Psychological General Well-being, Cognitive Failure, and Inflammation Biomarkers Among Workers 4 Months After a Mild/Asymptomatic SARS-CoV-2 Infection

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Objective: To investigate the relationship between cognitive complaints, systemic inflammatory biomarkers, and psychological general well-being (PGWB) after mild/asymptomatic SARS-CoV-2 infection, according to the presence of long COVID and work tasks. **Methods:** University employees and metal workers were recruited in a cross-sectional study 4 months after SARS-CoV-2 infection to assess cognitive impairment, individual PGWB index, inflammatory biomarkers, namely platelet-lymphocyte, neutrophil-lymphocyte, and lymphocyte-monocyte ratios, and the presence of long COVID symptoms. **Results:** A significant increase in the levels of inflammatory biomarkers was observed in subjects with long COVID. Furthermore, the PGWB index was influenced by long COVID symptoms and subjective cognitive and depressive symptoms, but not by work activity. **Conclusions:** In occupational settings, it is crucial to detect the presence of long COVID symptoms and systemic inflammation early, as they may be associated with lower PGWB.

Keywords: long COVID, well-being, cognitive failures, inflammatory index, workers

CME Learning Objectives

After completing this enduring educational activity, the learner will be better able to:

- Discuss the impact of Long Covid on general psychological well-being (PGWB) four months after mild infection.
- Outline its potential to alter individuals' overall quality of life.
- Discuss the interplay between the somatic-inflammatory component of Long COVID and psychological disorders.

The Ottawa Charter defined health as a state of holistic well-being, encompassing physical, mental, and social dimensions, that requires the ability of an individual or a community to recognize and achieve aspirations, fulfill needs, and adapt to or navigate their surroundings.[1] Health status, therefore, can be influenced by a complex interplay of social, economic, and environmental factors and is deeply connected to the health of ecosystems, according to a One Health approach.[2] In turn, well-being was defined in the Geneva Charter as a favorable state of individuals or communities that serves as a valuable asset in daily life, which can be regarded as a crucial dimension of quality of life.[3]

Psychological general well-being (PGWB), specifically, is a complex construct that encompasses optimal psychological functioning and experience, including hedonic (enjoyment, pleasure) and eudaimonic (meaning, fulfillment) happiness as well as resilience (coping, emotion regulation, health problem solving).[4] The importance of PGWB as part of the mental health status has been increasingly emphasized in recent decades, also for the evidence that it is an independent predictor of mortality and morbidity, both in patients and healthy populations. Accumulating scientific literature has supported a causal relationship between PGWB and disease-specific outcomes, resulting in salutary physiological/biological changes.[5]

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Data availability: The datasets generated and analyzed during the current study are available upon reasonable request. Interested parties may contact the corresponding author to obtain access to the data, subject to ethical and legal considerations. The data will be shared in compliance with relevant privacy and confidentiality regulations.
EQUATER Network Reporting Guidelines: The manuscript adhered to the STROBE guidelines for cross-sectional studies.
Ethical considerations and disclosures: This study was conducted in accordance with ethical guidelines and principles. The research protocol, including study design, participant consent, and data handling procedures, was reviewed and approved by the Independent Ethical Committee Policlinico di Bari Hospital (Protocol N. 6663, 2021). Informed consent was obtained from all participants before their involvement in the study. The study adheres to the ethical standards outlined in the Declaration of Helsinki and relevant local regulations.
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PGWB, moreover, has also been linked to greater productivity in the workplace, mediated probably by more effective learning, increased creativity, and positive relationships.[6]

A decrease in well-being and quality of life has been observed during the COVID-19 pandemic due to the tremendous impact on ordinary societal functioning at many levels.[7] However, the highest impact of COVID-19 on well-being seems to be linked to the postacute effects of the disease, defined as long COVID, that may contribute to reducing specifically the PGWB. Indeed, psychological and neuropsychiatric disorders, including fatigue and cognitive dysfunctions such as brain fog, memory problems, attention and sleep disorders, are among the most common features of long COVID.[8] The persistence of these psychological symptoms after acute COVID-19 has caused a new large cohort of chronically ill employees impacting the overall quality of working life.[9,10]

SARS-CoV-2 infection can provoke an uncontrolled massive inflammatory response in the course of the disease, leading to local and systemic tissue damage.[11] As blood cells, such as neutrophils, lymphocytes, monocytes, and platelets, play an important role in the systemic immune and inflammation response, biomarkers calculated from the blood count, including neutrophil-to-lymphocyte ratio (NLR), lymphocyte-to-monocyte ratio (LMR), and platelet-to-lymphocyte ratio (PLR), could be used as critically important indicators in routine diagnostics of inflammatory diseases, including COVID-19.[12] Moreover, these indicators have recently be also considered in providing prognostic predictive biomarkers in many diseases characterized by systemic inflammation, including in the course of COVID-19[13] Unlike other traditional inflammation factors, these indexes have the advantages of high efficiency, low price, and simplicity in clinical practice and show a better predictive ability, with their levels correlating with a severe disease course, a less favorable prognosis, and shorter overall survival.[14,15] Furthermore, alterations in these indicators have recently been associated with a significant reduction in quality of life, and with symptoms such as chronic fatigue and anxiety as clinical manifestations of different inflammatory diseases.[16] However, to date, these indicators have not been quantified in patients with long COVID syndrome.

Therefore, a multidisciplinary approach to long COVID syndrome appears necessary, also following recent evidence suggesting that a biopsychosocial model should underpin the understanding of long COVID by evaluating the possibility of a relationship between the somatic-inflammatory component, typical of this syndrome, and psychological disorders.[17]

This study, therefore, aimed to investigate individual PGWB, cognitive failure, and specific inflammatory indicators 4 months after a mild COVID-19 or asymptomatic SARS-CoV-2 infection, focusing on the relationship with working activity and the presence of the long COVID syndrome.

MATERIALS AND METHODS

Study Population

This cross-sectional study was conducted between January and June 2022, among 2 different working populations, both located in the same geographical area (Bari, Apulia, Italy), namely the University employees and the frontline workers of an engineering industry. During the study period, the Omicron variant was prevalent in the area.[18] The 2 cohorts of workers were recruited to participate in the study during the occupational health surveillance performed according to the internal procedures for SARS-CoV-2–positive employees. In particular, all subjects diagnosed with SARS-CoV-2 infection, after having notified their company of their positivity, were invited for a medical examination to assess their fitness for returning to work. During this visit, the workers were informed on the aims and procedures of the study, signed the informed consent form, and were asked to return for a subsequent assessment after 4 months. All workers enrolled at the first visit returned for the second visit.

The University cohort included 2 different subgroups, ie, a subgroup of professors and researchers (Academics) and a subgroup of technical and administrative employees (Clerks). Academics were primarily engaged in teaching and scientific research carried out with flexible work schedules, adhering to a maximum of 8 hours per day and 143 hours per month. Technical clerks provided support for research activities, such as laboratory and informatics tasks, whereas administrative employees handled front and back-office responsibilities as supporting the teaching activities and managing documentation and records related to the professors and students. Technical and administrative clerks carried out their activities in fixed 8-hour shifts from 8 AM to 4 PM. During the COVID-19 restriction period in Italy (March 9 to June 14, 2020, and October 8 to April 25, 2021), all the University employees performed their duties in teleworking mode, whereas during the study period, all of them performed their work on site.

The recruited frontline employees (metalworkers) were engaged in the automated assembly or fitting of automotive components, carried out in 3 rotating different shifts with start and end times at 6 AM, 2 PM, 10 PM They were exposed to a controlled chemical risk from cooling liquids and a risk from manually handling loads. Even during the COVID-19 pandemic, metalworkers performed their activities always on site.

Inclusion criteria comprised a SARS-CoV-2 infection diagnosed by nasopharyngeal swab with antigenic and/orRT-PCR analysis, followed by a nasopharyngeal swab with negative antigenic and/orRT-PCR analysis 4 months earlier.

Exclusion criteria comprised having been hospitalized with moderate infection, defined as subjects with clinical signs of pneumonia (fever, cough, dyspnea, and fast breathing) or having been affected by severe pneumonia during the COVID-19 such as $SpO_2 \leq 90\%$ on room air, the lack of full vaccination against COVID-19 at the time of recruitment, a previous diagnosis of other chronic viral infections such as HIV, HCV, and HBV, a solid organ or hematological transplantation in the past 5 years, and psychiatric or neurologic comorbidity at the recruitment.

Participation was voluntary and participants could withdraw from the study at any time. The principles of ICH Good Clinical Practice, the "Declaration of Helsinki," and national and international ethical guidelines were strictly followed during this study. The research was approved by the Independent Ethical Committee Policlinico di Bari Hospital (Protocol N. 6663, 2021).

The present study applied the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement to observational studies (Supplemental Digital Content, http://links.lww.com/JOM/B647).[19]

Demographics, Clinical Features, and Questionnaires

All participants were interviewed face to face by trained physicians to answer a questionnaire on demographic characteristics, smoking and alcohol habits, regular medication use, symptoms at COVID-19 diagnosis and COVID-19 treatment (corticosteroids, intravenous immunoglobulin, antibiotics, and antivirals), and type and number of comorbidities, investigated as described in Stufano et al. (2022).[20] Alcohol units per week were defined using the Center for Disease Control alcohol calculator (www.cdc.gov/alcohol/checkyourdrinking/index). Participants, moreover, were asked to report newly occurring and persistent symptoms, or any symptoms worse than before COVID-19 development, referring to the list of symptoms reported in Subramanian et al (2022).[21] Long COVID patients were defined as those reporting the continuation or development of at least 1 sequelae symptom, confirmed intermittently or continuously, based on the WHO definition.[22]

All the workers were asked to complete 4 further questionnaires, all validated for the Italian population:

1. Cognitive Failure Questionnaire (CFQ)[23,24]: 25-item self-reported assessment of failures in perception, memory, and motor function, including forgetfulness, distractibility, and false triggering subscales; 100, as the maximum total score, indicates the highest self-perceived cognitive impairment in daily life, and 43, as cutoff score, is indicative of significant cognitive complaints.[25]
2. Post–COVID-19 Functional Status (PCFS) Scale[26]: addressing limitations in usual tasks and activities at home and at work as well as lifestyle changes due to post–COVID-19 outcomes; results are reported as an ordinal scale of increasing severity from grade 0 to 4.
3. Patient Health Questionnaire-9 (PHQ-9)[27]: 9-item self-report scale assessing how often symptoms of depression have bothered the respondent over the past 2 weeks; item score ranges from "not at all" (score 0) to "nearly every day" (score 3) and total score from 5–9 (mild), 10–14 (moderate), 15–19 (moderately severe) to ≥20 (severe depressive symptoms).[28]
4. Psychological General Well-Being Index (PGWBI)[29,30]: 22-item self-reported questionnaire measuring the subjective well-being or discomfort referred to the last 4 weeks; it includes anxiety, depression, positive well-being, self-control, general health, and vitality subscales; item score ranges from 0 to 5 (6-point Likert scale), with 110 as maximum total score; scores ≤54 points reflect severe distress, between 55 and 65 moderate distress, and between 66 and 110, a positive psychological well-being or "no distress".[31]

Biochemical Assays

On the day of the questionnaire administration, venous blood samples (10 mL) were collected using 2 distinct vacutainer tubes with EDTA and a separating gel, respectively. The blood samples in the tubes with separating gel were allowed to coagulate at room temperature for 30 minutes and then were centrifuged at 1600 rpm for 10 minutes at 4°C. The separated sera were then aliquoted and stored at −70°C until the analysis were conducted.

Blood EDTA samples underwent blood cell counts with leukocyte subpopulation and platelet count for the calculation of inflammation indices PLR, NLR, and LMR, using an automated hematology analyzer (Sysmex XE-2100; Sysmex Corporation, Kobe, Japan). Serum samples were subjected to a chemiluminescent immunoassay to detect IgG against the SARS-CoV-2 nucleocapsid protein (Abbott SARS-CoV-2 IgG assay on the Abbott Architect i4000SR; Abbott Diagnostics, Chicago, IL). A signal/cut-off (S/CO) ratio ≥1.4 was considered reactive, while a ratio <1.4 was deemed nonreactive, following the manufacturer's instructions.

Statistical Analysis

Shapiro-Wilk test and graphical evaluations of each variable were performed to demonstrate correspondence with normal distribution. Student *t* test or Mann-Whitney *U* test were performed to assess comparisons among 2 groups in terms of continuous variables, while differences between more than 2 groups were studied through 2-way analysis of variance (ANOVA), followed by Tukey post hoc test, where necessary. Pearson χ^2 test was used for comparisons of categorical variables.

To examine how demographic data, occupational status, comorbidities, questionnaire results, and long COVID variables were associated with the outcomes of the PGWBI, dimensionality reduction techniques and linear regression were utilized. Specifically, categorical principal component analysis (CATPCA) was employed to reduce the dimensionality of the 88 variables investigated and to eliminate any redundancy, reducing multicollinearity.[32,33] To assess the significance of the loadings on the components, a nonparametric bootstrap was used to compute solutions for a range of dimensions between 4 and 8. Based on the results, the 6-dimension solution was selected for further analysis as all confidence intervals of the loadings on the seventh component included the value 0.[32] Linear regression was conducted using each of the 6 series of CATPCA scores, 1 for each component, as predictors for each of the 6 dimensions of the PGWBI and its total score.[34] In total, 7 regression tests were performed, and Bonferroni correction was applied to account for multiple comparisons.

A value of $P < 0.05$ was considered significant. All analyses were conducted using SPSS 28 (IBM Corp, Armonk, NY).

RESULTS

General characteristics and comorbidities, inflammation biomarkers and long COVID prevalence in the investigated workers subdivided according to working activity are summarized in Table 1. A significant difference among the 3 subgroups has been observed for mean age, smoking and alcohol habits, and cardiovascular disease prevalence; all resulted lower in Academics ($P < 0.05$ or $P < 0.01$), whereas female sex, respiratory diseases, and long COVID prevalence were lower in metalworkers ($P < 0.05$).

Table 2 shows general characteristics and comorbidities, duration and number of acute COVID-19 symptoms, IgG SARS-CoV-2 titer, and inflammation biomarkers, according to the occurrence of long COVID in the recruited employees. Compared to asymptomatic post-COVID workers, the long COVID group was significantly more female ($P < 0.001$), had a more frequent history of respiratory and autoimmune diseases ($P < 0.05$), and had a significantly higher percentage of workers referring more than 4 acute COVID-19 symptoms (both 4–6 and more than 6 symptoms, $P < 0.05$). Long COVID patients, moreover, exhibited mean IgG SARS-CoV-2 level and systemic inflammation biomarkers significantly higher than asymptomatic post-COVID workers ($P < 0.001$ and $P < 0.05$, respectively). The prevalence of the different referred long COVID symptoms is reported in Figure S1 (Supplementary Material, http://links.lww.com/JOM/B648), showing insomnia (17.3%), asthenia (16.0%), and difficulty concentrating (15.3%) as the most prevalent.

Table 3a, 3b shows the questionnaire scores in the 3 worker groups according to the long COVID condition. The 2-way analysis of variance showed that the CFQ and the PHQ-9 scores were significantly associated with the occurrence of long COVID, while no effect of the working activity was detected (model $P < 0.001$; long COVID $P < 0.001$), whereas, in all the 3 workers' groups, long COVID patients had a significantly higher percentage of grade 1 and 2 PCFS than asymptomatic post-COVID workers.

The mean total score of PGWBI in the whole recruited population (69.5 ± 26.2) was in the area of "moderate distress" (Supplementary Table 1, http://links.lww.com/JOM/B648), whereas the median scores in the 3 recruited workers' groups are reported in Table 3a, 3b. The 2-way analysis of variance showed a significant influence of the long COVID condition, but not of the working activity on the PGWBI total score and on the subscale scores of anxiety, self-control, general health and vitality scales (model $P < 0.001$ for all; long COVID $P < 0.001$ for all).

According to CATPCA, a cluster of variables related to long COVID symptoms, with the addition of sex, working activity, and respiratory symptoms during acute COVID-19, contributed the most to the first component, the one explaining the largest amount of the data variance (11.3%). The original variables loading on the first component with a coefficient higher than 0.4 are listed in Table 4. The second component accounted for 5.0% of the total variance and resulted to be

TABLE 1. General Characteristics, Systemic Inflammation Indices, and Long COVID Prevalence in the Recruited Workers Subdivided According to the Working Activity

	Academics (N = 50)			Administrative/ Technical Clerks (N = 56)			Metalworkers (N = 44)			
Variables	**N (%)**	**Mean ± SD**	**Range**	**N (%)**	**Mean ± SD**	**Range**	**N (%)**	**Mean ± SD**	**Range**	***P***
Age, y		42.9 ± 6.9	24.0–66.0		54.9 ± 4.9	33.0–68.0		48.9 ± 0.4	23.0–66.0	*P* = 0.002
Body mass index, kg/m^2		24.6 ± 0.8	18.0–34.0		26.1 ± 0.2	17.6–35.4		26.9 ± 1.4	18.9–36.6	NS
Female sex	28 (56.0)			27 (48.2)			2 (4.4)			*P* = 0.001
Smokers + ex-smokers	2 + 7 (18.0)			9 + 15 (42.9)			9 + 10 (43.2)			*P* = 0.03
Alcohol consumption, U/wk		1.3 ± 4.9	0–7.0		2.4 ± 3.1	0–9		2.2 ± 2.8	0–12	*P* = 0.01
Comorbidities										
Cardiovascular diseases	5 (10.0)			12 (21.4)			13 (29.5)			*P* = 0.02
Respiratory diseases	4 (8.0)			7 (12.5)			2 (4.5)			*P* = 0.03
Autoimmune diseases	2 (4.0)			4 (7.1)			2 (4.5)			NS
Platelet-to-lymphocyte ratio		7.4 ± 2.1	2.8–14.0		8.7 ± 4.2	4.4–14.5		7.1 ± 1.8	2.0–16.5	NS
Neutrophil-to-lymphocyte ratio		1.6 ± 0.3	0.7–3.0		2.1 ± 3.1	0.9–11.9		1.6 ± 0.9	0.2–3.6	NS
Lymphocyte to-monocyte ratio		4.5 ± 3.2	2.7–6.6		4.3 ± 1.5	1.4–7.2		4.4 ± 2.3	2.2–12.6	NS
Long COVID patients	22 (44.0)			33 (57.9)			5 (11.4)			*P* = 0.03
Female/male*	15/7 (51.7/33.3)			19/14 (70.4/48.3)			1/4 (50.0/9.5)			*P* = 0.02

*Percentages referred to the total female or male employees.

the combination of mainly biochemical parameters as well as sex, body mass index, as baseline variables and antibiotics and cortisone therapy during acute COVID-19. The third, fourth, fifth, and sixth components were the combination of the remaining original variable and explained the 4.7%, 4.2%, 3.8%, and 3.5% of the data variance, respectively.

Multiple linear regression conducted to determine the association of the 6 components with the normalized values of the total score and each of the 6 PGWBI subscores showed a significant regression between the first principal components and the total score ($F[6,143] = 7.4$, $P < 0.001$, $R^2 = 0.24$), with the first component that negatively predicted the total well-being score (beta = −8.4, $P < 0.001$) (Fig. 1). Similarly, significant regression equations were also found between the first principal components and the anxiety ($F[6,143] = 3.5$, $R^2 = 0.13$), positive well-being ($F[6,143] = 6.5$, $R^2 = 0.21$), self-control ($F[6,143] = 3.9$, $R^2 = 0.14$), general health ($F[6,143] = 12.3$, $R^2 = 0.34$), and vitality ($F[6,143] = 10.0$, $R^2 = 0.29$) subscores ($P < 0.001$ for all). The first component negatively predicted anxiety (beta = −1.6), positive well-being (beta = −1.8), self-control (beta = −1.0), general health (beta = −1.5), and vitality (beta = −2.1) ($P < 0.001$ for all). General health was additionally negatively predicted by the second component (beta = −0.6, $P < 0.001$). No significant regression was found for the depressed mood subscore.

Among the variables mainly contributing to the first component, the number of long COVID symptoms, PHQ-9 and CFQ total scores showed a direct positive association with the first component (Fig. 2), thus suggesting that total PGWBI score and the subscores anxiety, positive well-being, self-control, general health, and vitality decrease with a higher number of symptoms and with higher scores of the 2 questionnaires. Similarly, higher scores on the PCFS were associated with higher scores on the first principal component, which in turn was a significant predictor of lower PGWBI total and subscale

TABLE 2. General Characteristics and Comorbidities, Duration and Number of Acute COVID-19 Symptoms, IgG SARS-CoV-2 Antibody Titer, and Systemic Inflammation Indicators in Long COVID Patients and Asymptomatic Post-COVID Workers

	Long COVID Patients (N = 60)			Asymptomatic Post-COVID Workers (N = 90)			
Variables	**N (%)**	**Mean ± SD**	**Range**	**N (%)**	**Mean ± SD**	**Range**	***P***
Age, y		49.8 ± 8.6	26–66		48.8 ± 0.4	23–68	NS
Body mass index, kg/m^2		24.7 ± 0.9	17.5–24.6		26.5 ± 1.4	18.0–36.6	NS
Female sex	35 (58.4)			23 (25.6)			*P* = 0.001
Smokers + ex-smokers	6 + 15 (35.0)			14 + 18 (36.7)			NS
Alcohol consumption, U/wk		1.8 ± 3.6	0–7		2.1 ± 2.8	0–10	NS
Comorbidities							
Cardiovascular diseases	12 (20.0)			19 (21.1)			NS
Respiratory diseases	10 (16.6)			5 (5.6)			*P* = 0.01
Autoimmune diseases	7 (11.6)			2 (2.2)			*P* = 0.02
Duration of COVID-19 acute infection (*d*)		23.5 ± 1.7	8–64		20.4 ± 15.5	2–62	NS
No. acute COVID-19 symptoms							
0–3	21 (35.0)			50 (55.6)			NS
4–6[a]	31 (51.6)			35 (38.9)			*P* = 0.01
>6[a]	8 (13.4)			5 (5.5)			*P* = 0.03
IgG anti-SARS-CoV-2, UR/mL		583.6 ± 88.7	13.6–2864.4		240.7 ± 17.5	12.9–3148.9	*P* = 0.002
Platelet-to-lymphocyte ratio		12.6 ± 4.3	4.9–40.0		10.6 ± 5.3	2.2–20.9	*P* = 0.01
Neutrophil-to-lymphocyte ratio		2.8 ± 0.1	0.7–4.1		1.7 ± 0.9	0.8–4.5	*P* = 0.03
Lymphocyte to-monocyte ratio		35.5 ± 0.3	7.4–49.1		33.6 ± 10.5	10.5–47.9	*P* = 0.02

TABLE 3A. CFQ, PCFS, and PHQ-9 Questionnaire Scores in the Recruited Employees Subdivided According to the Working Activity and to the Presence of Long COVID

	Academics (N = 50)						Administrative/Technical Clerks (N = 56)						Metalworkers (N = 44)						
	Long COVID Patients (N = 22)			Asymptomatic Post-COVID Workers (N = 28)			Long COVID Patients (N = 33)			Asymptomatic Post-COVID Workers (N = 23)			Long COVID Patients (N = 5)			Asymptomatic Post-COVID Workers (N = 39)			
Questionnaire Scores	N (%)	Median	Range	N (%)	Median	Range	N (%)	Median	Range	N (%)	Median	Range	N (%)	Median	Range	N (%)	Median	Range	*P*
CFQ total score		27	1–54		10	0–36		27	3–64		13	6–50		21	3–24		15	0–40	*P* = 0.0001
Score >43	2 (9.1)			0 (0.0)			6 (18.2)			1 (4.3)			0 (0.0)			0 (0.0)			*P* = 0.002
PCFS scale																			
Grade 0[a]	5 (22.7)			16 (57.1)			11 (33.3)			14 (60.9)			3 (60.0)			27 (69.2)			*P* = 0.02
Grade 1[b]	11 (50.0)*			12 (42.9)			13 (39.4)			9 (39.1)			2 (40.0)			9 (23.1)			*P* = 0.002
Grade 2[b]	5 (22.7)			0 (0.0)			9 (27.3)			0 (0.0)			0 (0.0)			3 (7.7)			*P* = 0.001
Grade 3[b]	1 (4.6)			0 (0.0)			0 (0.0)			0 (0.0)			0 (0.0)			0 (0.0)			*P* = 0.003
PHQ-9 score[a]		5	0–15		2	0–7		5	0–16		1	0–7		5	0–5		2	0–7	*P* = 0.04
No symptoms[c]	13 (59.1)			26 (92.9)			23 (69.7)			13 (56.5)			2 (40.0)			29 (74.4)			*P* = 0.0001
Mild[b]	7 (31.8)			2 (7.1)			6 (18.2)			10 (43.5)			3 (60.0)			10 (25.6)			*P* = 0.003
Moderate	2 (9.1)			0 (0.0)			4 (12.1)			0 (0.0)			0 (0.0)			0 (0.0)			NS

scores. The remaining variables listed in Table 4 were quantified as binary in the CATPCA, and therefore, their relationship with the first component cannot be assumed to be linear.[31,32] These variables were associated with higher scores on the first component and accordingly with lower PGWBI scores (data not shown).

DISCUSSION

The results of our study highlighted that PGWBI investigated 4 months after a mild COVID-19 or asymptomatic SARS-CoV-2 infection was primarily associated with the presence of neuropsychological and other symptoms suggestive of long COVID. Furthermore, our results showed, for the first time, higher levels of hematological biomarkers of systemic inflammation in long COVID patients.

Among our entire population, a prevalence of nearly 40% long COVID patients was observed, higher than the 15% prevalence of postacute COVID-19 condition 3 months after the infection, recently reported by the Global Burden of Disease (GBD) on over 1 million SARS-CoV-2–infected subjects.[35] This difference in prevalence may be due to high numbers of unreported in conjunction with the nonspecific and nonquantifiable nature of mild long COVID cases.[36] In this sense, occupational health surveillance reported in our study may represent a useful tool for the early detection of all long COVID patients, also because many symptoms may only become evident upon return to the workplace.[37]

Our findings indicate that long COVID patients exhibited elevation in platelet-to-lymphocyte ratio (PLR), neutrophil-to-lymphocyte ratio (NLR), and lymphocyte-to-monocyte ratio (LMR) 4 months postinfection, signaling a sustained systemic inflammatory state. These proposed cost-effective indicators are widely available and easily measurable, therefore showing promise as diagnostic and prognostic biomarkers linked to the severity of tissue damage triggering systemic inflammatory responses, characteristic of various conditions, including infections, trauma, and cancer. Notably, NLR already emerged as a robust biomarker for assessing systemic inflammation intensity in acute COVID-19 patients, with elevated values associated with the presence of chronic comorbidities like hypertension and diabetes and indicating a more severe course of COVID-19.[38] Nevertheless, to our knowledge, our study is the first to confirm the increase of PLR, LMR, and NLR in long COVID patients after a prior paucisymptomatic or asymptomatic SARS-CoV-2 infection, distinguishing it from 2 earlier studies that reported similar findings but focused on patients with severe or moderate COVID-19 necessitating antiviral treatment.[39,40] Additionally, our results seem to align to the recent evidence that associated high PLR, LMR, and NLR values with severe fatigue, one of the most reported long COVID symptoms in our study population.[17] Our results, therefore, propose the potential utility of PLR, LMR, and NLR as effective biomarkers in occupational health surveillance, serving to monitor long COVID syndrome and assess the severity of systemic inflammation. These indicators may offer a practical alternative to other more expensive inflammation biomarkers due to their rapid and affordable obtainability and should be further investigated for the monitoring of inflammatory effect induced by other occupational factors.

The study population's PGWBI mean total score (69.5 ± 26.2) indicates "moderate distress," falling below the mean scores observed during the pandemic among Italian firefighters (94.3 ± 10.3), healthy Italian university workers without a previous SARS-CoV-2 infection (71.3 ± 19.9), and those susceptible due to a higher risk of severe COVID-19 (77.8 ± 17.4). Moreover, the study population's score is also lower than the normative prepandemic mean total score for the general Italian population (78.0 ± 17.8).[20,28,41]

Previous studies have reported lower quality of life in long COVID patients, but none of them focused on PGWBI.[10,42] The principal component analysis (CATPCA) showed that the PGWBI score observed in the study population could be largely explained by the persistence of a cluster of specific symptoms characterizing the

TABLE 3B. PGWBI Questionnaires Scores in the Recruited Employees Subdivided According to the Working Activity and to the Presence of Long COVID

	Academics (N = 50)				Administrative/Technical Clerks (N = 56)				Metalworkers (N = 44)				
	Long COVID Patients (N = 22)		Asymptomatic Post-COVID Workers (N = 28)		Long COVID Patients (N = 33)		Asymptomatic Post-COVID Workers (N = 23)		Long COVID Patients (N = 5)		Asymptomatic Post-COVID Workers (N = 39)		
Questionnaire Scores	Median	Range	Median	Range	Median	Range	Median	Range	Median	Range	Median	Range	*P*
PGWBI total score	68	42–88	82	23–100	56	24–90	86	45–103	64	44–94	66	22–99	$P = 0.006$
Anxiety	16	10–20	20	4–25	16	8–25	20	8–25	14	10–19	17	5–25	$P = 0.03$
Depressed mood	12	6–15	13	5–15	11	4–15	13	8–15	11	7–14	11	2–15	$P = 0.9$
Positive well-being	11	6–16	13	1–19	9	2–17	14	5–19	10	9–20	12	4–17	$P = 0.8$
Self-control	11	6–15	13	4–15	9	4–14	14	8–15	9	6–15	10	2–15	$P = 0.01$
General health	10	3–14	11	4–15	8	1–13	12	5–15	8	4–14	9	4–15	$P = 0.03$
Vitality	11	8–17	15	4–20	10	1–17	15	7–20	12	6–16	13	4–19	$P = 0.04$

post-COVID syndrome. Particularly, asthenia was one of the most frequently reported long COVID symptoms, showing a greater influence in determining PGWBI. The impairment of daily functions related to asthenia can be an important cause of disability and reduced quality of life, considering the very high number of SARS-CoV-2 infections worldwide, and should also be considered an occupational health issue, as it reduces the ability to perform usual work tasks.[43]

Alteration of PGWB in long COVID patients may be also related to the different and fluctuating symptoms they experience. Moreover, although different definitions of long COVID have been proposed, still a universal diagnostic criterion is lacking.[44,45] This uncertainty in the diagnosis can lead to a difference in the understanding and awareness of the subject's symptoms, also among employers and colleagues, causing mental distress and potential social stigmatization also in the occupational context.[46] In addition, the presence of ongoing symptoms may lead subjects to a prolonged social isolation, which, in turn, negatively impacts mental health, perceived quality of life, and well-being.[47]

TABLE 4. Variable Loadings on the First Principal Component (Variance Accounted for 11.3%) With Absolute Values Equal to or Higher than 0.4

Variable	Loading
No. symptoms 4 mo after SARS-CoV-2 infection	0.845
PHQ-9 total score	0.753
CFQ total score	0.720
Asthenia 4 mo after SARS-CoV-2 infection	0.691
Difficulty concentrating 4 mo after SARS-CoV-2 infection	0.683
Muscle pain 4 mo after SARS-CoV-2 infection	0.672
Insomnia 4 mo after SARS-CoV-2 infection	0.662
PCFS scales	0.661
Shortness of breath 4 mo after SARS-CoV-2 infection	0.616
Paresthesia 4 mo after SARS-CoV-2 infection	0.607
Subjective depressed mood 4 mo after SARS-CoV-2 infection	0.585
Palpitations 4 mo after SARS-CoV-2 infection	0.576
Headache 4 mo after SARS-CoV-2 infection	0.567
Joint pain 4 mo after SARS-CoV-2 infection	0.508
Subjective memory deficits 4 mo after SARS-CoV-2 infection	0.480
Tachycardia 4 mo after SARS-CoV-2 infection	0.480
Shortness of breath in acute setting	0.430
Diarrhea 4 mo after SARS-CoV-2 infection	0.423
Anxiety 4 mo after SARS-CoV-2 infection	0.416
Sex	0.412
Nausea 4 mo after SARS-CoV-2 infection	0.411

Cognitive failures are defined as errors in the completion of a task that a person is normally able to perform and seem to be associated negatively with alertness and memory function, and positively with fatigue, sleep disorders, low attention, and mental errors, resulting in higher probability of workplace accidents.[48] Our findings indicated cognitive failure as a major determinant of PGWBI (Table 4). In fact, frequent forgetfulness or difficulty concentrating, reducing the performance in various life domains, could be frustrating and lead to an increased anxiety.[49] Previous studies performed in a prepandemic setting demonstrated that otherwise healthy employees with higher CFQ scores can exhibit more frequently adverse psychological reaction and increased vulnerability to the onset of neuropsychological symptoms when exposed to work-related stress.[50] Likewise, the widespread and stressful circumstances stemming from the ongoing pandemic, which are also prevalent in occupational settings, might have played a role in exacerbating the adverse effects on the PGWB of individuals exhibiting elevated CFQ scores.

A previous survey found CFQ score 6 weeks after the hospital discharge for a moderate COVID-19 (mean 18.2 ± 13.1) similar to those found in our whole study population (mean 19.5 ± 10.4), although both indicated general low evidence of cognitive complaints.[51] To the best of our knowledge, our study is the first one revealing elevated CFQ scores in individuals with long COVID. It is noteworthy, however, that a minority of long COVID patients demonstrated substantial cognitive impairment, as indicated by a CFQ score higher than 43. Numerous past surveys have documented cognitive impairment in individuals experiencing long COVID, with approximately 3.2% of those previously infected with SARS-CoV-2 reporting self-perceived cognitive dysfunction.[35] Different mechanisms have been proposed to explain the prevalence of cognitive complaints in individuals with previous SARS-CoV-2 infection, such as activation of astroglia and microglia in specific brain areas, a significant decrease in brain metabolism, microvascular thrombosis, dysregulation of blood barrier, neurotransmission alteration, oxidative stress, and mitochondria dysfunction.[52,53] Our findings suggest that these mechanisms may also act as a consequence of a previous mild COVID-19 or asymptomatic SARS-CoV-2 infection.

PHQ-9 score was identified as another major factor influencing the PGWBI of the recruited workers (Table 4), also showing higher median scores in long COVID patients compared to asymptomatic post-COVID workers, with no influence by working activity. Different possible biological causes have been proposed to explain the increase in depressive symptoms in long COVID patients. The hyperinflammatory state induced by COVID-19 may cause a low-grade inflammation, which seems to be related to depressive symptoms even a long time after the resolution of the infection. Accordingly, elevated levels of proinflammatory cytokines were observed in subjects with mood disorders, in studies

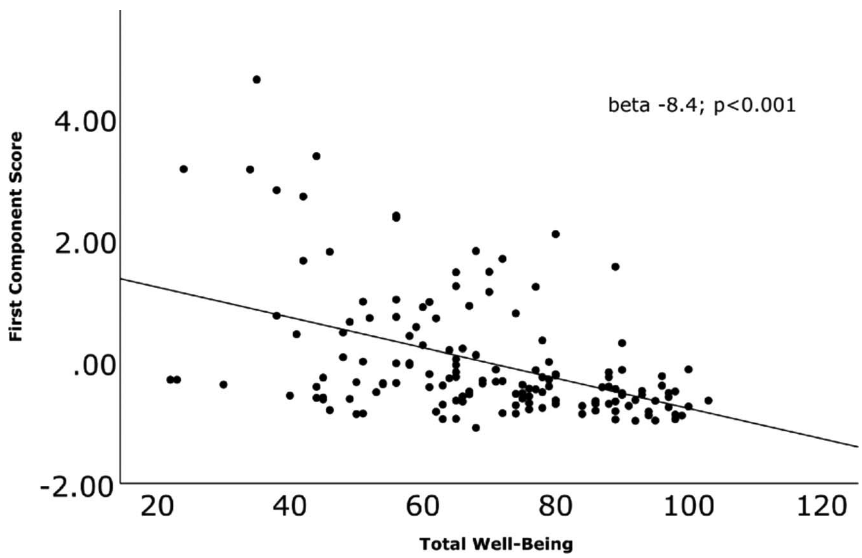

FIGURE 1. Inverse relationship between scores of the first principal component including the variables reported in Table 4, and total PGWBI score, as shown by the significant regression analysis.

performed before the COVID-19 pandemic too.[54,55] Proinflammatory cytokines could influence serotonin levels, hypothalamic-pituitary-adrenal axis, and neuroplasticity, negatively regulating brain function.[56] Moreover, long COVID patient's depressive psychopathology seemed to be also associated with a decreasing gray matter volume in the anterior cingulate and with an autoimmune etiology.[57]

Interestingly, the metalworkers included in the study showed PGWBI levels indicating moderate discomfort, with no differences between the few patients with long COVID and the asymptomatic post-COVID workers, but with lower median values than the other 2 groups of asymptomatic post-COVID workers (Table 3a, 3b). This could be because the pandemic led to economic disruptions in metalworking activities and many frontline operators faced possible job loss or reduced working hours, resulting in financial strain and insecurity.[58] The total scores documented for metalworkers were comparatively lower than those recorded across various sites within a manufacturing industry specializing in the production of home and personal hygiene products.[7] This discrepancy was notable in sectors unaffected by comparable financial insecurity. The lack of prepandemic data, however, does not allow a definitive conclusion. These results, therefore, indicate the need to investigate PGWBI in different work contexts, and further studies seem necessary to understand the impact of work on PGWB, regardless of the COVID-19 pandemic.

Among the possible factors potentially associated with long COVID, our study highlighted the female sex, in agreement with multicentric studies showing a higher prevalence of some long COVID clinical manifestations among women.[59,60] Overall, data on the association between female sex, COVID-19, and long COVID seem to be conflicting, probably due to differences in ethnicity, geographical origin, and perhaps socioeconomic status.[61] Furthermore, we also found a higher prevalence of long COVID in workers with previous acute COVID-19 characterized by a higher number of symptoms (Table 2). This finding seems to be in line with previous reports conducted on patients not hospitalized describing a higher number of symptoms as a risk factor for developing long-term sequelae.[62,63] However, most studies did not find any association between long COVID and initial severity during acute COVID-19, and the influence of acute phase symptoms on the risk of developing long COVID still deserves further investigation.[64]

This study has some limitations. Firstly, it was conducted in a single center, on a limited sample size, and considering only 3 different working tasks. Thus, the generalization of our findings might be limited, although the use of CATPCA to analyze the large number of variables investigated may have partially counterbalanced this limitation. Secondly, workers who did not suffer from COVID-19 were not included as a control group for the comparison of PGWBI scores. However, the prepandemic Italian PGWBI normative values were used for the comparison, which proved to be reliable and valid.[30] Another possible limitation of the study might be the lack of objective cognitive testing, in addition to our CFQ, which only assesses subjective cognitive impairments. The choice of this instrument was motivated by the fact that it is very sensitive for the assessment of the mild and nuanced cognitive alterations that characterize long COVID syndrome.[52,65] Future studies should additionally include sensitive objective cognitive testing, particularly those regarding cognitive domains affected in mild long COVID such as memory, attention and concentration, processing speed, and executive function.

We would like to point out several strengths of the current study. It represents the first study to specifically analyze PGWB, cognitive failure, systemic inflammation biomarkers, and long COVID symptoms 4 months after an asymptomatic SARS-CoV-2 infection or a mild COVID-19, taking into account the different working activities performed by the participants. Recruitment during occupational health surveillance, moreover, made it possible to minimize the selection bias as it was possible to intercept all individuals with previous COVID-19 in the investigated workplaces, and not only workers seeking care for long COVID syndrome. In addition, the examination of clinical characteristics and the use of multiple questionnaires administered in the presence of trained personnel allowed for a thorough assessment of the factors determining PGWB, avoiding the problems that rely on self-administration of questionnaires, including difficulties in understanding items, distraction and interruptions, or variations in motivation, considering that the lack of direct supervision could lead to variations in participants' motivation to complete the questionnaire, affecting the consistency of responses.[66]

In conclusion, PGWB should be an important condition to be monitored in employees returning to work after an infectious disease such as COVID-19, in accordance with the suggestions of the

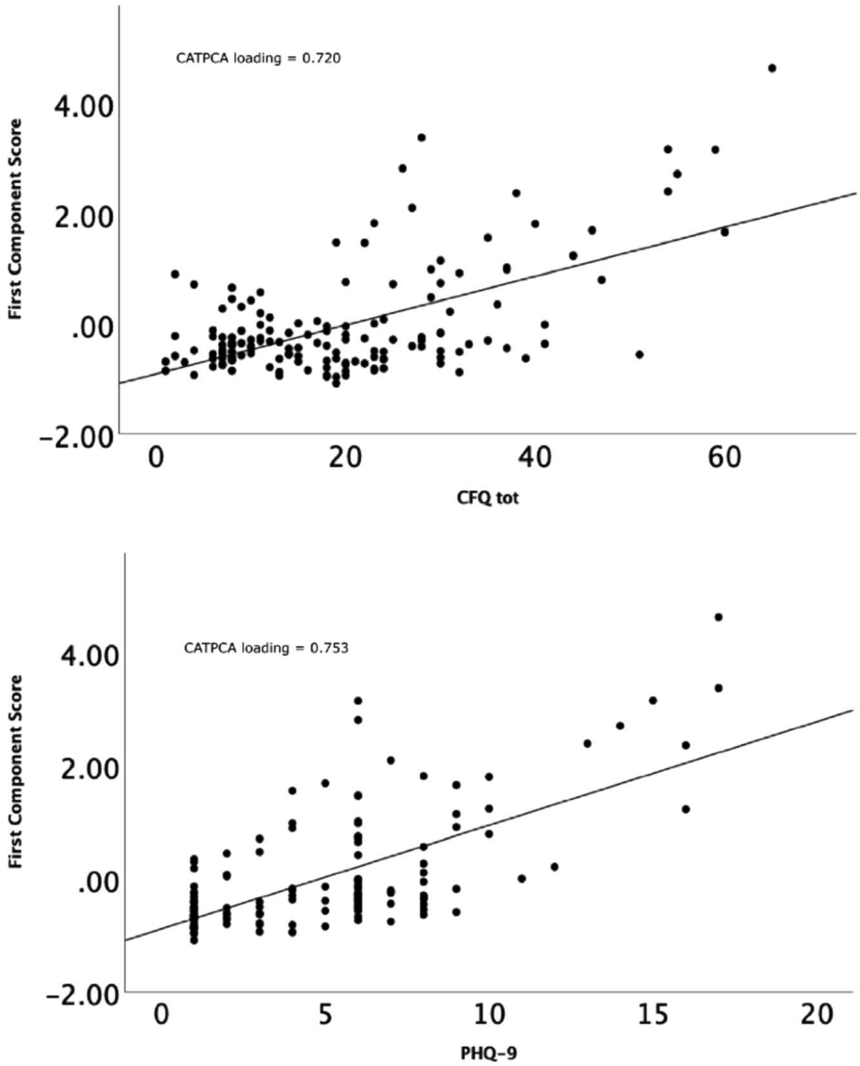

FIGURE 2. Relationships between the original variables Patient Health Questionnaire-9 (PHQ-9), Cognitive Failure Questionnaire—Total (CFQ tot), and the scores of the first component. The direct correlation corresponds to the high positive loadings presented in Table 4.

biopsychosocial model, which indicates that several chronic inflammatory diseases may result in a complex interaction of different physical and mental factors rather than from a simple cause-effect relationship of a specific biological pathogenic process.[17]

According to this, our findings emphasize that subjective cognitive disturbances, depressive symptoms, asthenia, and other long COVID symptoms such as insomnia and headache following asymptomatic SARS-CoV-2 infection or mild COVID-19 have a significant impact on the PGWB of a working age population. The results also support the hypothesis that long COVID symptoms may be associated with the presence of systemic inflammation as a consequence of a previous infectious disease. The report, therefore, highlights the need for further studies to understand the validity of simple diagnostic tools, such as inflammatory biomarkers and questionnaires, for use during occupational health surveillance. Occupational health professionals will be faced with large numbers of workers with prolonged COVID and should be specifically trained to recognize this condition. Therefore, future work on longitudinal changes in these conditions and treatment strategies to address these issues is urgently needed.

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