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Brief Report

Immune Fitness, Mood, Fatigue, and Quality of Life Prior to SARS-CoV-2 Infection Were Not Identified as Independent Predictors of PASC Fatigue Severity

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Abstract

Post-acute sequelae of SARS-CoV-2 infection (PASC), also referred to as Long COVID, affects millions worldwide and is characterized by persistent fatigue, reduced immune fitness, and mood disturbances. The aim of the current study was to identify if immune fitness, mood, fatigue, and quality of life prior to SARS-CoV-2 infection could predict PASC fatigue severity. A retrospective cross-sectional survey was conducted among 299 Dutch PASC patients. Participants completed validated measures of immune fitness, fatigue (assessed with both the Fatigue Severity Scale and a single-item scale), mood (including stress, anxiety, depression, hostility, loneliness, and happiness) and quality of life for the three months prior to SARS-CoV-2 infection. The same assessments were made for the month before survey completion (i.e., during PASC). Correlational and regression analyses were conducted to identify possible predictors of PASC fatigue severity. Participants were predominantly female (90%): mean age 44.1 (SD 11.2) years. Both assessments of PASC fatigue did not correlate significantly with the prior SARS-CoV-2 assessments of immune fitness, fatigue, mood, and quality of life. The regression analyses revealed no significant predictors for PASC fatigue severity. In conclusion, immune fitness, fatigue, mood and quality of life prior to SARS-CoV-2 infection were not identified as independent predictors of PASC fatigue severity.

Keywords: PASC; Long COVID; immune fitness; fatigue; mood; SARS-CoV-2; predictors

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1. Introduction

At the end of 2019, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) emerged in China and rapidly spread worldwide. In March 2020, the World Health Organization (WHO) declared coronavirus disease 2019 (COVID-19) a global pandemic [1].

It appeared that after resolving the SARS-CoV-2 infection, a substantial proportion of patients continued to experience symptoms. This condition, termed post-acute sequelae of SARS-CoV-2 infection (PASC), also referred to as Long COVID, is recognized as a multisystem disorder with major public health implications [2]. The WHO defines PASC as the continuation or development of new symptoms three months after the initial SARS-CoV-2 infection, persisting for at least two months [2]. It is estimated that 10–30% of individuals infected with SARS-CoV-2 develop persistent symptoms lasting more than 12 weeks, though prevalence rates vary depending on population and study design [3,4]. PASC poses a considerable burden on individuals, healthcare systems, and economies [5,6].

PASC is associated with a wide range of symptoms. Fatigue reduced immune fitness, cognitive dysfunction ("brain fog"), dyspnea, sleep disturbances, and mood alterations such as anxiety and depression are among the most frequently reported PASC symptoms [2,7]. Additional manifestations such as chest pain, palpitations, gastrointestinal complaints, and dysautonomia highlight the multisystemic nature of the condition [7]. These sequelae substantially impair quality of life and contribute to societal and economic costs through prolonged sick leave, increased healthcare utilization, and reduced productivity [5,6].

Identifying risk factors that predispose individuals to PASC is crucial for prevention, early intervention, and effective resource allocation. Proposed demographic and clinical factors that put individuals at increased risk for developing PASC include female sex, older age, higher body mass index (BMI), and pre-existing conditions such as asthma, cardiovascular disease, and diabetes [5,8]. Lifestyle-related factors, such as poor sleep, smoking, and psychological distress, have also been suggested [9,10].

However, the results of studies that aimed to identify PASC predicting factors are inconsistent with significant variability in clinical outcomes. For example, while some studies suggested that acute immune activation and markers such as RNAemia or autoantibodies are linked to increased PASC risk [11,12], other studies found no clear association between the severity of PASC fatigue and levels of inflammatory markers such as c-reactive protein (CRP) or interleukin (IL)-6 [13,14]. Additionally, fatigue and self-reported health status prior to SARS-CoV-2 infection showed only modest predictive value for the severity of PASC-related symptoms, and paradoxical associations have been observed with physical activity levels [3,15–17]. These inconsistent findings underscore the heterogeneity of PASC pathophysiology and highlight the need for additional research into possible predictors of PASC development and its severity [18,19].

One construct of interest in relation to PASC is immune fitness, defined as the body's ability to mount an adequate immune response to challenges. It is shaped by factors including genetic predisposition, nutrition, physical activity, stress, and sleep quality [20,21]. Previous research has shown that immune fitness prior to SARS-CoV-2 infection was the sole and significant predictor of the number and severity of experienced COVID-19 symptoms [22]. Therefore, it can be assumed that pre-existing immune fitness might also play a role in PASC pathology. Fatigue, which is closely linked to immune dysregulation, has long been recognized as both a symptom and a determinant of recovery in infectious diseases. It is therefore hypothesized that individuals with lower immune fitness and higher fatigue levels prior to infection may be more vulnerable to persistent post-viral sequelae. Against this background, the present study investigated whether self-reported immune fitness, fatigue, mood, and quality of life prior to SARS-CoV-2 infection predict PASC fatigue severity.

2. Materials and Methods

This retrospective cross-sectional study comprised a retrospective online survey among Dutch adults with self-reported PASC. Participants were recruited via the website

of the Dutch Lung Foundation (Longfonds) and Long COVID Facebook groups. The study was conducted between 16 December 2021 and 10 March 2022. Ethics approval for the study was obtained from the Institutional Review Board of OLVG hospital (Study number: 21.036; approval date: 27 October 2021), and all participants provided electronic informed consent. Individuals were eligible to participate if they were ≥18 years old and self-reported PASC symptoms persist for at least three months after SARS-CoV-2 infection. The survey was conducted in Dutch language. There were no exclusion criteria.

The survey assessed immune fitness, fatigue, and mood for two predefined windows: the three months prior to SARS-CoV-2 infection ("pre-infection") and the month prior to survey completion ("during PASC"). Immune fitness was measured with a single-item immune fitness rating from 0 ("very poor") to 10 ("excellent") [20]. To aid understanding of the construct of immune fitness, a definition was provided along with the survey question ("Immune fitness is the capacity of the body to respond to negative health challenges such as infection or fever, by activating an appropriate immune response, which is essential to maintain healthy, prevent or resolve disease, and improve quality of life"). Fatigue was measured with the Fatigue Severity Scale (FSS; 9 items scored 1–7; higher scores indicate greater fatigue) [23] and a single-item fatigue scale, ranging from 0 (absent) to 10 (extreme) [24]. Mood was assessed using single-item scales ranging from 0 (absent) to 10 (extreme) including stress, anxiety, depression, hostility, loneliness, and happiness, on scales [24]. Finally, quality of life was assessed with a single-item scale ranging from 0 (very poor) to 10 (excellent) [25].

Data were collected electronically via the SurveyMonkey platform. Statistical analyses were conducted in IBM SPSS Statistics, version 30.0 (IBM Corp., Armonk, NY, USA). Mean and standard deviation (SD) were computed for each variable. Data distributions were examined by visual inspection (histograms and Q–Q plots) and the Kolmogorov–Smirnov test. Given the observed non-normality of most variables, nonparametric methods were used to analyze the data. Assessments of the two time periods were compared with the Related-Samples Wilcoxon Signed-Ranks Test. Differences for immune fitness, fatigue and quality of life were considered statistically significant if $p < 0.05$. Differences for mood items were considered statistically significant if $p < 0.0083$, after applying a Bonferroni's correction for multiple comparisons. Spearman's correlations were computed between pre-infection assessments and the corresponding PASC outcomes (two-tailed). Correlations were computed between pre-infection and PASC assessments for all self-reported measures. Statistical significance was set at $p < 0.05$, except for mood items where a Bonferroni-corrected threshold of $p < 0.0083$ was applied. Finally, stepwise regression analysis was used as an exploratory method to identify potential predictors of PASC fatigue, given the absence of strong a priori hypotheses. The analyses investigated to what extent demographics (age and sex), and self-reported immune fitness, fatigue, mood, and quality of life prior to SARS-CoV-2 infection are predictors of PASC fatigue severity, assessed with either the FSS or the single-item fatigue scale.

3. Results

The survey was completed by 299 participants with self-reported PASC. The majority of the participants were female (90%), with a mean (SD) age of 44.1 (11.2) years. Mean (SD) scores of immune fitness, fatigue, mood and quality of life prior to SARS-CoV-2 infection and during PASC are summarized in Table 1. Compared to before the SARS-CoV-2 infection, during PASC immune fitness, mood and quality of life were significantly poorer, whereas fatigue levels were significantly increased during PASC (all $p < 0.001$). Mood assessments prior to SARS-CoV-2 infection and during PASC, except happiness, correlated significantly with each other (all $p < 0.001$). The correlation

between the two assessments of immune fitness was low, but also statistically significant. However, no significant correlations were found for quality of life and the assessments of fatigue with either the FSS or the single-item scale.

Table 1. Immune fitness, fatigue, and mood prior to SARS-CoV-2 infection and during PASC.

	Prior to SARS-CoV-2 Infection		During PASC		Comparison	Correlation	
Measure	**Mean (SD)**	**Median (IQR)**	**Mean (SD)**	**Median (IQR)**	***p*-Value**	**r**	***p*-Value**
Immune fitness	7.7 (1.5)	8 (2)	4.1 (1.9)	5 (3)	<0.001 *	0.141	0.021 *
FSS fatigue	23.1 (10.0)	20 (14)	54.9 (7.0)	55 (8.5)	<0.001 *	−0.095	0.132
Fatigue (single item)	3.5 (2.0)	3 (3)	8.3 (1.7)	8 (3)	<0.001 *	−0.071	0.252
Anxiety	1.5 (2.2)	0 (2)	3.9 (3.0)	3 (5)	<0.001 *	0.400	<0.001 *
Depression	1.0 (1.8)	0 (2)	3.1 (2.7)	2 (5)	<0.001 *	0.478	<0.001 *
Stress	3.7 (2.5)	3 (4)	5.6 (2.7)	6 (5)	<0.001 *	0.270	<0.001 *
Hostility	0.8 (1.7)	0 (1)	2.1 (2.6)	1 (3)	<0.001 *	0.433	<0.001 *
Loneliness	1.1 (2.0)	0 (1)	3.6 (2.9)	3 (5)	<0.001 *	0.387	<0.001 *
Happiness	7.5 (1.6)	8 (1)	4.8 (1.9)	5 (3)	<0.001 *	0.007	0.263
Quality of life	8.1 (1.2)	8 (1)	4.5 (2.1)	4 (3)	<0.001 *	0.028	0.643

Mean and standard deviation (SD) are shown. Significant differences and Spearman's correlations ($p < 0.05$ for immune fitness and fatigue, and $p < 0.0012$ for mood) between the assessments prior to SARS-CoV-2 infection and during PASC are indicated by *. Abbreviations: FSS = Fatigue Severity Scale, IQR = interquartile range, SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2, SD = standard deviation, PASC = post-acute sequelae of SARS-CoV-2 infection.

All self-reported domains changed significantly during PASC (see Table 1), with lower immune fitness, mood, and quality of life, and higher fatigue levels (all $p < 0.001$). Despite these marked shifts, moderate positive correlations were observed between pre-infection and PASC scores for most mood variables and immune fitness, suggesting that individuals who reported higher stress, anxiety, or depression before infection tended to report relatively higher levels during PASC as well. In contrast, correlations for fatigue, happiness, and quality of life were nonsignificant, indicating that these domains were profoundly affected by PASC irrespective of their pre-infection baseline. As expected, PASC fatigue severity scores obtained from the FSS and the single-item fatigue scale correlated positively ($r = 0.43$, $p < 0.001$), confirming that both instruments assess overlapping aspects of fatigue intensity.

However, both assessments of PASC fatigue did not correlate significantly with the prior SARS-CoV-2 assessments of immune fitness, fatigue, mood, and quality of life. This suggests that immune fitness, fatigue, mood, and quality of life prior to SARS-CoV-2 infection are poor predictors of PASC fatigue severity. To confirm these findings, subsequent regression analyses were conducted to evaluate to what extent demographics (age and sex), immune fitness, fatigue, mood, and quality of life assessed prior to SARS-CoV-2 infection could predict PASC fatigue severity. Two analyses were conducted, one for PASC fatigue assessed with the FFS, and another analysis for the single-item PASC fatigue assessment. Both analyses did not yield a model that significantly predicted PASC fatigue severity. In other words, the assessed demographics, immune fitness, mood, fatigue, and quality of life prior to SARS-CoV-2 infections are no significant predictors of PASC fatigue severity.

4. Discussion

In contrast to previous findings showing that immune fitness prior to SARS-CoV-2 infection was the best predictor of the number and severity of experienced symptoms

during COVID-19 [22], the current analyses revealed that immune fitness prior to SARS-CoV-2 infection does not predict PASC fatigue severity. In addition, mood, fatigue and quality of life prior to SARS-CoV-2 infection did not predict PASC fatigue severity. Mood assessments (except happiness) and the immune fitness ratings prior to SARS-CoV-2 infection were positively correlated with the same assessment during PASC, suggesting that pre-existing mood states may be exaggerated during PASC. However, this was not the case for quality of life, happiness, and the assessments of fatigue. The regression analyses confirmed that self-assessments of immune fitness, fatigue, mood and quality of life for the period prior to SARS-CoV-2 infection have no relevant prognostic value for the course of PASC fatigue.

In line with the current findings, previous research also showed that pre-existing self-reports and standard inflammatory biomarkers are poor predictors of long-term outcomes. Freidin et al. [26] reported that pre-pandemic IL-6 levels did not identify individuals at risk of PASC-related fatigue. Townsend et al. [13] and Charoenporn et al. [14] found CRP and IL-6 concentrations assessed after SARS-CoV-2 infection were not associated with PASC fatigue severity.

By contrast, demographic and clinical characteristics, including female sex, elevated BMI, and comorbidities, together with pre-infection factors such as psychological distress and poor sleep quality, have more consistently been associated with an increased risk of developing PASC [5,8–10]. However, in the current regression analysis, these factors did not contribute to a significant model predicting PASC fatigue. The absence of predictive power may be explained by underlying pathophysiological processes that arise during or after acute infection, such as immune dysregulation, viral persistence, microvascular dysfunction, and autonomic or mitochondrial disturbances [18,19]. Retrospective self-reports are unlikely to capture these processes and may also be affected by recall bias. Moreover, the heterogeneity of PASC, encompassing diverse symptom phenotypes, complicates prediction when outcomes are aggregated.

The strengths of this study include a relatively large sample size, use of validated scales to assess the constructs under evaluation [20,23–25], and clearly defined assessment windows. Limitations include the retrospective and self-reported nature of the study, the predominantly female sample (90%), absence of biomarker data, and lack of adjustment for confounders such as underlying diseases, possible treatments for COVID-19 or PASC, vaccination status, viral variant, duration between COVID-19 and PASC, and COVID-19 and PASC duration. Furthermore, although the majority of participants had COVID-19 confirmed by PCR-test (91.7%), the presence of PASC was self-diagnosed. This may have resulted in misclassification. Second, recruitment was done through the Longfunds website and Facebook groups for Long COVID. The nature of this convenience sample may limit generalizability. Finally, this study limited the analyses to find predictors of PASC fatigue, while PASC is also characterized by other symptoms that were not evaluated in the current study. Future studies should employ prospective longitudinal designs, integrate biological, psychosocial, and lifestyle factors to improve prediction of PASC fatigue and other relevant PASC outcomes.

In summary, self-reported immune fitness, fatigue, and mood prior to infection do not meaningfully predict PASC fatigue severity. This observation underlines the need for further research into the possible predictors of PASC fatigue severity and other PASC symptoms as well as the development of multidimensional risk models that combine clinical, biological, and lifestyle determinants to achieve better prognostic accuracy and to guide personalized treatment of PASC.

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Data Availability Statement: The data are available from the corresponding author upon reasonable request.

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Abbreviations

The following abbreviations are used in this manuscript:

BMI	body mass index
COVID-19	Coronavirus disease 2019
FSS	Fatigue Severity Scale
IQR	Interquartile range
PASC	post-acute sequelae of SARS-CoV-2 infection
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SD	Standard deviation
WHO	World Health Organization

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