

CLINICAL, NEUROLOGICAL AND SEX-SPECIFIC FEATURES OF POST-COVID SYNDROME AND ITS MANAGEMENT WITH A GABA- AND GLYCINE CONTAINING NEUROMETABOLIC SUPPLEMENT: A PROSPECTIVE CONTROLLED STUDY

(Running title: Sex differences and management of post-COVID syndrome)

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Abstract

Background. Post-COVID syndrome (PCS) is dominated by neurological and neuropsychiatric symptoms, and its presentation may differ between women and men. Data from Central Asia are scarce, and no disease-modifying therapy is currently available.

Aim. To characterise the clinical, epidemiological and sex-specific features of PCS after COVID-19 pneumonia and to evaluate the effect of adding Glycevit, a neurometabolic supplement containing gamma-aminobutyric acid (GABA), glycine, L-glutamine, pyridoxine and folic acid, to standard rehabilitation.

Methods. This prospective, open-label, controlled study enrolled 120 patients (69 women, 51 men; aged 18–58 years) with PCS after bilateral community-acquired COVID-19 pneumonia (Khorezm region, Uzbekistan; hospitalised in July–August 2020). The main group (n = 69; 40 women, 29 men) received Glycevit for 30 days in addition to standard therapy, and the comparison group (n = 51; 29 women, 22 men) received standard therapy alone; the groups were comparable by sex (p = 0.903). Symptoms, HADS, SF-36, COMPASS-31, the Epworth Sleepiness Scale, CFIS, FAS, MFI-20, C-reactive protein (CRP) and interleukin-6 (IL-6) were assessed before and after treatment; fibrinogen, 25(OH) vitamin D and EEG were assessed at baseline. Between-group differences were analysed by ANCOVA adjusted for baseline values; sex was included as a covariate and as a group × sex interaction term.

Results. The leading manifestations were cognitive complaints (“brain fog”, 69.2%), autonomic dysfunction (60.0%), sleep disturbance (60.0%) and headache (56.7%). CRP >5 mg/L was found in 89.2% and vitamin D deficiency (<20 ng/mL) in 88.3% of patients. Men more often had brain fog (80.4% vs. 60.9%; p = 0.022) and clinically significant anxiety (47.1% vs. 26.1%), whereas women more often had subclinical anxiety (46.4% vs. 19.6%; p = 0.007) and increased theta activity on EEG





(72.5% vs. 51.0%; $p = 0.045$); mean scale scores and biomarkers did not differ by sex. After adjustment for baseline values, Glycevit was associated with a greater reduction in IL-6 (-5.2 pg/mL; $p < 0.001$) and CFIS score (-12.9 points; $p = 0.002$); CFIS normalised in 55.1% vs. 9.8% of patients (number needed to treat 2.2). Quality of life also improved more (SF-36, $+3.1$ points; $p = 0.001$). Fatigue (MFI-20), anxiety and depression did not differ between groups. The effects on CFIS and IL-6 did not depend on sex (group $\times$ sex interaction $p = 0.681$ and $p = 0.268$).

Conclusion. PCS shows sex-specific features: brain fog and clinical anxiety predominate in men, and subclinical anxiety and EEG theta activity in women. Adding Glycevit to standard therapy was associated with a greater reduction in the impact of fatigue on daily functioning and in IL-6 in both sexes. These findings require confirmation in a randomised controlled trial.

Keywords: Post-acute COVID-19 syndrome; long COVID; sex characteristics; cognitive dysfunction; fatigue; interleukin-6; vitamin D deficiency; gamma-aminobutyric acid.

Introduction

Abbreviations

ANCOVA - analysis of covariance; CFIS - Cognitive, Physical and Social Fatigue Impact Scale; CG - comparison group; CI - confidence interval; COMPASS-31 - Composite Autonomic Symptom Score 31; CRP - C-reactive protein; EEG - electroencephalography; FAS - Fatigue Assessment Scale; GABA - gamma-aminobutyric acid; HADS - Hospital Anxiety and Depression Scale; IL-6 - interleukin-6; MFI-20 - Multidimensional Fatigue Inventory; MG - main group; NNT - number needed to treat; OR - odds ratio; PCS - post-COVID syndrome; SF-36 - 36-Item Short Form Health Survey.

1. Introduction

Post-COVID syndrome (PCS, long COVID) remains one of the major medical and social consequences of the COVID-19 pandemic. According to the World Health Organization (WHO), it is a condition in which symptoms persist or appear 3 months after SARS-CoV-2 infection, last for at least 2 months and cannot be explained by an alternative diagnosis [1]. In 2024, the US National Academies of Sciences, Engineering, and Medicine proposed a broader definition of long COVID as an infection-associated chronic condition that lasts for at least 3 months and affects one or more organ systems [2]. Hundreds of millions of people worldwide are estimated to have experienced PCS, which reduces work capacity and quality of life in people of working age [3,4].

The clinical spectrum of PCS includes more than 200 symptoms, but neurological and neuropsychiatric manifestations predominate: fatigue, cognitive impairment (“brain fog”), sleep disturbances, headache, autonomic dysfunction, anxiety and depression [4,5]. In a population-based study of more than 100,000 participants, objective cognitive deficits were detected even after symptom resolution and were greatest in those with persistent symptoms and in those who had had severe COVID-19 [6]. Moderate-to-severe autonomic dysfunction (COMPASS-31 >20 points) was reported by 66% of 2,314 surveyed patients with PCS, irrespective of the severity of the acute illness [7].





The pathogenesis of PCS is multifactorial. Proposed mechanisms include persistence of viral antigens, autoimmune reactions, reactivation of latent viruses, endothelial dysfunction with microthrombosis and imbalance of the autonomic nervous system [3,5]. Chronic systemic inflammation is considered particularly important: in patients with PCS, levels of IL-1 β , IL-6 and tumour necrosis factor remain elevated for months, forming a self-sustaining cytokine loop [8]. Low 25(OH) vitamin D levels are associated with the development of PCS in COVID-19 survivors [9].

The risk and pattern of PCS depend on sex. A meta-analysis identified female sex as one of the most consistent risk factors for PCS [10]. In the RECOVER cohort (12,276 adults), the risk in women was 31% higher (risk ratio 1.31; 95% CI 1.06–1.62), most markedly at the age of 40–54 years [11]. A 2025 meta-analysis showed that fatigue, headache, brain fog, depression and anosmia were 1.4–1.6 times more frequent in women [12]. These differences are thought to reflect sex-specific features of the immune response and hormonal regulation [3]. However, most studies have been conducted in the United States and Europe, and sex differences in symptom patterns and inflammatory burden among patients in Central Asia, including the Khorezm region of Uzbekistan, remain virtually unexplored.

No approved disease-modifying therapy for PCS is available yet; treatment remains symptomatic and rehabilitative [4]. Multicomponent neurometabolic products that combine amino acids and vitamins are therefore of interest. One tablet of Glycevit contains GABA 125 mg, glycine 75 mg, L-glutamine 100 mg, pyridoxine hydrochloride (vitamin B₆) 0.5 mg and folic acid 50 μ g [13]. GABA is the principal inhibitory neurotransmitter of the central nervous system, although the penetration of orally administered GABA across the blood–brain barrier is limited and its central mechanisms of action remain debated [14]. Glycine is an inhibitory neurotransmitter and an NMDA receptor co-agonist, and L-glutamine is a precursor of glutamate and GABA and a cellular energy source. Vitamin B₆ (as pyridoxal 5'-phosphate) is a cofactor of GABA synthesis via glutamate decarboxylase and, together with folic acid, is involved in neurotransmitter synthesis and homocysteine metabolism. Thus, the components of the product may act on neurotransmitter imbalance and neuronal energy deficiency, which are among the mechanisms underlying the neurological manifestations of PCS. We found no clinical data on the use of Glycevit in PCS, including sex-stratified data, which prompted the present study.

The aim of this study was to characterise the clinical, epidemiological and sex-specific features of PCS in patients who had recovered from COVID-19 pneumonia and to evaluate the effectiveness of adding Glycevit to comprehensive therapy using clinical, psychometric and laboratory outcomes, including the dependence of the treatment effect on patient sex.

2. Materials and Methods

2.1. Study design and participants

This was a prospective, open-label, controlled study. It enrolled 120 patients aged 18–58 years who were hospitalised in July–August 2020 with a diagnosis of “COVID-19, bilateral community-acquired pneumonia, respiratory failure grade I–II” (Urgench, Khorezm region, Uzbekistan) and followed up after discharge. The study was performed as part of the second author’s dissertation research at Bukhara State Medical Institute named after Abu Ali ibn Sino.



**Inclusion criteria were:**

- age 18–60 years;
- COVID-19 with bilateral pneumonia confirmed by polymerase chain reaction and chest computed tomography;
- at least one neurological or asthenic symptom persisting for ≥ 12 weeks from disease onset and not explained by an alternative diagnosis (WHO criteria) [1];
- MFI-20 “general fatigue” subscale score ≥ 12 points;
- written informed consent.

Exclusion criteria were:

- neurological disease before COVID-19 (stroke, dementia, epilepsy, multiple sclerosis, traumatic brain injury with residual deficits);
- psychiatric disorders, alcohol or substance abuse;
- decompensated somatic disease, diabetes mellitus with polyneuropathy, hypothyroidism, anaemia, cancer;
- pregnancy or lactation;
- use of nootropics, antidepressants or vitamin supplements within the preceding month;
- intolerance to any component of Glycevit.

2.2. Ethics statement

The study was conducted in accordance with the Declaration of Helsinki and was approved by the Ethics Committee of Bukhara State Medical Institute named after Abu Ali ibn Sino (Protocol No. 3, dated 5 May 2020). All patients provided written informed consent before enrolment.

2.3. Groups and interventions

Patients were allocated to two groups. The main group (MG, $n = 69$) included 40 women (58.0%) and 29 men (42.0%), and the comparison group (CG, $n = 51$) included 29 women (56.9%) and 22 men (43.1%); the groups were comparable by sex ($\chi^2 = 0.015$; $p = 0.903$; Cramér's $V = 0.01$). The groups also did not differ in age (43.8 ± 1.3 vs. 40.1 ± 1.5 years; $p = 0.067$), place of residence, month of hospitalisation, number of symptoms, HADS, SF-36, FAS and MFI-20 scores, inflammatory markers, vitamin D or EEG findings. Baseline differences were found only for CFIS (higher in the MG; $p = 0.003$) and the Epworth Sleepiness Scale (lower in the MG; $p = 0.040$), and the length of hospital stay was borderline longer in the MG (8.70 ± 0.55 vs. 6.86 ± 0.49 days; $p = 0.050$); these differences were accounted for in the covariance and multivariable analyses.

Both groups received 30 days of standard rehabilitation therapy for PCS in accordance with current recommendations [4,15,16]: patient education and energy management (pacing, alternation of activity and rest, monitoring for post-exertional symptom exacerbation); breathing exercises (diaphragmatic breathing and prolonged exhalation, 10–15 min twice daily); graded low-intensity aerobic and stretching exercise; cognitive rehabilitation (training of attention, memory and executive functions, compensatory strategies); sleep hygiene advice (melatonin 3 mg at night for insomnia, if indicated); psychological support (psychoeducation and elements of cognitive behavioural therapy; psychiatric consultation and, if indicated, selective serotonin reuptake inhibitors for HADS ≥ 11





points); symptomatic treatment (paracetamol or non-steroidal anti-inflammatory drugs for headache, water-salt regimen for orthostatic symptoms); and correction of vitamin D deficiency (cholecalciferol 2,000 IU/day for 25(OH)D <20 ng/mL).

In addition to standard therapy, the MG received Glycevit (Bless Laboratories (Pvt.) Ltd., Pakistan; registered in the Republic of Uzbekistan as a dietary supplement, one tablet three times daily with meals for 30 days [13]. The daily dose (3 tablets) provided GABA 375 mg, glycine 225 mg, L-glutamine 300 mg, pyridoxine hydrochloride 1.5 mg and folic acid 150 µg. Glycevit does not contain vitamin D. The CG received standard therapy alone. Patients were assessed before treatment and after completion of the 30-day course. Patient sex was recorded from medical records.

2.4. Clinical and psychometric assessment

The neurological examination included recording of eight symptoms (present/absent): fatigue (asthenia), cognitive complaints (brain fog), headache, autonomic disturbances, sleep disturbances, restricted movement, sensory disturbances and cranial nerve involvement. The following scales were used:

- HADS [17] - anxiety and depression subscales, 0–21 points each: 0–7, normal; 8–10, subclinical; ≥11, clinically significant;
- SF-36 [18] - quality of life (0–100 points; higher scores indicate better health);
- COMPASS-31 [19] - autonomic symptoms (0–100): 0–10, normal; 11–20, mild; 21–40, moderate dysfunction; >40, severe dysfunction;
- Epworth Sleepiness Scale [20] (0–24): 0–9, normal; 10–12, mild; 13–15, moderate; 16–24, severe sleepiness;
- FAS [21] - fatigue (10–50; ≥22, fatigue; ≥35, severe fatigue);
- MFI-20 [22] - five fatigue subscales (general fatigue, physical fatigue, mental fatigue, reduced motivation and reduced activity), 4–20 points each, total score 20–100;
- CFIS - a scale assessing the impact of fatigue on cognitive, physical and psychosocial functioning, based on the Fatigue Impact Scale (40 items, 0–160 points) [23]. Scores were categorised as normal (≤40), mild (41–80), moderate (81–120) and severe (>120) impact. CFIS reflects the self-reported impact of fatigue on daily functioning rather than objective cognitive performance.

2.5. Laboratory and instrumental methods

Fasting blood samples were collected in the morning. CRP was measured by immunoturbidimetry (reference ≤5 mg/L), IL-6 by enzyme-linked immunosorbent assay (≤7 pg/mL), fibrinogen by the Clauss method (2–4 g/L) and 25(OH) vitamin D by chemiluminescent immunoassay (deficiency <20 ng/mL; severe deficiency <12 ng/mL). CRP and IL-6 were measured before and after treatment, and fibrinogen and vitamin D at baseline. EEG was recorded before treatment during quiet wakefulness using the international 10–20 system. Alpha-rhythm desynchronisation, increased beta activity and increased theta rhythm (none/mild/marked) and the presence of delta activity were assessed visually.

2.6. Statistical analysis

Normality was assessed with the Shapiro–Wilk test; most variables were not normally distributed. Data are presented as mean ± standard error of the mean (SEM) or n (%). Independent samples were



compared with the Mann–Whitney U test, within-group changes with the Wilcoxon signed-rank test, frequencies with Pearson's χ^2 test or Fisher's exact test, and changes in symptom frequency with McNemar's test. Between-group differences after treatment were assessed by analysis of covariance (ANCOVA) with the baseline value as a covariate and the Holm correction for multiple comparisons; partial η^2 was used as the effect size. The proportions of patients reaching predefined response criteria were compared with relative risks and the number needed to treat (NNT). The dependence of the treatment effect on sex was tested in linear models of change ($\Delta = \text{group} \times \text{sex} + \text{baseline value}$). Associations were assessed using Spearman's rank correlation coefficient (ρ) with the Benjamini–Hochberg correction. Outcome predictors were identified using multiple linear and logistic regression adjusted for group, age, sex, place of residence, length of hospital stay, baseline IL-6, vitamin D, fibrinogen and the baseline value of the respective outcome; logistic model calibration was assessed with the Hosmer–Lemeshow test and discrimination with the area under the ROC curve (AUC; 95% CI by bootstrap, 1,000 replicates). Statistical significance was set at $p < 0.05$. Analyses were performed in Python (SciPy, statsmodels).

3. Results

3.1. Clinical and epidemiological characteristics

Women (57.5%), patients aged 50–58 years (35.0%) and urban residents (80.0%) predominated. The mean age was 42.2 ± 1.0 years, and the mean length of hospital stay was 7.9 ± 0.4 days. Women and men did not differ in age, place of residence or length of stay (Table 1). Men were more often hospitalised in July and women in August 2020 ($p = 0.019$).

Table 1. Clinical and epidemiological characteristics of patients by sex, n (%)

Characteristic	Total (n = 120)	Women (n = 69)	Men (n = 51)	p
Age, years (mean $\pm$ SEM)	42.2 ± 1.0	42.6 ± 1.3	41.7 ± 1.5	0.636
18–29 years	19 (15.8)	12 (17.4)	7 (13.7)	0.868
30–39 years	29 (24.2)	15 (21.7)	14 (27.5)	
40–49 years	30 (25.0)	17 (24.6)	13 (25.5)	
50–58 years	42 (35.0)	25 (36.2)	17 (33.3)	
Urban (Urgench)	96 (80.0)	57 (82.6)	39 (76.5)	0.406
District/rural	24 (20.0)	12 (17.4)	12 (23.5)	
Hospitalised in July 2020	70 (58.3)	34 (49.3)	36 (70.6)	0.019
Hospitalised in August 2020	50 (41.7)	35 (50.7)	15 (29.4)	
Length of stay, days (mean $\pm$ SEM)	7.9 ± 0.4	7.7 ± 0.5	8.2 ± 0.7	0.842
PCS symptoms per patient (mean $\pm$ SEM)	4.4 ± 0.1	4.5 ± 0.1	4.3 ± 0.1	0.509

Note: Length of stay, n = 119 (one record with a date error was excluded). p, Mann–Whitney U test or χ^2 test. PCS, post-COVID syndrome; SEM, standard error of the mean.

As shown in Table 1, more than half of the patients (60.0%) were older than 40 years, and the smallest age group was 18–29 years (15.8%). The age structure was almost identical in women and men: the proportion of patients aged 50–58 years was 36.2% and 33.3%, respectively ($p = 0.868$). Four out of five patients lived in Urgench; rural residents were slightly more common among men (23.5% vs. 17.4%), but the difference was not significant. The only significant difference concerned the timing of hospitalisation: 70.6% of men were admitted in July, whereas women were evenly distributed between the two months. Length of stay and the number of PCS symptoms (4–5 per patient on average) did not depend on sex. Consequently, the sex differences described below cannot be explained by age, place of residence or severity of the acute illness as assessed by length of hospital stay.

The laboratory profile indicated persistent low-grade systemic inflammation and vitamin D deficiency. CRP was 11.04 ± 0.39 mg/L (>5 mg/L in 107 patients, 89.2%), IL-6 was 22.12 ± 0.89 pg/mL (>7 pg/mL in all patients) and fibrinogen was 4.30 ± 0.07 g/L (>4 g/L in 73 patients, 60.8%). The 25(OH) vitamin D level was 14.74 ± 0.37 ng/mL: deficiency (<20 ng/mL) was found in 106 (88.3%) and severe deficiency (<12 ng/mL) in 39 (32.5%) patients.

The severity of PCS was high. Severe autonomic dysfunction (COMPASS-31 >40 points) was found in 63.3% and moderate dysfunction in 33.3% of patients; no patient had a normal score. Pathological daytime sleepiness (Epworth ≥ 10) was found in 82.5% of patients (mild, 29.2%; moderate, 28.3%; severe, 25.0%). None of the patients had a normal CFIS score; the impact of fatigue on daily functioning was mild in 31.7%, moderate in 41.7% and severe in 26.7%. Anxiety (HADS ≥ 8) was found in 70.0% (clinical level, 35.0%) and depression in 67.5% (clinical level, 42.5%) of patients. The total MFI-20 score was 82.75 ± 0.51 points.

3.2. Sex-specific features of post-COVID syndrome

Because the treatment groups were balanced by sex ($p = 0.903$), the sex differences described below are independent of treatment group allocation. Cognitive complaints, autonomic dysfunction and sleep disturbances were the leading manifestations of PCS (Table 2). Most patients had a combination of 4–5 symptoms. Brain fog was the only symptom with a significant sex difference: it was 1.3 times more frequent in men (80.4% vs. 60.9%; $p = 0.022$; OR for women 0.39; 95% CI 0.17–0.90). The frequencies of the remaining seven symptoms were almost identical in women and men (differences <5 percentage points; all $p > 0.6$).

Table 2. Frequency of clinical manifestations of post-COVID syndrome in women and men before treatment, n (%)

Symptom	Total (n = 120), % [95% CI]	Women (n = 69)	Men (n = 51)	p
Cognitive complaints (brain fog)	69.2 [60.4–76.7]	42 (60.9)	41 (80.4)	0.022
Autonomic disturbances	60.0 [51.1–68.3]	42 (60.9)	30 (58.8)	0.821
Sleep disturbances	60.0 [51.1–68.3]	41 (59.4)	31 (60.8)	0.880
Headache	56.7 [47.7–65.2]	38 (55.1)	30 (58.8)	0.682

Symptom	Total (n = 120), % [95% CI]	Women (n = 69)	Men (n = 51)	p
Sensory disturbances	51.7 [42.8–60.4]	36 (52.2)	26 (51.0)	0.897
Restricted movement	50.8 [42.0–59.6]	34 (49.3)	27 (52.9)	0.691
Fatigue (asthenia)	45.8 [37.2–54.7]	33 (47.8)	22 (43.1)	0.610
Cranial nerve involvement	45.8 [37.2–54.7]	32 (46.4)	23 (45.1)	0.889

Note: 95% CI, Wilson score method; p, Pearson's χ^2 test. CI, confidence interval.

The frequency of the eight symptoms ranged from 46% to 69%. Brain fog ranked first in men (80.4%), whereas in women it shared first place with autonomic disturbances (60.9%). The width of the 95% CIs (approximately ± 8 percentage points) indicates that a larger sample would be required to detect weaker sex differences.

Mean scale scores and laboratory parameters did not differ between women and men (Table 3; all $p > 0.1$; all $q > 0.6$ after the Benjamini–Hochberg correction). However, differences were found in the distribution of severity categories (Table 4): clinically significant anxiety was almost twice as frequent in men (47.1% vs. 26.1%), whereas subclinical anxiety predominated in women (46.4% vs. 19.6%; $p = 0.007$). Increased theta rhythm on EEG was more frequent in women (72.5% vs. 51.0%; $p = 0.045$). No sex differences were found in the severity of depression, autonomic dysfunction, daytime sleepiness, CFIS categories or other EEG features. CRP was slightly higher (11.7 vs. 10.6 mg/L) and IL-6 slightly lower (20.9 vs. 23.0 pg/mL) in men, but the differences were not significant. Vitamin D deficiency was found in 89.9% of women and 86.3% of men.

Table 3. Rating scale scores and laboratory parameters in women and men before treatment (mean $\pm$ SEM)

Parameter	Women (n = 69)	Men (n = 51)	p
CFIS, points	100.6 $\pm$ 3.4	95.8 $\pm$ 3.4	0.409
Epworth Sleepiness Scale, points	13.1 $\pm$ 0.4	12.5 $\pm$ 0.4	0.199
COMPASS-31, points	48.0 $\pm$ 2.0	48.1 $\pm$ 2.5	0.953
SF-36, points	45.8 $\pm$ 1.7	49.1 $\pm$ 1.9	0.219
MFI-20, total score	82.7 $\pm$ 0.6	82.8 $\pm$ 0.8	0.708
FAS, points	34.5 $\pm$ 0.9	34.3 $\pm$ 1.1	0.962
HADS anxiety, points	8.8 $\pm$ 0.3	9.6 $\pm$ 0.6	0.281
HADS depression, points	10.1 $\pm$ 0.4	9.6 $\pm$ 0.5	0.323
CRP, mg/L	10.6 $\pm$ 0.5	11.7 $\pm$ 0.6	0.170
IL-6, pg/mL	23.0 $\pm$ 1.2	20.9 $\pm$ 1.4	0.244
Fibrinogen, g/L	4.24 $\pm$ 0.09	4.38 $\pm$ 0.09	0.347
Vitamin D, ng/mL	14.6 $\pm$ 0.5	14.9 $\pm$ 0.6	0.652

Note: p, Mann–Whitney U test. CFIS, Cognitive, Physical and Social Fatigue Impact Scale; COMPASS-31, Composite Autonomic Symptom Score 31; CRP, C-reactive protein; FAS, Fatigue Assessment Scale; HADS, Hospital Anxiety and Depression Scale; IL-6, interleukin-6; MFI-20,



Table 4. Severity categories and EEG features in women and men before treatment, n (%)

Parameter	Category	Women (n = 69)	Men (n = 51)	p
HADS anxiety	Normal	19 (27.5)	17 (33.3)	0.007
	Subclinical	32 (46.4)	10 (19.6)	
	Clinical	18 (26.1)	24 (47.1)	
HADS depression	Normal	23 (33.3)	16 (31.4)	0.359
	Subclinical	14 (20.3)	16 (31.4)	
	Clinical	32 (46.4)	19 (37.3)	
COMPASS-31	Mild	2 (2.9)	2 (3.9)	0.953
	Moderate	23 (33.3)	17 (33.3)	
	Severe	44 (63.8)	32 (62.7)	
CFIS	Mild	22 (31.9)	16 (31.4)	0.476
	Moderate	26 (37.7)	24 (47.1)	
	Severe	21 (30.4)	11 (21.6)	
EEG: increased theta rhythm	None	19 (27.5)	25 (49.0)	0.045
	Mild	33 (47.8)	19 (37.3)	
	Marked	17 (24.6)	7 (13.7)	
EEG: delta activity	Absent	53 (76.8)	37 (72.5)	0.594
	Present	16 (23.2)	14 (27.5)	

Note: p, Pearson's χ^2 test. Abbreviations as in Table 3.

3.3. Effectiveness of conservative therapy

In both groups, all rating scale scores and laboratory parameters improved significantly after treatment (Wilcoxon signed-rank test, $p < 0.001$ for all). After adjustment for baseline values, the MG showed an advantage for IL-6, CFIS, SF-36, the Epworth Sleepiness Scale, COMPASS-31, FAS and CRP (Table 5). After the Holm correction for multiple comparisons, the differences in IL-6, CFIS and SF-36 remained significant.

The largest between-group differences were observed for IL-6 and CFIS. IL-6 decreased 3.7-fold (by 72.7%) in the MG and 2.0-fold (by 51.0%) in the CG (partial $\eta^2 = 0.26$, large effect); after treatment, the mean level in the MG (5.9 pg/mL) returned to within the reference range, whereas in the CG (11.2 pg/mL) it remained elevated. The CFIS score decreased by 58.9 points (2.3-fold) in the MG and by 32.2 points in the CG. Importantly, the MG had a higher baseline CFIS score (104.7 vs. 90.1) but a lower post-treatment score (45.8 vs. 58.0; $p < 0.001$); that is, the groups “swapped places”. The group $\times$ baseline CFIS interaction was not significant ($p = 0.304$); therefore, the effect cannot be explained by regression to the mean.



Table 5. Changes in outcomes in the main group (MG, n = 69) and comparison group (CG, n = 51), mean $\pm$ SEM

Parameter	MG before	MG after	CG before	CG after	Adjusted difference MG–CG [95% CI]	p	η^2
IL-6, pg/mL	21.63 $\pm$ 1.20	5.91 $\pm$ 0.37	22.79 $\pm$ 1.33	11.16 $\pm$ 0.80	-5.23 [-6.83; -3.62]	<0.001*	0.26
CFIS, points	104.74 $\pm$ 3.16	45.83 $\pm$ 3.08	90.14 $\pm$ 3.44	57.96 $\pm$ 2.02	-12.94 [-21.15; -4.73]	0.002*	0.08
SF-36, points	47.49 $\pm$ 1.66	78.25 $\pm$ 0.65	46.90 $\pm$ 2.03	75.16 $\pm$ 0.62	+3.10 [1.27; 4.94]	0.001*	0.09
Epworth, points	12.38 $\pm$ 0.35	9.06 $\pm$ 0.25	13.49 $\pm$ 0.41	10.20 $\pm$ 0.30	-1.01 [-1.78; -0.23]	0.011	0.05
COMPASS-31, points	50.52 $\pm$ 2.07	23.06 $\pm$ 1.06	44.61 $\pm$ 2.29	26.47 $\pm$ 1.31	-4.14 [-7.43; -0.86]	0.014	0.05
FAS, points	34.03 $\pm$ 0.94	19.95 $\pm$ 0.42	34.98 $\pm$ 0.97	22.41 $\pm$ 0.91	-2.40 [-4.26; -0.53]	0.012	0.05
CRP, mg/L	10.56 $\pm$ 0.51	5.83 $\pm$ 0.30	11.69 $\pm$ 0.59	7.29 $\pm$ 0.50	-1.16 [-2.18; -0.14]	0.026	0.04
HADS anxiety, points	9.23 $\pm$ 0.38	4.67 $\pm$ 0.29	8.94 $\pm$ 0.47	5.29 $\pm$ 0.37	-0.66 [-1.59; 0.27]	0.162	0.02
HADS depression, points	9.72 $\pm$ 0.39	4.57 $\pm$ 0.29	10.10 $\pm$ 0.53	4.49 $\pm$ 0.41	+0.10 [-0.87; 1.08]	0.839	<0.01
MFI-20, total score	82.71 $\pm$ 0.70	37.23 $\pm$ 0.64	82.80 $\pm$ 0.73	37.92 $\pm$ 0.70	-0.67 [-2.54; 1.19]	0.475	<0.01

Note: Adjusted difference, between-group difference in post-treatment means adjusted for the baseline value (ANCOVA; MG minus CG); p, ANCOVA; *, significant after the Holm correction; η^2 , partial η^2 . Within-group changes were significant for all parameters (Wilcoxon signed-rank test, $p < 0.001$). FAS after treatment in the MG, n = 65. Abbreviations as in Table 3.

For SF-36 and the Epworth Sleepiness Scale, improvement was similar in both groups (+64.8% and +60.2%; -26.8% and -24.4%), but after adjustment for baseline values the MG achieved better final scores (small-to-medium effect, $\eta^2 = 0.05$ –0.09); the difference in Epworth scores lost significance after the Holm correction ($p = 0.077$). The COMPASS-31 score decreased by 54.4% in the MG and by 40.7% in the CG, and the FAS score by 41.4% and 35.9%, respectively; these differences were significant but did not survive correction for multiple comparisons and should be regarded as trends. CRP decreased by 44.8% and 37.6% ($p = 0.026$; $p = 0.105$ after the Holm correction), and anxiety by 49.5% and 40.9% ($p = 0.162$). Depression (-53.1% and -55.5%) and total fatigue on MFI-20 (-55.0% and -54.2%) decreased almost equally in both groups.

After treatment, no patient in the MG had severe autonomic dysfunction (normal COMPASS-31 score in 5.8% and mild symptoms in 50.7%), whereas in the CG severe dysfunction decreased from 54.9% to 7.8%. The proportion of patients without pathological sleepiness increased from 20.3% to 56.5% in the MG and from 13.7% to 25.5% in the CG ($\chi^2 = 14.89$; $p < 0.001$). The rate of regression of individual neurological symptoms did not differ between groups (Fisher's exact test, all $p > 0.08$);



complete regression of neurological symptoms was observed in 7 (10.1%) patients in the MG and 2 (3.9%) in the CG ($p = 0.298$).

The clinical relevance of the treatment effect was assessed using predefined response criteria (Table 6). Normalisation of CFIS was 5.6 times more frequent in the MG (55.1% vs. 9.8%; NNT 2.2), as were a $\geq 50\%$ reduction in CFIS (71.0% vs. 25.5%; NNT 2.2), normalisation of IL-6 (79.7% vs. 45.1%; NNT 2.9) and normalisation of CRP (62.3% vs. 37.3%; NNT 4.0). The groups did not differ in the proportion of patients with a $\geq 50\%$ reduction in MFI-20, absence of clinical fatigue on FAS, normalisation of anxiety and depression, or complete regression of neurological symptoms.

Table 6. Proportion of patients achieving clinically relevant response criteria, n (%)

Response criterion	MG (n = 69)	CG (n = 51)	Difference, % (95% CI)	RR	NNT	p
CFIS normalisation (≤ 40 points)	38 (55.1)	5 (9.8)	45.3 (31.0; 59.6)	5.62	2.2	<0.001
$\geq 50\%$ reduction in CFIS	49 (71.0)	13 (25.5)	45.5 (29.5; 61.6)	2.79	2.2	<0.001
$\geq 50\%$ reduction in MFI-20	54 (78.3)	37 (72.5)	5.7 (-9.9; 21.4)	1.08	17.5	0.470
FAS <22 points (no clinical fatigue)	33 (50.8)	25 (49.0)	1.7 (-16.6; 20.1)	1.04	57.2	0.852
HADS anxiety ≤ 7 points	59 (85.5)	36 (73.5)	12.0 (-2.9; 26.9)	1.16	8.3	0.104
HADS depression ≤ 7 points	58 (84.1)	38 (74.5)	9.5 (-5.2; 24.3)	1.13	10.5	0.196
IL-6 ≤ 7 pg/mL	55 (79.7)	23 (45.1)	34.6 (18.0; 51.2)	1.77	2.9	<0.001
CRP ≤ 5 mg/L	43 (62.3)	19 (37.3)	25.1 (7.5; 42.6)	1.67	4.0	0.007
Complete regression of neurological symptoms	7 (10.1)	2 (3.9)	6.2 (-2.7; 15.1)	2.59	16.1	0.298

Note: RR, relative risk (probability of reaching the criterion in the MG relative to the CG); NNT, number needed to treat to achieve one additional response; p, Pearson's χ^2 test or Fisher's exact test. FAS in the MG, n = 65; HADS anxiety in the CG, n = 49. Abbreviations as in Tables 3 and 5.

3.4. Effect of sex on treatment response

The sex balance of the groups made it possible to assess whether the treatment effect depended on sex (Table 7). The treatment effect on fatigue (CFIS, FAS, MFI-20), autonomic dysfunction, sleepiness and inflammatory markers was the same in women and men (group $\times$ sex interaction, all $p > 0.2$). For psychoemotional outcomes, however, the interaction was significant: in the MG, quality of life improved more in women (SF-36 +35.1 vs. +24.8 points; $p = 0.007$; interaction $p = 0.004$), and anxiety tended to decrease more in men (-5.6 vs. -3.8 points); in the CG, depression decreased more in women (HADS depression -7.1 vs. -3.6 points; $p = 0.006$); the interaction p-values for HADS anxiety and depression were <0.001. Thus, the effect of Glycevit on CFIS and IL-6 did not depend on sex, whereas psychoemotional outcomes may differ by sex.



Table 7. Changes in outcomes (Δ , after minus before; mean) in women and men by treatment group

Parameter, Δ	MG: women (n = 40)	MG: men (n = 29)	p	CG: women (n = 29)	CG: men (n = 22)	p	p (group $\times$ sex)
Number of symptoms	-0.8	-0.6	0.637	-1.1	-0.8	0.577	0.790
HADS anxiety	-3.8	-5.6	0.109	-4.2	-3.2	0.367	<0.001
HADS depression	-5.0	-5.4	0.586	-7.1	-3.6	0.006	<0.001
SF-36	+35.1	+24.8	0.007	+27.9	+28.7	0.783	0.004
COMPASS-31	-26.9	-28.3	0.469	-17.8	-18.5	0.962	0.916
Epworth	-3.4	-3.2	1.000	-3.9	-2.5	0.114	0.787
CRP, mg/L	-4.5	-5.0	0.385	-4.3	-4.5	0.827	0.698
IL-6, pg/mL	-14.9	-16.9	0.319	-14.7	-7.6	0.064	0.268
CFIS	-61.4	-55.5	0.395	-34.0	-29.7	0.594	0.681
FAS	-14.6	-13.1	0.413	-10.7	-15.1	0.054	0.516
MFI-20, total score	-44.9	-46.3	0.352	-44.3	-45.6	0.493	0.680

Note: p, Mann–Whitney U test (women vs. men within a group); p (group $\times$ sex), interaction term in the linear model Δ = group $\times$ sex + baseline value. Abbreviations as in Tables 3 and 5.

3.5. Correlations and predictors of outcome

Baseline inflammatory markers and vitamin D did not correlate with the severity of fatigue (MFI-20, FAS), fatigue impact (CFIS) or autonomic dysfunction (COMPASS-31). After correction for multiple comparisons, only the moderate correlation between HADS anxiety and depression remained significant ($\rho = 0.35$; $p < 0.001$; $q = 0.010$). Among weak, uncorrected associations, CRP correlated positively with sleepiness ($\rho = 0.25$; $p = 0.007$), and fibrinogen negatively ($\rho = -0.23$; $p = 0.013$). The treatment-related decreases in IL-6 and CRP were not significantly correlated with the magnitude of clinical improvement on the scales.

In multivariable models that included sex (Table 8), baseline IL-6 was an independent predictor of the post-treatment CFIS score along with group allocation: each 1 pg/mL increase in baseline IL-6 was associated with a 0.62-point higher post-treatment CFIS score (95% CI 0.21–1.02; $p = 0.003$). In the logistic model, each 1 pg/mL increase in IL-6 reduced the odds of CFIS normalisation by 6.1% (OR 0.939; 95% CI 0.894–0.986; $p = 0.012$), whereas allocation to the MG increased them (OR 13.9; 95% CI 4.2–46.0; $p < 0.001$). Sex was not an independent predictor of either the post-treatment CFIS score ($p = 0.464$) or CFIS normalisation ($p = 0.326$). The model was well calibrated (Hosmer–Lemeshow $p = 0.137$), with an AUC of 0.83. On its own, baseline IL-6 had only moderate predictive value for CFIS normalisation (AUC 0.634; 95% CI 0.525–0.736; cut-off ≤ 21.5 pg/mL; sensitivity 62.8%, specificity 60.5%).

A lower baseline vitamin D level was independently associated with more severe residual fatigue: each 1 ng/mL increase in vitamin D was associated with a 0.32-point lower post-treatment MFI-20 score (95% CI 0.09–0.55; $p = 0.007$); urban residence was also associated with a lower final MFI-20 score ($B = -2.86$; $p = 0.019$). Accordingly, the reduction in MFI-20 during treatment was proportional to the baseline vitamin D level (median reduction 42, 46 and 49 points in patients with severe

deficiency, deficiency and insufficiency, respectively; Kruskal–Wallis $p = 0.004$). For post-treatment SF-36, allocation to the MG ($B = +2.88$; $p = 0.003$) and female sex ($B = +2.38$; $p = 0.012$) were independent factors.

Table 8. Independent predictors of treatment outcome (multivariable regression)

Outcome (model)	Predictor	B or OR	95% CI	p
Post-treatment CFIS (linear; $R^2 = 0.18$)	Group (MG)	$B = -11.17$	$-19.56; -2.78$	0.010
	Baseline IL-6, pg/mL	$B = 0.62$	$0.21; 1.02$	0.003
	Baseline CFIS, points	$B = 0.08$	$-0.07; 0.24$	0.286
	Age, years	$B = -0.15$	$-0.52; 0.21$	0.401
	Sex (female)	$B = -2.94$	$-10.84; 4.97$	0.464
CFIS normalisation (logistic; AUC = 0.83)	Group (MG)	OR = 13.9	4.20; 46.00	<0.001
	Baseline IL-6, pg/mL	OR = 0.939	0.894; 0.986	0.012
	Baseline CFIS, points	OR = 0.985	0.966; 1.004	0.126
	Sex (female)	OR = 1.60	0.63; 4.09	0.326
Post-treatment MFI-20 (linear; $R^2 = 0.16$)	Vitamin D, ng/mL	$B = -0.32$	$-0.55; -0.09$	0.007
	Urban residence	$B = -2.86$	$-5.24; -0.48$	0.019
	Baseline MFI-20, points	$B = 0.26$	$0.09; 0.43$	0.004
	Group (MG)	$B = -0.88$	$-2.77; 1.00$	0.356
Post-treatment SF-36 (linear; $R^2 = 0.19$)	Group (MG)	$B = +2.88$	$1.00; 4.76$	0.003
	Sex (female)	$B = +2.38$	$0.54; 4.22$	0.012

Note: B, regression coefficient; OR, odds ratio. Models were adjusted for group, age, sex, place of residence, length of hospital stay, baseline IL-6, vitamin D, fibrinogen (HADS depression instead of fibrinogen in the SF-36 model) and the baseline value of the respective outcome; the main and significant predictors are shown; $n = 119$. Abbreviations as in Tables 3 and 5.

4. Discussion

In our sample, PCS manifested predominantly as cognitive complaints, autonomic dysfunction and sleep disturbances, consistent with reviews and large cohort studies [4–7]. The proportion of patients with moderate-to-severe autonomic dysfunction on COMPASS-31 (96.7%) exceeded the 66% reported in the literature [7], probably because our study included only hospitalised patients with pneumonia. The high prevalence of elevated CRP and IL-6 indicates persistent systemic inflammation, which is considered one of the key mechanisms of PCS [3,8]. Vitamin D deficiency was found in almost 90% of patients; its independent association with residual fatigue supports monitoring and correcting vitamin D levels in such patients and is consistent with data linking low vitamin D levels to PCS [9].





The sex-stratified analysis showed that women and men had similar mean severity of fatigue, autonomic dysfunction, sleepiness and inflammatory markers, but differed in the structure of the syndrome: brain fog and clinically significant anxiety were more frequent in men, whereas subclinical anxiety and increased theta activity on EEG were more frequent in women. This is consistent with the concept that PCS symptoms depend on sex [10–12]. Unlike the meta-analysis [12], however, fatigue and depression were not more frequent in women in our sample, and brain fog was, conversely, more frequent in men. This may be because only patients with established and severe PCS after hospitalisation for pneumonia were included, so sex differences manifested in the structure rather than the severity of symptoms. In practical terms, men with PCS should undergo targeted assessment of cognitive function and anxiety, and women should be screened for subclinical anxiety. The addition of Glycevit was associated with a greater reduction in the impact of fatigue on daily functioning (CFIS) and in IL-6, as well as a moderate improvement in quality of life. Because the groups were balanced by sex and sex was not an independent predictor of the CFIS outcome, and because the group $\times$ sex interaction for CFIS and IL-6 was not significant, the observed effect cannot be attributed to differences in the sex composition of the groups. We hypothesise that the effect may be related to the combined action of GABA, glycine, glutamine and B vitamins on the balance of inhibition and excitation and on neuronal energy metabolism; however, the central effects of orally administered GABA remain debated [14], and this hypothesis requires verification. Since Glycevit does not contain vitamin D and both groups received cholecalciferol according to the same indication, its effect cannot be explained by vitamin D supplementation. The reduction in IL-6 did not correlate with clinical improvement and should therefore be regarded as an independent laboratory effect. High baseline IL-6 predicted a worse CFIS outcome regardless of treatment, although its predictive value on its own was moderate.

The scales showed discordant results: Glycevit had a clear advantage on CFIS, whereas the groups improved almost equally on MFI-20, and the difference on FAS did not survive the Holm correction. First, the scales measure different constructs: MFI-20 and FAS assess fatigue itself (its intensity and structure), whereas CFIS assesses the impact of fatigue on cognitive, physical and psychosocial functioning, and the effect of the product may have manifested mainly in the latter. Second, the open-label design may have influenced subjective ratings. Glycevit showed no advantage for fatigue (MFI-20), anxiety or depression; their changes probably reflect natural recovery and the effect of standard therapy. The sex-dependent changes in quality of life and anxiety–depression scores are exploratory and require confirmation.

4.1. Limitations

This study has several limitations. First, patients were allocated to groups without randomisation, and the study was open-label. Although the groups were comparable by sex, age and most baseline parameters, the MG had a higher baseline CFIS score, a lower Epworth score and a borderline longer hospital stay; these differences were accounted for by covariance and multivariable analyses, and the group $\times$ baseline CFIS interaction was not significant. Second, the sample was drawn from a single region and included only hospitalised patients with pneumonia, which limits the generalisability of the findings to patients with milder COVID-19. Third, follow-up was limited to the 30-day treatment course, so the durability of the effect was not assessed. Fourth, all scales were self-reported: CFIS





reflects the impact of fatigue on daily functioning and the Epworth scale reflects daytime sleepiness, so conclusions on cognitive function and sleep should be confirmed by objective methods (neuropsychological tests, polysomnography). Finally, EEG was assessed visually.

5. Conclusions

1. In patients who have recovered from COVID-19 pneumonia, cognitive complaints (69.2%), autonomic dysfunction (60.0%), sleep disturbances (60.0%) and headache (56.7%) are the leading manifestations of post-COVID syndrome. Most patients have persistent low-grade systemic inflammation (CRP >5 mg/L in 89.2%, IL-6 >7 pg/mL in 100%) and vitamin D deficiency (88.3%).
2. Post-COVID syndrome has sex-specific features: brain fog (80.4% vs. 60.9%) and clinically significant anxiety (47.1% vs. 26.1%) are more frequent in men, whereas subclinical anxiety (46.4% vs. 19.6%) and increased EEG theta activity (72.5% vs. 51.0%) are more frequent in women. Mean scale scores and inflammatory markers do not differ by sex.
3. Adding Glycevit to standard rehabilitation therapy is associated with a greater reduction in the impact of fatigue on daily functioning (CFIS normalisation in 55.1% vs. 9.8%; NNT 2.2) and in IL-6 (adjusted difference -5.2 pg/mL), as well as a moderate improvement in quality of life. No additional effect on fatigue (MFI-20), anxiety or depression was found. The effects on CFIS and IL-6 do not depend on patient sex.
4. High baseline IL-6 is an independent predictor of a worse CFIS outcome, and low baseline vitamin D is an independent predictor of more severe residual fatigue.
5. Because the study was non-randomised and open-label, the effectiveness of Glycevit requires confirmation in a randomised controlled trial.

Declarations

Ethics approval and consent to participate. The study was approved by the Ethics Committee of Bukhara State Medical Institute named after Abu Ali ibn Sino (Protocol No. 3, dated 5 May 2020).

Written informed consent was obtained from all participants.

Funding. This research received no external funding.

Conflict of interest. The authors declare no conflict of interest.

Author contributions. Z.I. Adambaev: conceptualisation, methodology, formal analysis, writing - original draft, supervision. A.B. Nurjonov: investigation, data curation, writing - review and editing. All authors have read and approved the final manuscript.

Data availability. The data supporting the findings of this study are available from the corresponding author upon reasonable request.

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