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Research Article

Factors Associated with Post-Exertion Malaise in Patients Suffering from Post-COVID-19 Syndrome

Alaa Ghali[1*], Valentin Lacombe[2,3], Christian Lavigne[1], Maria Ghali[4,5]

[1]Department of Internal Medicine and Clinical Immunology, Angers University Hospital, France

[2]Department of Internal Medicine, Haut-Anjou Hospital, Chateau-Gontier-sur-Mayenne, France

[3]University of Angers, Inserm, CNRS, MITOVASC, Equipe MitoLab, SFR ICAT, Angers, France

[4]University of Angers, Department of General Medicine, F-49000 Angers, France

[5]University of Angers, POPS, SFR ICAT, F-49000 Angers, France

[*]**Corresponding author:** Alaa Ghali, Department of Internal Medicine and Clinical Immunology, University Hospital of Angers, 4 rue Larrey 49000 Angers – France

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Abstract

Background: Some, but not all, of patients experiencing Post-COVID-19 Syndrome (PCS) develop Post-Exertional Malaise (PEM) and meet criteria of Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS). PEM is associated with a poor outcome in ME/CFS patients. We attempted to identify potential factors associated with PEM occurrence in PCS patients, and to assess the prognosis of PCS patients with and without PEM. **Methods:** We retrospectively included patients meeting the World Health Organization definition of PCS who attended the post-COVID clinic at the Internal Medicine Department of Angers University Hospital, France, between June 2020 and June 2024. We reviewed their medical records and gathered data including epidemiological characteristics and information concerning COVID-19 infection, PEM features, fatigue severity, and work-related outcomes. **Results:** The included 281 PCS patients were classified into 2 groups according to the presence or not of PEM. Factors that persisted to be positively associated with PEM on multivariate analysis were: COVID onset in 2020/2021 (OR 2.75 [95% CI: 1.04-7.25], p=0.04), POTS (OR 4.38 [95% CI: 1.43-13.38], p=0.01), and high fatigue levels (OR 1.93 [95% CI: 1.34-2.78], p<0.001). The follow-up assessment showed that PCS patients with PEM had significant higher fatigue levels in (5.2 [4.3-5.8] vs. 4.7 [3.8-5.3], p=0.002), and lower recovery/improvement rates (30/58 (51.7%) vs. 127/162 (78.4%), p<0.001). **Conclusion:** PEM was more prevalent in PCS patients with COVID onset in the pre-omicron era, and was associated with post-COVID POTS and a poor prognosis. Consequently, PEM and autonomic dysfunction, particularly POTS, should be systematically screened in PCS patients.

Keywords: Post-COVID syndrome; Post-exertional malaise; Postural orthostatic tachycardia syndrome; Pre-omicron era; Vaccination; Outcome

Abbreviations: PCS: Post-COVID-19 Syndrome; PEM: Post-Exertional Malaise; ME/CFS: Myalgic Encephalomyelitis/Chronic Fatigue Syndrome; EBV: Epstein-Barr Virus; MCAS: Mast Cell Activation Syndrome; MCAD: Mast Cell Activation Disorder; POTS: Postural Orthostatic Tachycardia Syndrome; CNIL: French Data Protection Authority; CCC: Canadian Consensus Criteria; ICC: International Consensus Criteria; CDC SI: Center for Disease Control and Prevention Symptom Inventory; FSS: Fatigue Severity Scale; OH: Orthostatic Hypotension; OI: Orthostatic Intolerance

Introduction

Post-COVID-19 Syndrome (PCS), commonly known as long COVID, refers to the continuation or development of new symptoms 3 months after the initial SARS-CoV-2 infection,

with these symptoms lasting for at least 2 months with no other explanation [1].

Approximately 10-20% of non-hospitalized [2] and 10-12% of vaccinated patients [3] experience post-COVID symptoms, which are heterogeneous, involving multiple organ systems, and severely impacting patients' quality of life [4]. PCS was linked to unemployment and inversely associated with working full time [5].

Fatigue is a prevalent complaint, manifesting in over 90% of PCS patients [6]. Other frequent symptoms include cognitive dysfunction, sleep disturbances, orthostatic intolerance, myalgia, headaches, dyspnea, palpitations, dizziness, balance disorders, and Post-Exertional Malaise (PEM) [7].

PEM is the hallmark symptom of Myalgic Encephalomyelitis/ Chronic Fatigue Syndrome (ME/CFS), and its presence is mandatory to establish this diagnosis [8-10]. PEM is characterized by an exacerbation of some or all baseline ME/CFS symptoms after exposure to physical, cognitive, emotional, or orthostatic exertion that were normally tolerated before [8-10], and in some patients, the emergence of new unusual symptoms [11]. The onset of PEM typically occurs several hours after the initial stressor, with an onset that may reach the next day or even later [8-10]. PEM usually necessitates 24 hours or longer to recover [8,9], and is significantly associated with disability [12], and poorer outcomes for patients [13].

PEM was observed in PCS patients, and was persisting in 73.3 % of PCS patients beyond 6 months [7]. In fact, PCS and ME/ SFC exhibit numerous shared characteristics. ME/CFS is often triggered by viral infections, especially Epstein-Barr virus [14], and similar to PCS, ME/CFS is frequently associated with reactivated herpesviruses such as EBV and human cytomegalovirus [15,16]. Both conditions occur predominantly in previously healthy and active females [17]. The majority of PCS symptoms are similar to those observed in ME/CFS [18], and they are often exacerbated or relapsed after minimal physical or mental exertion as is the case with ME/CFS [7]. The overlap in the clinical features of PCS and ME/CFS prompted some authors to propose the term "post-COVID-19 ME/CFS" [7,18,19].

Despite insufficient current knowledge regarding the precise pathophysiology of both conditions, some mechanisms were reported, including mitochondrial dysfunction, systemic and neuro-inflammation, and inappropriate immune response in both PCS and ME/CFS patients [20]. Other examples of the similarities between PCS and ME/CFS include the absence of biomarkers [21], the lack of an approved treatment, and the effectiveness of pacing strategies [22].

Furthermore, some comorbidities are frequently associated with both conditions such as Mast Cell Activation Syndrome (MCAS) [23-25], Mast Cell Activation Disorder (MCAD) [26], and Postural Orthostatic Tachycardia Syndrome (POTS) [27-30]. The POTS, which is a variant of cardiovascular autonomic disorder is characterized by excessive heart rate increase on standing, in association with various symptoms that are reported in both PCS and ME/CFS patients. These symptoms include postural light-headedness, presyncope, palpitations, chest pain, dyspnea, headache, cognitive impairment, nausea, gastrointestinal symptoms, sleep disturbances, and fatigue [31]. It is noteworthy that POTS can be triggered by various viral infections, including SARS-CoV-2, which is now recognized as a distinct phenotype of PCS [32]. A notable body of evidence was emerged indicating the potential involvement of mast cell activation in the pathogenesis of POTS [33].

Given that some, but not all, of PCS patients develop PEM, the primary aim of the study was to define possible factors that could be associated with the emergence of PEM in patients suffering from PCS. In addition, owing to the fact that PEM is known to be significantly associated with disability and poorer outcomes in ME/CFS patients [12,13], we hypothesized that PEM could have similar effects in PCS patients. Thus, the secondary objective of the study was to assess the prognosis of PCS patients with and without PEM.

Patients and Methods

Ethics

The study was approved by the Ethics Committee of Angers University Hospital (2024/154) and was conducted in compliance with the Helsinki Agreement. Data collection was approved by the French Data Protection Authority (CNIL).

Study population and data collection

We retrospectively reviewed all medical records of patients who attended the post-COVID clinic at the Internal Medicine Department of Angers University Hospital between June 2020 and June 2024. Medical records with missing data were excluded. Patients with a history of COVID-related hospitalization as well as those with a prior diagnosis of ME were not included.

The diagnosis of PCS in all patients was established according to the World Health Organization clinical case definition [1]. All patients were referred to our post-COVID clinic from primary care physicians or specialists. They all underwent a standardized assessment that was carried out by the same physician, and included a detailed medical history taking and in-depth clinical examination. Data about epidemiological characteristics, occupational status, current therapies and associated conditions, especially MCAS or MCAD, and POTS, were recorded for all

patients. Information concerning COVID-19 infection was also noted: date of onset, number of episodes, vaccination status, and related clinical manifestations including, persistent, recurrent, and/or new-onset symptoms and signs, 12 weeks after infection.

A special attention was paid for the presence or not of PEM. The identification of PEM was made according to the Canadian Consensus Criteria (CCC) [8] and the International Consensus Criteria (ICC) [9] for ME/CFS. When present, information concerning PEM was noted. Basal fatigue severity and its impact on personal and professional patients' activities were evaluated for all patients.

PEM definition

PEM is the worsening of some or all baseline symptoms after exposure to physical, cognitive, emotional, or orthostatic exertion that were normally tolerated before [8-10]. Some patients may also experience the emergence of new unusual symptoms [11]. Its onset can be immediate or delayed by several hours or longer after the stressor. PEM duration varies largely between patients and within the same patient. It can last several days, weeks or even months. PEM duration required for diagnosis is 24 hours or longer [8,9].

Analysis of PEM Features

We collected data concerning PEM features by means of a standardized questionnaire (Additional file 1) that we have designed and previously used in ME/CFS patients for the analysis of PEM occurring in PCS patients [11]. All PCS patients experiencing PEM were asked about the type of PEM stressors, the timing of onset of baseline symptom exacerbation, elapsed time between the exposure to a stressor and symptom exacerbation, PEM manifestations and worsened symptoms, potential emergence of new or unusual symptoms, the time of occurrence of new or non-typical symptoms, and the duration of PEM recovery.

PEM assessment

The PEM item from the standardized auto-questionnaire of Center for Disease Control and Prevention Symptom Inventory (CDC SI) [34] was used to measure PEM symptoms over the past month. Perceived frequency of PEM was rated on a 4-point scale (1 = a little of the time, 2 = some of the time, 3 = most of time, 4 = all of the time), and its intensity was measured on a 3-point scale (1 = mild, 2 = moderate, 3 = severe). The intensity score was converted into equidistant score (0 = symptom not reported, 1 = mild, 2.5 = moderate, 4 = severe). The PEM severity score was obtained by the multiplication of the frequency and intensity scores, ranging from 0-16.

Fatigue assessment

The Fatigue Severity Scale (FSS) [35] was used to evaluate fatigue levels in all patients at the initial and the follow-up visits. This reliable and valid nine-item auto questionnaire measures the impact of fatigue and detects change over time [36]. Each item is rated on seven-point scales from 1 (completely disagree) to 7 (completely agree). A mean fatigue score ranging from 1 to 7 was obtained by averaging the nine items. A mean FSS score ≥ 4 is in favour of clinically significant fatigue, and a reduction of 0.5 points is clinically significant [37].

POTS assessment

POTS was confirmed by active standing test and/or head-up tilt [38].

Standing test

Blood pressure and heart rate are measured after the patient has been supine for at least 5 minutes, and again after 1, 3, 5, and 10 minutes of standing. POTS patients should exhibit orthostatic tachycardia in the absence of orthostatic hypotension.

Passive head-up tilt table testing

Blood pressure and heart rate are measured while the patient is supine on a standard tilt table, and after an incline to greater than 60° head-up angle.

Orthostatic hypotension (OH) assessment

Blood pressure and heart rate are measured after five minutes in the supine position and three minutes after moving to a standing position. A decrease in blood pressure ≥20 mm Hg systolic or ≥10 mm Hg diastolic within three minutes of standing from the supine position is diagnostic of OH [39].

Work-related outcomes

We referred to the definition of patient's recovery and patient's improvement described elsewhere [40,41]. Recovered patients were able to return to work, on a full or part-time basis while improved patients were not able to return to work but they experienced a reduction in the number and/or severity of symptoms thanks to pacing strategies.

Patients' grouping

We classified the study population into 2 groups for comparative analysis according to the presence or absence of PEM.

Statistical analysis

Quantitative data were presented in medians and quartiles, and were compared between two groups for univariate analysis using a Student's t-test or a Mann-Whitney test according to distribution normality, assessed by using the D'Agostino-Pearson test. Qualitative data were presented as absolute values and percentages, and were compared using the Fisher's test or Chi-square test as appropriated. Multivariate analysis was performed by means of

binary logistic regression. The variables included in the model were age, sex, and those showing significant statistical difference between PCS/PEM+ and PSC/PEM- groups in univariate analysis. The Odds Ratios (OR) were presented with a 95% confidence interval (CI). The alpha risk was set at 5%. The analyses were performed using Graphpad Prism v6.01 (Graphpad Software, La Jolla, CA, USA) and Jamovi software v2.3.9.

Results

Characteristics of the study population

We collected retrospective data from medical records of 313 patients with PCS. After exclusion of 32 patients (12 with missing medical record data, 17 patients with a history of COVID-related hospitalization, and 3 with prior diagnosis of ME/CFS), the study's final sample size was 281 patients (Figure 1).

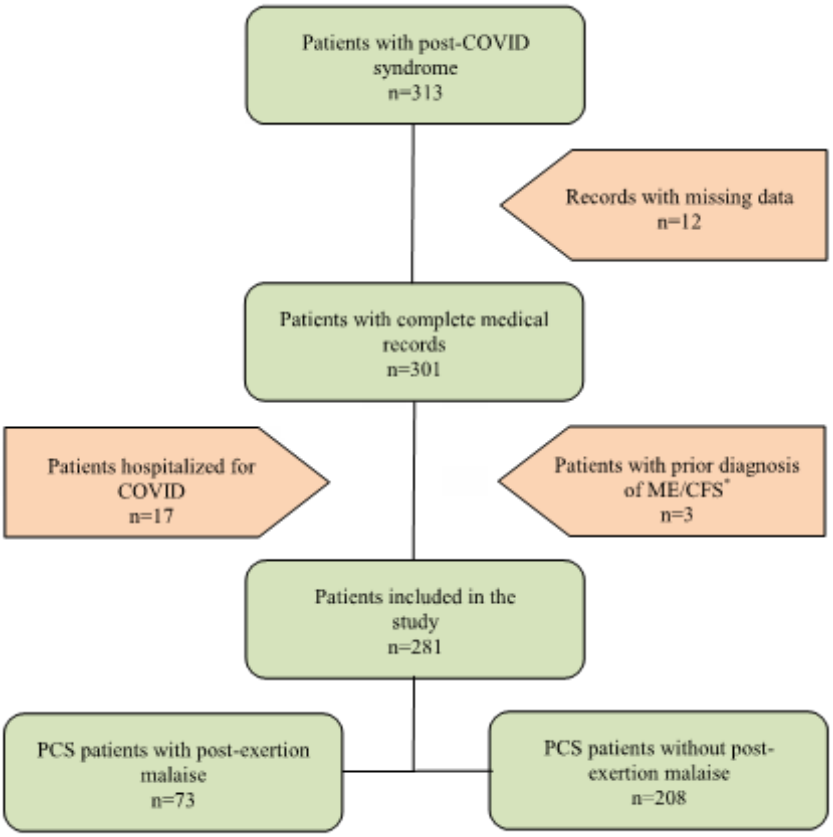

Figure 1: Flowchart of patients' inclusion. *Myalgic encephalomyelitis/chronic fatigue syndrome.

The characteristics of the study population are presented in Table 1. Patients primarily were women (228/281, 85.1%), the median age at the onset of the disease was 43 [34 -50] years, and the median time since infection to diagnosis was 16 [9-25] months. The overall population included 162/281 (57.7%) unvaccinated patients. The most prevalent symptom was fatigue, reported by 274/281 (97.5%) patients, followed by cognitive deficit (219/281,77.9%), and sleep disturbance (189/281,67.3%). PEM was found in 73/281 (26.0%) patients.

	PCS patients overall n=281	**PCS patients with PEM n (%) = 73 (26)**	**PCS patients without PEM n (%) =208 (74)**	**p-value**
Demographic characteristics				
Female, n (%)	228 (81.1)	57 (78.1)	171 (82.2)	0.547
Year of COVID onset, n (%)				
2020/21	163 (58.0)	54 (74)	109 (52.4)	**0.001**
2022/23	118 (42.0)	19 (26.0)	99 (47.6)	
Unvaccinated patients, n%	162 (57.7)	50 (68.5)	112 (53.8)	**0.04**
Age at disease onset, years	43 [34-50]	43 [34-47]	43 [34-51]	0.217
Time since infection, months	16 [9-25]	18 [11-27]	16 [9-24]	0.140
Clinical manifestations, n (%)				
Fatigue	274 (97.5)	72 (98.6)	202 (97.1)	0.681
Fever	24 (8.5)	10 (13.7)	14 (6.7)	0.087
Palpitation	74 (26.3)	33 (45.2)	41 (19.7)	**<0.001**
Inappropriate sinus tachycardia	11 (3.9)	5 (6.8)	6 (2.9)	0,16
Orthostatic hypotension	29 (10.3)	15 (20.5)	14 (6.7)	**<0.001**
Chest pain	40 (14.2)	12 (16.4)	28 (13.5)	0.531
Dyspnea	156 (55.5)	41 (56.2)	115 (55.3)	0.896
Cough	85 (30.2)	18 (24.7	67 (32.2)	0.226
Chest tightness	82 (29.2)	26 (35.6)	56 (26.9)	0.159
Cognitive deficit	219 (77.9)	61 (83.6)	158 (76.0)	0.177
Brain fog	146 (52.0)	44 (60.3)	102 (49.0)	0.098

Headache	187 (66.5)	55 (75.3)	132 (63.5)	0.088
Vertigo/balance disorder	115 (41.0)	36 (49.3)	79 (38.0)	0.090
Neurosensory dysfunction	71 (25.3)	23 (31.5)	48 (23.1)	0.153
Sleep	189 (67.3)	54 (74.0)	135 (64.9)	0.202
Ear, nose and throat	81 (28.8)	27 (37.0)	54 (26.0)	0.101
Myalgia	179 (64.0)	53 (72.6)	126 (38.0)	0.066
Arthralgia	87 (31.0)	29 (39.7)	58 (27.9)	0.059
Neuralgia	53 (18.9)	18 (724.)	35 (16.8)	0.141
Psychiatric disorders	145 (51.6)	36 (49.3)	109 (52.4)	0.750
Gastrointestinal	114 (40.6)	24 (32.9)	90 (43.3)	0.156
Eye involvement	16 (5.7)	1 (1.4)	15 (7.2)	0.079
Fatigue assessment				
Baseline FSS score	6.2 [5.2 – 6.8]	6.8 [6.2 - 7]	6.1 [5.1- 6.8]	**<0.001**
Associated conditions, n (%)				
POTS	18 (6.4)	11 (15.1)	7 (3.4)	**0.001**
Mast cell activation	191 (68.0)	51 (69.9)	140 (67.3)	0.797
Fibromyalgia	19 (6.8)	6 (8.2)	13 (6.3)	0.372

Qualitative data are expressed as absolute number and percentage. Qualitative data are expressed as median and quartiles. PCS: Post-COVID Syndrome; PEM: Post-Exertion Malaise; ear, nose and throat symptoms: sore throat, dysphonia, dysphagia, anosmia, dysgeusia and rhinorrhea; psychiatric disorders: anxiety and depression; gastrointestinal: nausea, vomiting, abdominal pain, abdominal distention, diarrhea; eye involvement: keratoconjunctivitis, uveitis, central retinal vein and artery occlusions; FSS: fatigue severity scale; POTS: Postural Orthostatic Tachycardia Syndrome.

Table 1: Characteristics of patients with post-COVID syndrome with and without post-exertion malaise.

Factors associated with PEM in PCS patients

We classified included patients into 2 groups according to the presence or absence of PEM for comparison. The presence of PEM among PCS patients was associated with the onset of more cases of COVID infection in years 2020/2021 (p=0.001), a higher number of unvaccinated patients (p=0.04), a higher frequency of palpitations (p<0.001) and OH (p<0.001), and the occurrence of more frequent cases of POTS (p=0.001). PCS patients with PEM had significantly higher basal FSS scores than those without PEM (p<0.001).

Variables that persisted to be positively associated with PEM occurrence in PCS patients on the multivariate binary logistic regression analysis were the years of COVID onset 2020/2021 (OR 2.75 [95% CI: 1.04-7.25], p=0.04), the presence of POTS (OR 4.38 [95% CI: 1.43 - 13.38], p=0.01), and higher FSS score (OR 1.93 [95% CI: 1.34-2.78], p<0.001) (Table 2).

	OR (95% CI)[a]	p-value
Age at disease onset [b]	1.48 [95% CI: 0.81 - 2.69]	0.20
Female sex	0.68 [95% CI: 0.33 - 1.39]	0.28
Years of COVID onset 2020/2021	2.75 [95% CI: 1.04 - 7.25]	**0.04**
Absence of vaccination	0.50 [95% CI: 0.19 - 1.33]	0.16
Fatigue severity score	1.93 [95% CI: 1.34 - 2.78]	**<0.001**
POTS	4.38 [95% CI: 1.43 - 13.38]	**0.01**
Orthostatic hypotension	1.01 [95% CI: 0.39 - 2.61]	0.98
Palpitation	1.81 [95% CI: 0.89 - 3.66]	0.10

Multivariate analysis was performed with binary logistic regression. The variable to explain was post-exertion malaise occurrence. The variables included were age at disease onset, sex, and those showing significant statistical difference between patients having post-COVID syndrome with and without post-exertion malaise in univariate analysis (p<0.05).

[a] Odds Ratio with 95% Confidence interval

[b] Age as a categorical variable with a cut-off ≥ the median age of the study population (43 years)

Table 2: Multivariate analysis of factors associated with post-exertion malaise occurrence in patients with post-COVID syndrome.

Prognosis of PCS patients according to the presence of PEM

Follow-up data were available for (220/281, 78.3%) of patients. The median time of follow-up did not differ between patients with and without PEM (11 [7-22] vs. 9 [6-14] months, p=0.07).

Compared to PCS patients without PEM, PCS patients with PEM had significantly higher FSS scores at last follow-up assessment (5.2 [4.3-5.8] vs. 4.7 [3.8-5.3], p=0.002), and lower recovery/improvement rates (30/58 (51.7%) vs. 127/162 (78.4%), p<0.001) (Figure 2).

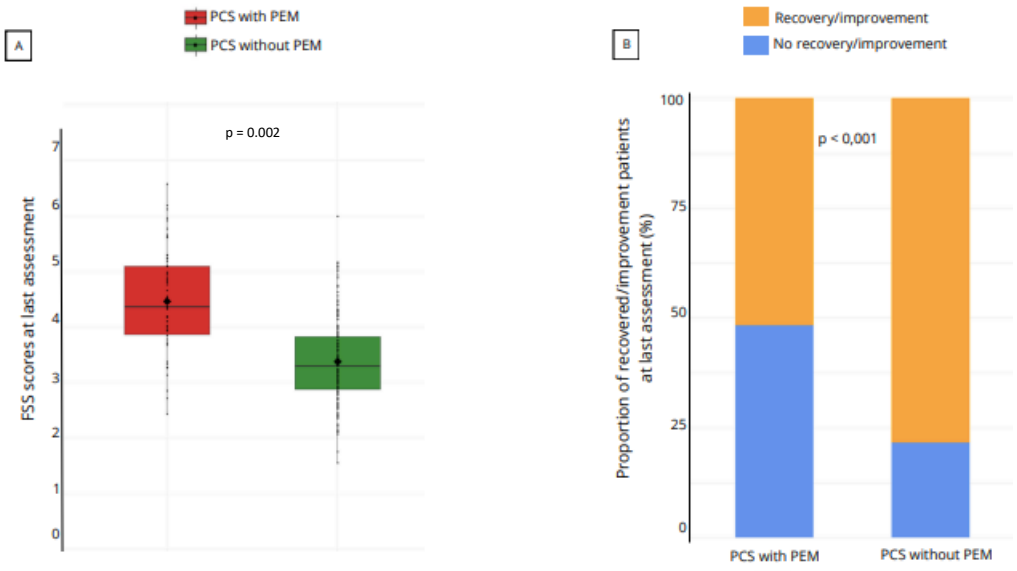

Figure 2: Prognosis of patients with post-COVID syndrome with and without post-exertion malaise. A. FSS scores of PCS patients with and without PEM at last assessment. B. Recovered/improved PCS patients with and without PEM at last assessment. FSS: Fatigue severity scale. PCS; Post-COVID syndrome. PEM: Post-exertion malaise.

Discussion

PCS is a common condition that affects approximately 10-20% of non-hospitalized patients [2], and severely impacts their quality of life [4]. PCS was linked to unemployment and inversely associated with working full time [5].

PEM, a hallmark symptom of ME/CFS, is one of the symptoms frequently encountered in PCS and its presence suggests the diagnosis of post-COVID-19 ME/CFS [18,42]. Given that not all PCS patients develop PEM, and that PEM is associated with disability [12], and poorer outcomes [13] in ME/CFS patients, the current study focused primarily on identifying factors that could contribute to the occurrence of PEM in a PCS population, and secondarily on assessing the prognosis of PCS patients with and without PEM.

Population characteristics

The study included 281 PCS patients with a median age at disease onset of 43 [34-50] years. The higher prevalence of women (81.1%) in the current study was comparable to that previously reported [6,43]. The most prevalent symptom reported by 97.5% of patients was fatigue, which aligns with the previously documented prevalence rate of 92.6% [6].

Prevalence of PEM

The proportion of PCS patients who experienced PEM was 26%. The prevalence of PEM in PCS patients varies widely across studies, ranging from 17.5% to 94.8% [44-48]. These variations can be attributed to various factors, including the sample size, the patients' selection (hospitalized/non-hospitalized, or vaccinated/non-vaccinated), the timing of the study (pre-omicron or omicron era), the criteria used for diagnosis, the definition of PEM, pre-existing health conditions, and the length of follow-up.

For instance, a recent study [46] reported that 72.4% of patients experienced PEM 3-6 months after acute infection. Over half of these patients (52.7%) fulfilled Fukuda criteria, while only around 20% met criteria for ME diagnosis [8,9]. A similar trend was observed in another study [47], where PEM was reported by 82.2% of patients, while only 43% of them fulfilled IOM criteria [10]. Another study [48] found a post-exertional symptom exacerbation in 94.8% of participants; however, only 58.7% met the PEM scoring thresholds used in ME/CFS patients. In our study, PEM identification was based on the CCC and ICC for ME diagnosis [8,10], which could explain the relative low prevalence rate. The observed variations in the prevalence of PEM across studies may also be due the varying definitions of PEM used in these studies. Kedor, et al. [45] found that 19 out of 42 (45%) PCS

patients experienced PEM and met the CCC for ME diagnosis; however, they used a minimum of 14 h of PEM contrary to the original case definition that required a PEM period of 24 hours or longer for diagnosing ME. The high prevalence of PEM in some studies could also be due to the fact that they included patients 4 weeks and more post-COVID and symptoms could be worse early after the acute phase [47,48].

The comparison between PCS patients with and without PEM showed that they were different on multivariate analysis in terms of years of COVID onset 2020/2021, the presence of POTS, and higher fatigue levels.

Onset of Covid infection

The SARS-CoV-2 wild type strain was dominant in France from March 2020 to November 2020. Thereafter, the predominant circulating SARS-CoV-2 variant changed from alpha to delta in June 2021, and then to omicron variant in December 2021 till now [49]. On the other hand, the wild-type, alpha, and delta variants were reported to yield similar long term covid-19 sequelae [50]. In the absence of genomic study of SARS-CoV-2 variants, we chose to compare PCS patients with and without PEM according to pre-omicron era (years 2020/21) with omicron era (years 2022/23). The univariate analysis showed a statistically significant difference in PEM occurrence among patients who contracted COVID infection in years 2020/21, and this difference persisted on multivariate analysis (OR 2.75 [95% CI: 1.04-7.25], p=0.04). On other words, the incidence of PEM was threefold higher among patients with COVID onset in the pre-omicron era than among those with COVID onset in the omicron era. The current study cannot determine however, whether this finding is due to the viral virulence or because the absence of an acquired immunity through natural infection or vaccination. Further studies are therefore needed to clarify this point.

Vaccination status

Findings concerning the relationship between vaccination status and long-COVID symptoms are contradictory. While some studies [51,52] reported no effect on the number, severity or frequency of PCS symptoms, others found an association between vaccine administration and the improvement of symptoms on one hand [53,54], and on the other hand, the prevention of long COVID occurrence [54,55]. The present study found that the presence of PEM among PCS patients was associated with a significantly higher number of unvaccinated patients (p=0.04) only on univariate analysis. To date, no study has examined the impact of the vaccination status on the emergence of PEM in PCS patients.

Post-COVID-19 POTS

POTS is frequent among young and middle-age people with a female preponderance [56], and its onset is most commonly triggered by viral infection, especially EBV [57,58]. SARS-CoV-2 is another viral infection that can trigger POTS. Many stressors such as high temperature, dehydration, physical strain, or fever may exacerbate POTS symptoms that significantly impact patients' quality of life and many patients become bedridden [59].

The precise pathophysiological mechanisms underlying POTS remain to be fully elucidated; however, numerous hypotheses have been postulated, including autonomic denervation, hyperadrenergic stimulation, and hypovolemia. In the context of post-COVID-19 POTS, the autonomic nervous system dysfunction could be related to a direct toxic action of SARS-CoV-2 on target cells, viral invasion of the brain stem with alteration of medullary centers function, or autoantibodies production against autonomic ganglia and nerve fibers or other neuronal or cardiovascular receptors [57,58,60,61]. Infection-related stress could stimulate the sympathetic nervous system, and initiates pro-inflammatory cytokine production, and sympathetic overstimulation [57]. Moreover, hypovolemia due to fever, excessive sweating, nausea, and prolonged bed rest will increase cardiac sympathetic noradrenergic system outflow [58].

In the current study, POTS was observed in 6.4% of the study population, which is online with results of a recent study [57] showing that 2-14% of PCS patients develop POTS within 6-8 months of the acute infection, however higher (22% and 30%) as well lower (0.1%) prevalence were also reported [62-64].

Another finding was the significant association of POTS with the presence of PEM in PCS patients (OR 4.38 [95% CI: 1.43-13.38], p=0.01). In view of this result, it is important to note that despite the frequent association of POTS with ME/CFS, PEM the hallmark of ME/CFS, is not one of the features encountered in POTS. It is still unclear whether POTS and ME/CFS are sharing a common underlying immunological and/or inflammatory pathway or they represent two distinct conditions that can occur in the same individual.

Orthostatic hypotension & palpitations

OH is one of the most prevalent forms of orthostatic intolerance (OI), along with POTS and neurally mediated hypotension. OI is frequently encountered in PCS patients [66], and constitutes one of the diagnostic criteria for ME/CFS [10]. POTS-like symptoms such as palpitations and tachycardia are also frequent in both PCS and ME/CFS patients [7,30]. In our study population, the prevalence of OH and palpitations were 10.3% and 26.3%, respectively, which in line with results of other studies that reported OH and palpitation prevalence in PCS of 9%-13.8% [65,66], and 25-50% [32], respectively. In the current study, OH and palpitations were more frequent in the group of PCS patients with PEM than those without PEM (p=<0.001 for both comparison) but this difference did not persist on multivariate analysis.

Fatigue severity

In our study, PCS patients with PEM exhibited higher levels of baseline fatigue, as indicated by significantly higher FSS scores, compared to those without PEM. Furthermore, they experienced more persistent higher fatigue levels with significantly higher FSS scores at last assessment, and poorer prognosis with significantly lower recovery/improvement rates.

These results are consistent with findings of many studies that compared PCS patients with and without PEM [44,45,48]. The presence of PEM was associated with higher fatigue levels, more severe persistent symptoms, and diminished functional status.

Limitations and Strengths

One source of weakness in this study was the absence of data concerning the genomic study of SARS-CoV-19 variants. Furthermore, the follow-up period was not exhaustive for all participants, yet the missing data did not demonstrate statistical disparities between the two groups. Another limitation was the retrospective character of the study; nevertheless, all patients were examined and diagnosed and followed up by the same physician, and underwent a same standardized procedure including the assessment of PEM, fatigue, and associated conditions, namely POTS.

On the other hand, we would like to highlight the sizable number of the study population, and the fact that PEM identification in all patients was based on the same criteria for ME [8,9].

Conclusion

Given that some, but not all, of PCS patients develop PEM as well as prolonged symptoms that meet ME/CFS criteria, and knowing that PEM is associated with disability and poorer outcomes in ME/CFS patients, we attempted to identify factors that may be associated with PEM occurrence in PCS patients and to assess their outcomes.

We observed that PEM was more prevalent in patients who contracted the SARS-CoV-2 virus in the pre-omicron era, and among those who experienced post-COVID POTS. Consequently, autonomic dysfunction, especially POTS should be thoroughly investigated in PCS patients and appropriately treated.

Another important finding of our study was that PCS patients with PEM presented persistent elevated fatigue levels, diminished functional capacity, and a more unfavorable prognosis than those without PEM. It seems, therefore, necessary to systematically screen patients with PCS for the presence of PEM in order to adapt and individualize the disease management, particularly in the absence of curative treatment for PCS. This approach is further underscored by the potential of exercise-based protocols to trigger PEM and exacerbate patient's symptoms. To achieve this objective, it is important to enhance awareness among health professionals, particularly primary care physicians, regarding the implications of PEM, including its detrimental impact on patients' health status and quality of life. Patients who experience PEM must identify and recognize the factors that trigger PEM and adhere more rigorously to pacing strategies to prevent its occurrence. This comprehensive approach is expected to enhance the course of the disease and improve the quality of life for patients affected by PEM.

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Competing Interests

The authors declare that they have no competing interests.

Authors' Contributions

AG contributed to the concept and design, to the acquisition of data, to the interpretation of the data and to the critical writing, revised the intellectual content, and approved the final version of the manuscript. VL and CL contributed to the interpretation of data, revised the intellectual content, and approved the final version of the manuscript. MG contributed to the concept and design, to the analysis and the interpretation of the data, and to the critical writing, revised the intellectual content, and approved the final version of the manuscript. All authors read and approved the final manuscript.

Availability of Data and Materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

References

1. World Health Organization (2021) A clinical case definition of post COVID-19 condition by a Delphi consensus.
2. World Health Organization (2021) Post COVID-19 condition (Long COVID).
3. Ayoubkhani D, Bosworth ML, King S, Pouwels KB, Glickman M, et al. (2022) Risk of Long COVID in People Infected with Severe Acute Respiratory Syndrome Coronavirus 2 After 2 Doses of a Coronavirus Disease 2019 Vaccine: Community-Based, Matched Cohort Study. Open Forum Infect Dis 9: ofac464.
4. Havervall S, Rosell A, Phillipson M, Mangsbo SM, Nilsson P, et al. (2021) Symptoms and Functional Impairment Assessed 8 Months

After Mild COVID-19 Among Health Care Workers. JAMA 325: 2015-2016.

5. Perlis RH, Lunz Trujillo K, Safarpour A, Santillana M, Ognyanova K, et al. (2023) Association of Post–COVID-19 Condition Symptoms and Employment Status. JAMA Netw Open 6: e2256152.
6. Kokolevich ZM, Crowe M, Mendez D, Biros E, Reznik JE (2022) Most Common Long COVID Physical Symptoms in Working Age Adults Who Experienced Mild COVID-19 Infection: A Scoping Review. Healthcare 10: 2577.
7. Davis HE, Assaf GS, McCorkell L, Wei H, Low RJ, et al. (2021) Characterizing long COVID in an international cohort: 7 months of symptoms and their impact. EClinicalMedicine 38: 101019.
8. Carruthers BM, Jain AK, De Meirleir KL, Peterson DL, Klimas NG, et al. (2003) Myalgic Encephalomyelitis/Chronic Fatigue Syndrome: Clinical Working Case Definition, Diagnostic and Treatment Protocols. J Chronic Fatigue Syndr 11: 7-115.
9. Carruthers BM, van de Sande MI, De Meirleir KL, Klimas NG, Broderick G, et al. (2011) Myalgic encephalomyelitis: International Consensus Criteria. J Intern Med 270: 327-338.
10. Committee on the Diagnostic Criteria for Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (2015) Beyond Myalgic Encephalomyelitis/Chronic Fatigue Syndrome: Redefining an Illness. Mil Med 180: 721-723.
11. Ghali A, Lacout C, Ghali M, Gury A, Delattre E, et al. (2021) Warning Signals of Post-Exertional Malaise in Myalgic Encephalomyelitis/Chronic Fatigue Syndrome: A Retrospective Analysis of 197 Patients. J Clin Med 10: 2517.
12. Nyland M, Naess H, Birkeland JS, Nyland H (2014) Longitudinal follow-up of employment status in patients with chronic fatigue syndrome after mononucleosis. BMJ Open 4: e005798.
13. Taylor RR (2004) Quality of life and symptom severity for individuals with chronic fatigue syndrome: findings from a randomized clinical trial. Am J Occup Ther 58: 35-43.
14. Jones JF, Ray CG, Minnich LL, Hicks MJ, Kibler R, et al. (1985) Evidence for Active Epstein-Barr Virus Infection in Patients with Persistent, Unexplained Illnesses: Elevated Anti-Early Antigen Antibodies. Ann Intern Med 102: 1-7.
15. Shikova E, Reshkova V, Kumanova A, Raleva S, Alexandrova D, et al. (2020) Cytomegalovirus, Epstein-Barr virus, and human herpesvirus-6 infections in patients with myalgic encephalomyelitis/chronic fatigue syndrome. J Med Virol 92: 3682-3688.
16. Peluso MJ, Deveau TM, Munter SE, Ryder D, Buck A, et al. (2022) Impact of Pre-Existing Chronic Viral Infection and Reactivation on the Development of Long COVID. medRxiv 2022.06.21.22276660.
17. Poenaru S, Abdallah SJ, Corrales-Medina V, Cowan J (2021) COVID-19 and post-infectious myalgic encephalomyelitis/chronic fatigue syndrome: a narrative review. Ther Adv Infect Dis 8: 204993612110093.
18. Wong TL, Weitzer DJ (2021) Long COVID and Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS)—A Systemic Review and Comparison of Clinical Presentation and Symptomatology. Medicina (Mex) 57: 418.
19. Petracek LS, Suskauer SJ, Vickers RF, Patel NR, Violand RL, et al. (2021) Adolescent and Young Adult ME/CFS After Confirmed or Probable COVID-19. Front Med 8: 668944.
20. Paul BD, Lemle MD, Komaroff AL, Snyder SH (2021) Redox imbalance links COVID-19 and myalgic encephalomyelitis/chronic fatigue syndrome. Proc Natl Acad Sci U S A 118: e2024358118.
21. Townsend L, Dyer AH, Jones K, Dunne J, Mooney A, et al. (2020) Persistent fatigue following SARS-CoV-2 infection is common and independent of severity of initial infection. Madeddu G, editor. PLoS One 15: e0240784.
22. Ghali A, Lacombe V, Ravaiau C, Delattre E, Ghali M, et al. (2023) The relevance of pacing strategies in managing symptoms of post-COVID-19 syndrome. J Transl Med 21: 375.
23. Theoharides TC, Tsilioni I, Ren H (2019) Recent advances in our understanding of mast cell activation – or should it be mast cell mediator disorders? Expert Rev Clin Immunol 15: 639-656.
24. Weinstock LB, Brook JB, Walters AS, Goris A, Afrin LB, et al. (2021) Mast cell activation symptoms are prevalent in Long-COVID. Int J Infect Dis 112: 217-226.
25. Wechsler JB, Butuci M, Wong A, Kamboj AP, Youngblood BA (2022) Mast cell activation is associated with post-acute COVID-19 syndrome. Allergy 77: 1288-1291.
26. Valent P, Hartmann K, Bonadonna P, Niedoszytko M, Triggiani M, et al. (2022) Mast Cell Activation Syndromes: Collegium Internationale Allergologicum Update 2022. Int Arch Allergy Immunol 183: 693-705.
27. Hoad A, Spickett G, Elliott J, Newton J (2008) Postural orthostatic tachycardia syndrome is an under-recognized condition in chronic fatigue syndrome. QJM Mon J Assoc Physicians 101: 961-965.
28. Hatziagelaki E, Adamaki M, Tsilioni I, Dimitriadis G, Theoharides TC (2018) Myalgic Encephalomyelitis/Chronic Fatigue Syndrome—Metabolic Disease or Disturbed Homeostasis due to Focal Inflammation in the Hypothalamus? J Pharmacol Exp Ther 367: 155-167.
29. Johansson M, Ståhlberg M, Runold M, Nygren-Bonnier M, Nilsson J, et al. (2021) Long-Haul Post–COVID-19 Symptoms Presenting as a Variant of Postural Orthostatic Tachycardia Syndrome. JACC Case Rep 3: 573-580.
30. Blitshteyn S, Whitelaw S (2021) Postural orthostatic tachycardia syndrome (POTS) and other autonomic disorders after COVID-19 infection: a case series of 20 patients. Immunol Res 69: 205-211.
31. Sheldon RS, Grubb BP, Olshansky B, Shen W-K, Calkins H, et al. (2015) 2015 heart rhythm society expert consensus statement on the diagnosis and treatment of postural tachycardia syndrome, inappropriate sinus tachycardia, and vasovagal syncope. Heart Rhythm 12: e41-e63.
32. Ståhlberg M, Reistam U, Fedorowski A, Villacorta H, Horiuchi Y, et al. (2021) Post-COVID-19 Tachycardia Syndrome: A Distinct Phenotype of Post-Acute COVID-19 Syndrome. Am J Med 134: 1451-1456.
33. Doherty TA, White AA (2018) Postural orthostatic tachycardia syndrome and the potential role of mast cell activation. Auton Neurosci 215: 83-88.
34. Wagner D, Nisenbaum R, Heim C, Jones JF, Unger ER, et al. (2005) Psychometric properties of the CDC Symptom Inventory for assessment of chronic fatigue syndrome. Popul Health Metr 3: 8.

35. Krupp LB, LaRocca NG, Muir-Nash J, Steinberg AD (1989) The fatigue severity scale. Application to patients with multiple sclerosis and systemic lupus erythematosus. Arch Neurol 46: 1121-1123.

36. Whitehead L (2009) The Measurement of Fatigue in Chronic Illness: A Systematic Review of Unidimensional and Multidimensional Fatigue Measures. J Pain Symptom Manage 37: 107-128.

37. Smedal T, Beiske AG, Glad SB, Myhr K-M, Aarseth JH, et al. (2011) Fatigue in multiple sclerosis: associations with health-related quality of life and physical performance. Eur J Neurol 18: 114-120.

38. Arnold AC, Ng J, Raj SR (2018) Postural tachycardia syndrome - Diagnosis, physiology, and prognosis. Auton Neurosci Basic Clin 215: 3-11.

39. Freeman R, Wieling W, Axelrod FB, Benditt DG, Benarroch E, et al. (2011) Consensus statement on the definition of orthostatic hypotension, neurally mediated syncope and the postural tachycardia syndrome. Clin Auton Res 21: 69-72.

40. Devendorf AR, Jackson CT, Sunnquist M, Jason LA (2019) Defining and measuring recovery from myalgic encephalomyelitis and chronic fatigue syndrome: the physician perspective. Disabil Rehabil 41: 158-165.

41. Ghali A, Lacout C, Fortrat J-O, Depres K, Ghali M, et al. (2022) Factors Influencing the Prognosis of Patients with Myalgic Encephalomyelitis/ Chronic Fatigue Syndrome. Diagnostics 12: 2540.

42. Davis HE, McCorkell L, Vogel JM, Topol EJ (2023) Long COVID: major findings, mechanisms and recommendations. Nat Rev Microbiol 21: 133-146.

43. Subramanian A, Nirantharakumar K, Hughes S, Myles P, Williams T, et al. (2022) Symptoms and risk factors for long COVID in non-hospitalized adults. Nat Med 28: 1706-1714.

44. Karyakarte RP, Das R, Rajmane MV, Dudhate S, Agarasen J, et al. (2023) The Burden and Characteristics of Post-COVID-19 Conditions Among Laboratory-Confirmed Delta and Omicron COVID-19 Cases: A Preliminary Study From Maharashtra, India. Cureus 15: 44888.

45. Kedor C, Freitag H, Meyer-Arndt L, Wittke K, Hanitsch LG, et al. (2022) A prospective observational study of post-COVID-19 chronic fatigue syndrome following the first pandemic wave in Germany and biomarkers associated with symptom severity. Nat Commun 13: 5104.

46. Cornelissen MEB, Bloemsma LD, Vaes AW, Baalbaki N, Deng Q, et al. (2024) Fatigue and symptom-based clusters in post COVID-19 patients: a multicentre, prospective, observational cohort study. J Transl Med 22: 191.

47. Bonilla H, Quach TC, Tiwari A, Bonilla AE, Miglis M, et al. (2023) Myalgic Encephalomyelitis/Chronic Fatigue Syndrome is common in post-acute sequelae of SARS-CoV-2 infection (PASC): Results from a post-COVID-19 multidisciplinary clinic. Front Neurol 14: 1090747.

48. Twomey R, DeMars J, Franklin K, Culos-Reed SN, Weatherald J, et al. (2022) Chronic Fatigue and Postexertional Malaise in People Living with Long COVID: An Observational Study. Phys Ther 102: pzac005.

49. Deroche L, Bellecave P, David R, Ouattara E, Garcia M, et al. (2023) One year of SARS-CoV-2 circulation in the Nouvelle-Aquitaine region, February 2021–2022, France. Front Microbiol 14: 1176575.

50. Mizrahi B, Sudry T, Flaks-Manov N, Yehezkelli Y, Kalkstein N, et al. (2023) Long covid outcomes at one year after mild SARS-CoV-2 infection: nationwide cohort study. BMJ 380: e072529.

51. Wisnivesky JP, Govindarajulu U, Bagiella E, Goswami R, Kale M, et al. (2022) Association of Vaccination with the Persistence of Post-COVID Symptoms. J Gen Intern Med 37: 1748-1753.

52. Mclaughlin M, Cerexhe L, Macdonald E, Ingram J, Sanal-Hayes NEM, et al. (2023) A Cross-Sectional Study of Symptom Prevalence, Frequency, Severity, and Impact of Long-COVID in Scotland: Part I. Am J Med 138: 121-130.

53. Strain WD, Sherwood O, Banerjee A, Van der Togt V, Hishmeh L, et al. (2022) The Impact of COVID Vaccination on Symptoms of Long COVID: An International Survey of People with Lived Experience of Long COVID. Vaccines 10: 652.

54. Maier HE, Kowalski-Dobson T, Eckard A, Gherasim C, Manthei D, et al. (2024) Reduction in Long COVID Symptoms and Symptom Severity in Vaccinated Compared to Unvaccinated Adults. Open Forum Infect Dis 11: ofae039.

55. Lippi G, Sanchis-Gomar F, Henry BM (2023) COVID-19 and its long-term sequelae: what do we know in 2023? Pol Arch Intern Med 133: 16402.

56. Bai F, Tomasoni D, Falcinella C, Barbanotti D, Castoldi R, et al. (2022) Female gender is associated with long COVID syndrome: a prospective cohort study. Clin Microbiol Infect 28: 611.e9-611.e16.

57. Ormiston CK, Swiatkiewicz I, Taub PR (2022) Postural orthostatic tachycardia syndrome as a sequela of COVID-19. Heart Rhythm 19: 1880-1889.

58. Thieben MJ, Sandroni P, Sletten DM, Benrud-Larson LM, Fealey RD, et al. (2007) Postural Orthostatic Tachycardia Syndrome: The Mayo Clinic Experience. Mayo Clin Proc 82: 308-313.

59. Taub PR, Zadourian A, Lo HC, Ormiston CK, Golshan S, et al. (2021) Randomized Trial of Ivabradine in Patients With Hyperadrenergic Postural Orthostatic Tachycardia Syndrome. J Am Coll Cardiol 77: 861-871.

60. Andargie TE, Tsuji N, Seifuddin F, Jang MK, Yuen PST, et al. (2021) Cell-free DNA maps COVID-19 tissue injury and risk of death and can cause tissue injury. JCI Insight 6: e147610.

61. Goldstein DS (2021) The possible association between COVID-19 and postural tachycardia syndrome. Heart Rhythm 18: 508-509.

62. Shouman K, Vanichkachorn G, Cheshire WP, Suarez MD, Shelly S, et al. (2021) Autonomic dysfunction following COVID-19 infection: an early experience. Clin Auton Res 31: 385-394.

63. Hira R, Baker JR, Siddiqui T, Ranada SI, Soroush A, et al. (2023) Objective Hemodynamic Cardiovascular Autonomic Abnormalities in Post-Acute Sequelae of COVID-19. Can J Cardiol 39: 767-775.

64. Tanking C, Lakkananurak C, Srisakvarakul C, Jitpreeda A, Threechod K, et al. (2024) Postural orthostatic tachycardia syndrome and other autonomic dysfunctions following COVID-19: Incidence, characteristics, and associated factors. J Arrhythmia 40: 230-236.

65. Isaac R, Corrado J, Sivan M (2023) Detecting Orthostatic Intolerance in Long COVID in a Clinic Setting. Int J Environ Res Public Health 20: 5804.

66. Stella AB, Furlanis G, Frezza NA, Valentinotti R, Ajcevic M, et al. (2022) Autonomic dysfunction in post-COVID patients with and witfhout neurological symptoms: a prospective multidomain observational study. J Neurol 269: 587-596.