;25(28):3669–3683. doi:10.3748/wjg.v25.i28.3669
29. Younossi ZM, Kremer AE, Swain MG, et al. Assessment of fatigue and its impact in chronic liver disease. *J Hepatol*. 2024;81(4):726–742. doi:10.1016/j.jhep.2024.04.008
30. Ruetsch C, Brglez V, Crémoni M, et al. Functional exhaustion of type I and II interferons production in severe COVID-19 patients. *Front Med Lausanne*. 2020;7:603961. doi:10.3389/fmed.2020.603961
31. Schultheiß C, Willscher E, Paschold L, et al. The IL-1β, IL-6, and TNF cytokine triad is associated with post-acute sequelae of COVID-19. *Cell Rep Med*. 2022;3(6):100663. doi:10.1016/j.xcrm.2022.100663
32. Souza-Silva NG, Rosa DV, de Paula JJ, Coimbra RS, Miranda DM, Romano-Silva MA. Follow-up of cognitive impairment and inflammatory profile in individuals with mild COVID-19. *J Neuroimmunol*. 2024;389:578327. doi:10.1016/j.jneuroim.2024.578327
33. Jammoul M, Naddour J, Madi A, et al. Investigating the possible mechanisms of autonomic dysfunction post-COVID-19. *Auton Neurosci*. 2023;245:103071. doi:10.1016/j.autneu.2022.103071
34. Yavropoulou MP, Tsokos GC, Chrousos GP, Sfikakis PP. Protracted stress-induced hypocortisolemia may account for the clinical and immune manifestations of Long COVID. *Clin Immunol*. 2022;245:109133. doi:10.1016/j.clim.2022.109133
35. Chrousos GP, Gold PW. The concepts of stress and stress system disorders. Overview of physical and behavioral homeostasis. *JAMA*. 1992;267 (9):1244–1252. doi:10.1001/jama.1992.03480090092034
36. Salzano C, Saracino G, Cardillo G. Possible adrenal involvement in long COVID syndrome. *Medicina*. 2021;57(10):1087. doi:10.3390/ medicina57101087
37. Engler-Chiurazzi E. B cells and the stressed brain: emerging evidence of neuroimmune interactions in the context of psychosocial stress and major depression. *Front Cell Neurosci*. 2024;18:1360242. doi:10.3389/fncel.2024.1360242
38. Derakhshan M, Ansarian HR, Ghomshei M. Possible effect of epinephrine in minimizing COVID-19 severity: a review. *J Int Med Res*. 2020;48 (9):300060520958594. doi:10.1177/0300060520958594
39. Sherif ZA, Gomez CR, Connors TJ, Henrich TJ, Reeves WB. RECOVER mechanistic pathway task force. pathogenic mechanisms of post-acute sequelae of SARS-CoV-2 infection (PASC). *Elife*. 2023;12:e86002. doi:10.7554/eLife.86002
40. Iosef C, Matusa AM, Han VKM, Fraser DD. Endocrine dysregulation in COVID-19: molecular mechanisms and insights. *Front Endocrinol*. 2024;15:1459724. doi:10.3389/fendo.2024.1459724