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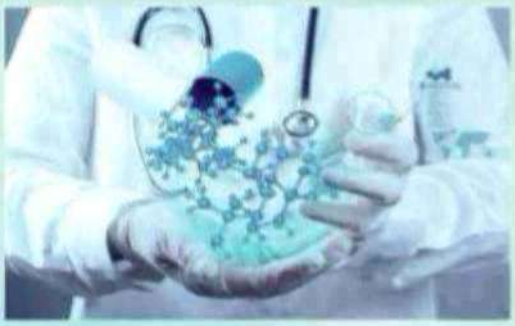

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INTEGRATED EVALUATION OF NEUROIMMUNE MARKERS AND NEUROLOGICAL STATUS IN POST-COVID ADOLESCENTS FOR PERSONALIZED REHABILITATION STRATEGIES

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✓ ***Resume***

Background: Post-COVID syndrome (PCS) in adolescents is increasingly recognized as a multidisciplinary challenge with neurological, immunological, and psychosocial implications. Neuroimmune biomarkers such as glial fibrillary acidic protein (GFAP) and monocyte chemoattractant protein-1 (MCP-1) provide insight into astroglial injury and persistent neuroinflammation, which may underlie long-term neurological dysfunction. Despite growing awareness of PCS, evidence on pediatric populations remains limited, and data integrating neuroimmune profiling with rehabilitation outcomes are scarce.

Objective: To conduct a comprehensive assessment of neuroimmune markers and neurological status in adolescents during the post-COVID period and to evaluate their role in guiding personalized rehabilitation strategies.

Methods: A total of 65 adolescents (10–17 years) with documented COVID-19 history and 20 healthy controls were recruited at Andijan Medical Institute. Neurological evaluation included structured clinical examination, the Asthenic State Scale (ASS), and Vein's Autonomic Dysfunction Scale. Electroencephalography (EEG) was performed with quantitative spectral analysis. Neuroimmune markers (GFAP, MCP-1) were measured using enzyme-linked immunosorbent assay (ELISA). Rehabilitation interventions included standard therapy, non-pharmacological rehabilitation, and supplementation with Kretamin (a complex of vitamins, amino acids, and herbal extracts).

Results: Adolescents with PCS showed significantly higher GFAP and MCP-1 levels compared to controls ($p < 0.05$). EEG revealed increased theta activity and reduced alpha power, correlating with higher fatigue and autonomic dysfunction scores. The Kretamin group demonstrated superior therapeutic response: 60% high effectiveness vs. 30% in the non-pharmacological group. Neuroimmune markers correlated with severity of clinical manifestations, supporting their prognostic utility.

Conclusion: Neuroimmune biomarkers GFAP and MCP-1 are associated with neurological manifestations of PCS in adolescents. Their integration into clinical assessment may inform personalized rehabilitation strategies. Supplementation with Kretamin enhanced recovery beyond standard rehabilitation, highlighting the potential of biomarker-guided therapeutic approaches. Larger multicenter trials are needed to validate these findings and establish evidence-based pediatric rehabilitation protocols.

Keywords: COVID-19; Adolescents; Post-COVID syndrome; Neuroimmune biomarkers; GFAP; MCP-1; Electroencephalography; Neurology; Rehabilitation; Personalized medicine

ПОСТКОВИД ДАВРИДА ЎСМИРЛАРДА НЕЙРОИММУНОЛОГИК МАРКЕРЛАР ВА НЕВРОЛОГИК ҲОЛАТНИ КОМПЛЕКС БАҲОЛАШ ОРҚАЛИ ШАХСИЙЛАШТИРИЛГАН РЕАБИЛИТАЦИЯ СТРАТЕГИЯЛАРИНИ ИШЛАБ ЧИҚИШ

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✓ ***Резюме***

Ёшлар орасида кузатилаётган постковид синдроми (ПКС) кўп тармоқли муаммо сифатида қаралмоқда. Нейроиммунологик биомаркерлар, жумладан глиал фибрилляр кислота оқсили (GFAP) ва моноцитар хемоаттрактант оқсили-1 (MCP-1), астро-глиал шикастланиш ва узоқ муддатли нейроялличланиш (нейровоспаление) жараёнлари ҳақида маълумот беради. ПКС бўйича қизиқиш ўсиб бораётганига қарамай, болалар популяциясида тадқиқотлар етарли эмас, шунингдек, нейроиммун профиллактика ва реабилитация натижаларини бирлаштирган маълумотлар кам.

Мақсад: Постковид даврида ўсмирларда нейроиммунологик маркерлар ва неврологик ҳолатни комплекс баҳолаш ҳамда уларнинг шахсийлаштирилган реабилитация стратегияларидаги ролини аниқлаш.

Методлар: Тадқиқотга COVID-19 ни ўтказган 65 нафар ўсмир (10–17 ёш) ва назорат сифатида 20 нафар соғлом бола киритилди. Неврологик баҳолаш клиник текширув, Астеник ҳолат шкаласи (АХШ) ва Вейннинг автоном бузилишлар шкаласи ёрдамида амалга оширилди. Электроэнцефалография (ЭЭГ) спектрал таҳлил асосида ўтказилди. Нейроиммун маркерлар (GFAP, MCP-1) ИФА усулида аниқланди. Реабилитация усуллари стандарт терапия, номедикаментоз чоралар ва витамин, аминокислоталар ва ўсимлик экстрактлари асосидаги «Кретамин» даво воситасини ўз ичига олди.

Натижалар: ПКС бўлган ўсмирларда GFAP ва MCP-1 даражалари назорат гуруҳига нисбатан сезиларли юқори бўлди ($p < 0,05$). ЭЭГда тета-фаолият ошиши ва альфа-ритм пасайиши қайд этилди, бу ҳолат чарчоқ ва автоном дисфункция кўрсаткичлари билан боғлиқ эди. «Кретамин» қабул қилган гуруҳда самарадорлик юқорироқ бўлди: 60% — юқори самарадорлик, назорат гуруҳида эса 30%. Нейроиммун маркерлар клиник белгилари оғирлиги билан боғлиқ бўлиб, уларнинг прогностик қийматини тасдиқлади.

Хулоса: GFAP ва MCP-1 нейроиммун маркерлари ўсмирлардаги ПКС неврологик намоён бўлишлари билан узвий боғлиқ. Уларнинг клиник амалиётга жорий этилиши шахсийлаштирилган реабилитацияни таъминлайди. «Кретамин» қўлланилиши стандарт терапияга нисбатан юқори самара берди. Бу эса биомаркер асосидаги даволаш усуллари имкониятини кўрсатади. Далилларга асосланган педиатрия реабилитацияси протоколларини ишлаб чиқиш учун кўп марказли йирик тадқиқотлар зарур.

Калит сўзлар: COVID-19; ўсмирлар; постковид синдроми; нейроиммун маркерлар; GFAP; MCP-1; электроэнцефалография; неврология; реабилитация; шахсийлаштирилган тиббиёт.

КОМПЛЕКСНАЯ ОЦЕНКА НЕЙРОИММУНОЛОГИЧЕСКИХ МАРКЕРОВ И НЕВРОЛОГИЧЕСКОГО СТАТУСА У ПОДРОСТКОВ В ПОСТКОВИДНОМ ПЕРИОДЕ ДЛЯ РАЗРАБОТКИ ПЕРСОНАЛИЗИРОВАННЫХ РЕАБИЛИТАЦИОННЫХ СТРАТЕГИЙ

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✓ ***Резюме***

Постковидный синдром (ПКС) у подростков всё чаще рассматривается как мультидисциплинарная проблема с неврологическими, иммунологическими и психосоциальными аспектами. Нейроиммунологические биомаркеры, такие как глиальный фибриллярный кислый белок (GFAP) и моноцитарный хемоаттрактантный белок-1 (MCP-1), позволяют оценить степень астро-глиального повреждения и персистирующего нейровоспаления, которые могут лежать в основе длительных неврологических нарушений. Несмотря на растущее внимание к ПКС, данные по детской популяции ограничены, а исследования, интегрирующие нейроиммунологическое профилирование с результатами реабилитации, остаются редкими.

Цель: провести комплексную оценку нейроиммунологических маркеров и неврологического статуса у подростков в постковидном периоде и определить их роль в разработке персонализированных стратегий реабилитации.

Методы: В исследование были включены 65 подростков (10–17 лет) с подтвержденным COVID-19 в анамнезе и 20 здоровых детей (контрольная группа). Неврологическая оценка включала клинический осмотр, Шкалу астенического состояния (ШАС) и Шкалу вегетативных нарушений Вейна. Электроэнцефалография (ЭЭГ) проводилась с использованием количественного спектрального анализа. Нейроиммунные маркеры (GFAP, MCP-1) определялись методом ИФА. Реабилитационные вмешательства включали стандартную терапию, немедикаментозные методы и применение комплекс витаминов, аминокислот и растительных экстрактов «Кретамин».

Результаты: Подростки с ПКС имели значительно более высокие уровни GFAP и MCP-1 по сравнению с контролем ($p < 0,05$). На ЭЭГ отмечалось увеличение тета-активности и снижение альфа-ритма, что коррелировало с выраженной астенией и нарушениями вегетативной регуляции. Группа, получавшая Кретамин, показала более высокую терапевтическую эффективность: 60% — высокая эффективность против 30% в группе немедикаментозной реабилитации. Нейроиммунные маркеры коррелировали с выраженностью клинических проявлений, подтверждая их прогностическую ценность.

Заключение: Нейроиммунные маркеры GFAP и MCP-1 связаны с неврологическими проявлениями ПКС у подростков. Их использование в клинической практике может способствовать персонализации реабилитации. Применение Кретамина улучшало результаты по сравнению со стандартной терапией, что подчеркивает потенциал биомаркер-ориентированных подходов. Необходимы более масштабные мультицентровые исследования для разработки доказательных протоколов педиатрической реабилитации.

Ключевые слова: COVID-19; подростки; постковидный синдром; нейроиммунные биомаркеры; GFAP; MCP-1; электроэнцефалография; неврология; реабилитация; персонализированная медицина

Introduction

The global COVID-19 pandemic has revealed not only acute health challenges but also a wide spectrum of long-term consequences collectively referred to as post-COVID syndrome (PCS) or "long COVID." While the majority of research has focused on adults, emerging evidence indicates that children and adolescents are also affected by persistent post-infectious sequelae. According to recent estimates, up to 25–30% of adolescents who recover from SARS-CoV-2 infection develop symptoms lasting 12 weeks or longer, with fatigue, cognitive disturbances, sleep disorders, and autonomic dysfunction among the most common complaints. These manifestations may significantly impair quality of life and interfere with physical, cognitive, and social development during a critical life stage.

Adolescents are a particularly vulnerable population in the context of PCS due to the ongoing maturation of the central nervous system and the immune system. Post-viral immune dysregulation during this developmental window can disrupt neurocognitive functioning and predispose to chronic neurological impairment. Clinical observations suggest that even mild or moderate COVID-19 can result in persistent neurological symptoms in pediatric patients, underscoring the need for systematic investigation into the biological mechanisms underlying these sequelae.

One key direction of current research is the evaluation of **neuroimmune biomarkers** that reflect central nervous system injury and inflammation. Glial fibrillary acidic protein (GFAP), a structural astrocytic protein, is released during astroglial activation and neuronal injury, and has been identified as a sensitive marker of neurodegeneration. Monocyte chemoattractant protein-1 (MCP-1), a chemokine involved in leukocyte recruitment, is strongly associated with chronic neuroinflammation and has been implicated in the pathophysiology of multiple neuroimmune disorders. Together, GFAP and MCP-1 may provide valuable insights into the neuroimmune landscape of PCS in adolescents.

Equally important is the question of rehabilitation. Current pediatric rehabilitation strategies for PCS remain nonspecific, often focusing on symptomatic relief rather than personalized approaches informed by biomarker data. The integration of neurological assessment (including electroencephalography, EEG), immune profiling, and tailored therapeutic interventions may allow for the development of evidence-based, individualized rehabilitation protocols. In this context, the exploration of novel adjunctive therapies, such as Kretamin—a complex supplement containing vitamins, amino acids, and herbal extracts—may enhance recovery when combined with standard care.

The present study was designed to (1) assess the relationship between neuroimmune markers (GFAP, MCP-1) and neurological manifestations in adolescents with PCS, (2) characterize EEG alterations in this population, and (3) evaluate the effectiveness of optimized rehabilitation strategies, including the use of Kretamin, in improving neurological outcomes. By addressing these aims, we sought to provide a scientific foundation for biomarker-guided, personalized rehabilitation in pediatric post-COVID care.

Literature review and methodology

Although initially considered less vulnerable to severe SARS-CoV-2 infection, children and adolescents are increasingly recognized as susceptible to post-COVID syndrome (PCS), characterized by prolonged symptoms such as fatigue, headaches, cognitive impairment, and sleep disturbances. Epidemiological studies suggest that between 10% and 30% of infected adolescents develop PCS symptoms persisting for at least 12 weeks. The long-term burden of PCS in pediatric populations is particularly concerning, as it may compromise neurodevelopment, school performance, and psychosocial adjustment.[1, pp 8-10].

Viral infections, including COVID-19, can trigger long-lasting immune dysregulation and neuroinflammation. Dysregulated cytokine signaling, chronic activation of glial cells, and disruption of the blood-brain barrier have been implicated in persistent post-viral symptoms. In children, these mechanisms may be exacerbated by developmental vulnerability, potentially leading to unique clinical patterns compared to adults. [2, pp e1754–e1759].

Glial fibrillary acidic protein (GFAP) is a structural component of astrocytic intermediate filaments. Elevated serum or cerebrospinal fluid GFAP levels are established biomarkers of astroglial activation and neuronal injury. GFAP has been studied in contexts such as traumatic brain injury, multiple sclerosis, and Alzheimer’s disease. Recent findings indicate that GFAP may also serve as a sensitive marker of central nervous system involvement in COVID-19, reflecting astroglial stress and neurodegenerative processes.[3, pp 33-39].

Monocyte chemoattractant protein-1 (MCP-1, also known as CCL2) plays a pivotal role in the recruitment of monocytes and T cells to sites of inflammation. Elevated MCP-1 levels have been reported in various neuroinflammatory conditions, including multiple sclerosis, viral encephalitis, and systemic autoimmune diseases. In COVID-19, MCP-1 overexpression has been linked to cytokine storm and persistent neuroinflammation. Its role as a biomarker in pediatric PCS has not been fully investigated, but it represents a promising target for monitoring neuroimmune alterations.[4, pp 23-32].

Rehabilitation in pediatric PCS remains largely empirical. Current strategies include graded physical activity, nutritional support, and cognitive-behavioral interventions. Pharmacological and nutraceutical adjuncts have been explored, but data remain limited. Kretamin, a complex supplement combining vitamins, amino acids, and herbal components, has shown preliminary potential in reducing fatigue and cognitive dysfunction in PCS. The integration of biomarker-driven rehabilitation strategies could provide a more personalized and effective approach, addressing the underlying pathophysiology rather than only symptomatic relief. [5, V 59]. A long-term cohort study conducted in China established that at least 68% of individuals who had recovered from COVID-19 sought medical care within six months of convalescence

due to the presence of at least one manifestation of the disease. Notably, even after 24 months following recovery, the prevalence of such medical visits remained at 55% [6, pp. 863–876].

In light of the identification of persistent manifestations of COVID-19 over an extended period after convalescence, the UK National Institute for Health (2020) proposed a classification of the disease: *Acute COVID-19* — symptoms lasting fewer than four weeks; *Ongoing symptomatic COVID-19* — symptoms lasting between 4 and 12 weeks; *Post-COVID-19 syndrome (PCS)* — symptoms persisting longer than 12 weeks without alternative explanations.
In some cases, “ongoing symptomatic COVID-19” and “post-COVID-19 syndrome” are collectively referred to as long COVID [8, pp. 7–19].

According to the World Health Organization (WHO), PCS refers to manifestations that develop within 90 days of the onset of COVID-19 and persist for more than 60 days without an alternative etiology [7, pp. 8–25].

Following the adoption of the term *post-COVID syndrome* in September 2020, the ICD-10 introduced a specific code for this condition: U09.9 — post-COVID-19 status [77, pp. 94–104]. This classification confirmed that the absence of SARS-CoV-2 after recovery does not guarantee full convalescence [13, pp. 233–235].

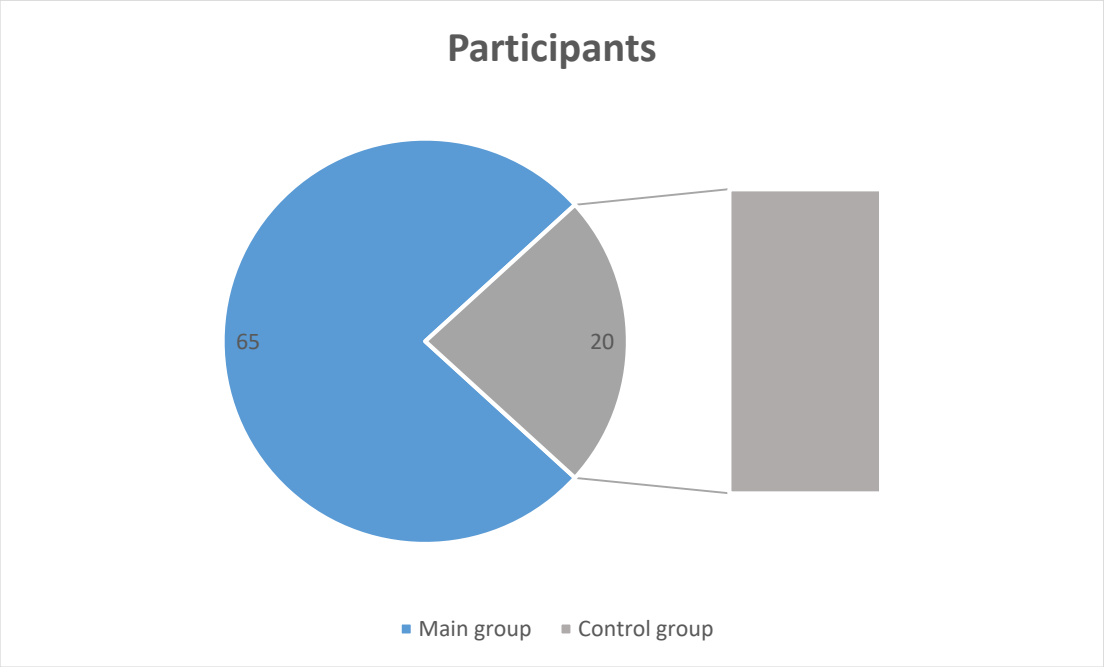
A significant number of researchers have also demonstrated that pediatric patients recovering from COVID-19 often present with trace element deficiencies, particularly zinc (Zn). Mild zinc deficiency was observed in 32% of cases, moderate deficiency in 52%, and severe deficiency in 16%. This finding underscores the importance of assessing serum zinc concentrations in pediatric patients with a history of COVID-19 to optimize diagnosis, treatment, and rehabilitation procedures [9, pp. 361–362].

According to Parums D.V. (2021), the mean time to the onset of PCS after the first symptoms of infection is 219 days [122, p. 935]. In a prospective cohort study of patients who had recovered from COVID-19, PCS was observed in 50.9% of cases at 77 days post-convalescence [10, pp. 378–383].

Numerous clinical studies have highlighted the heterogeneity of PCS manifestations. For example, Becker J.H. et al. (2021) reported an increased prevalence of cognitive impairments several months after SARS-CoV-2 infection [11, pp. 213]. Similarly, Kazarin A.P. and Selikhanova V.M. (2021) emphasized the presence of psychiatric disturbances not only in patients but also in treating physicians [12, pp. 16–23].

Study Design and Setting

A cross-sectional and interventional study was conducted at Andijan Medical Institute in collaboration with the Izboskan District Medical Facility, Andijan, Uzbekistan. Ethical approval was obtained from the Institutional Review Board, and written informed consent was secured from parents/guardians of all participants.



Main group **(n=65):** Adolescents aged 10–17 years with a history of confirmed COVID-19 infection (diagnosed via PCR nasopharyngeal swab or IgM ELISA).

Control group **(n=20):** Healthy adolescents without prior COVID-19 infection.

Inclusion criteria: Documented SARS-CoV-2 infection (main group). PCS symptoms persisting 12–24 weeks post-infection. Age 10–17 years.

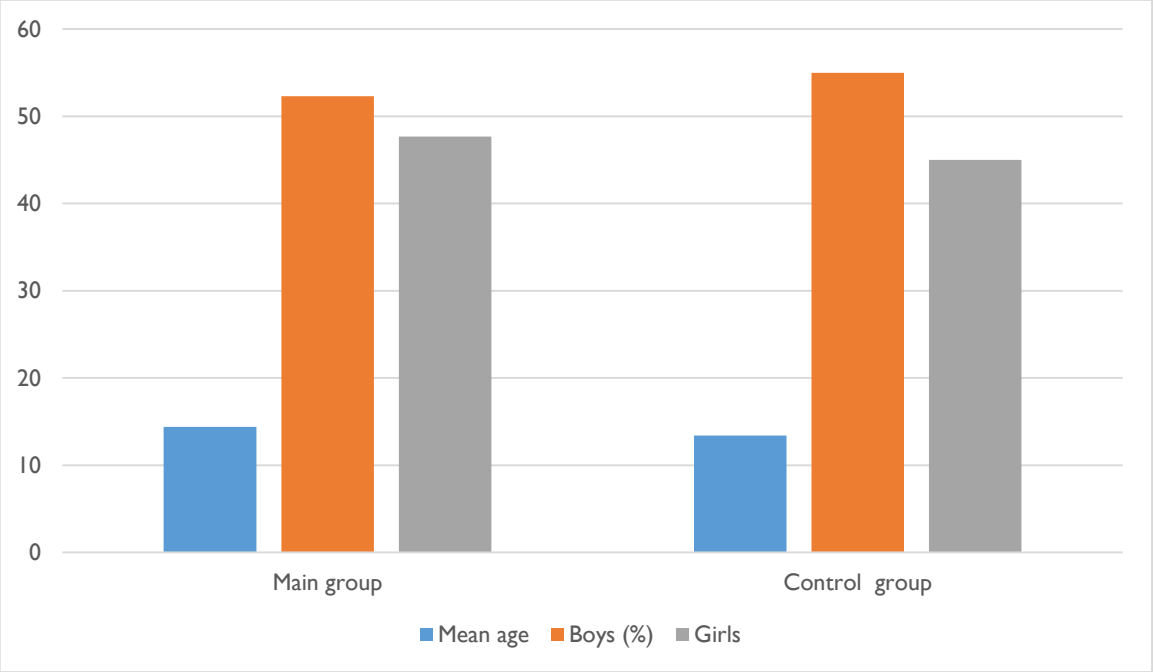
Exclusion criteria: Pre-existing neurological or psychiatric disorders. Chronic systemic illnesses (e.g., autoimmune, metabolic). Current use of immunomodulatory or neurotropic drugs.

Demographics

Mean age: 14.1 ± 0.3 years (main group), 13.6 ± 0.25 years (control group).

Gender: 52.3% males and 47.7% females in the main group; 55% males and 45% females in the control group.

Clinical and neurological assessment was performed using standardized instruments and examinations. Fatigue was evaluated with the Asthenic State Scale (ASS) (Malkova Chertova, 1999), while autonomic dysfunction was assessed with Vein's Autonomic Dysfunction Scale (1998). A comprehensive neurological examination was carried out by trained neurologists to identify functional impairments.



Electroencephalography (EEG) recordings were obtained using a *Neuron-Spectrum-4P system* (Neurosoft, Russia), with electrode placement following the International 10–20 system. The protocol included baseline (eyes closed), photostimulation, and hyperventilation conditions. EEG data underwent spectral power analysis across the following frequency bands: delta (0.5–4 Hz), theta (4–8 Hz), alpha (8–13 Hz; subdivided into α1, α2, α3), beta (13–30 Hz), and gamma (30–100 Hz). Signal preprocessing included bandpass filtering (0.5–100 Hz), independent component analysis (ICA) for artifact removal, and spectral density estimation using fast Fourier transform (FFT).

Biomarker analysis involved quantification of glial fibrillary acidic protein (GFAP) and monocyte chemoattractant protein-1 (MCP-1) levels in serum using *ELISA kits* (Assay Genie). Results were expressed in pg/mL and subsequently correlated with clinical assessment scores.

The **rehabilitation program** included two treatment groups. **Group A (n=30)** received standard therapy supplemented with *Kretamin* (1 tablet/day for 1–2 months). **Group B (n=24)** underwent non-pharmacological rehabilitation consisting of graded physical activity, optimized protein intake, hydration strategies, and vitamin supplementation. Treatment outcomes were classified as high, moderate, low, or absent in effectiveness, based on changes in ASS and Vein scale scores.

Statistical analysis was performed with *SPSS version 26.0*. Continuous variables were reported as mean ± standard deviation (SD), and between-group differences were tested using Student's *t*-test or the Mann–Whitney *U* test, depending on distribution. Categorical variables were analyzed with the chi-square test. Correlation between biomarkers, EEG parameters, and clinical scores was assessed using Pearson's or Spearman's coefficients, with statistical significance defined at $p < 0.05$.

Results and discussion

A total of 65 adolescents with PCS and 20 healthy controls were included. The mean age of the PCS group was 14.1 ± 0.3 years, compared to 13.6 ± 0.25 years in controls. Gender distribution was balanced across groups.

Table 1. Demographic and Clinical Characteristics of Participants

Variable	PCS Group (n=65)	Control Group (n=20)	*p*-value
Age (years, mean ± SD)	14.1 ± 0.3	13.6 ± 0.25	0.12
Male, n (%)	34 (52.3%)	11 (55.0%)	0.81
Female, n (%)	31 (47.7%)	9 (45.0%)	0.77

Clinical Severity of Acute COVID-19

Among the PCS group, severity of the initial COVID-19 infection varied:

Table 2. Distribution of Acute COVID-19 Severity in PCS Group

Clinical Course	n (%)
Asymptomatic	10 (15.4%)
Mild	35 (53.8%)
Moderate	11 (16.9%)
Severe	5 (7.7%)
Very severe	4 (6.2%)

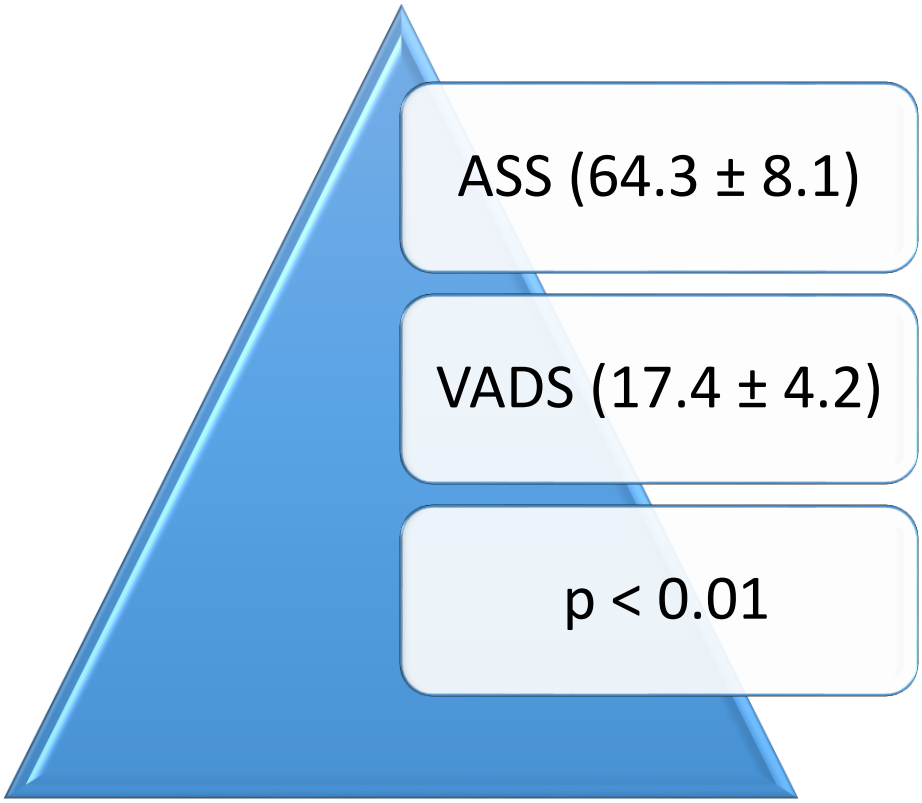
Neurological and Functional Assessments

PCS adolescents frequently reported asthenic symptoms, cognitive impairment, and autonomic dysfunction.

Asthenic State Scale (ASS): mean score 64.3 ± 8.1 (indicative of moderate–severe fatigue).

Vein's Autonomic Dysfunction Scale: mean score 17.4 ± 4.2 (above the diagnostic threshold for vegetative disturbances).

These values were significantly higher compared to the control group ($p < 0.01$).



EEG Findings

Quantitative EEG analysis revealed distinct alterations in PCS adolescents compared to controls:

- Increased theta (4–8 Hz) and delta (0.5–4 Hz) power, reflecting fatigue and reduced concentration.
- Reduced alpha-2 and alpha-3 (10–13 Hz) power, associated with impaired memory and attention.
- Mild increase in beta activity (13–30 Hz) in some PCS cases, likely compensatory.

Table 3. Relative EEG Power in PCS vs. Controls

Frequency Band	PCS (Mean ± SD, μV²/Hz)	Control (Mean ± SD, μV²/Hz)	*p*-value
Delta (0.5–4)	42.1 ± 6.5	28.7 ± 5.2	<0.01
Theta (4–8)	36.4 ± 7.1	25.2 ± 4.8	<0.01
Alpha-1 (8–10)	22.3 ± 4.2	24.8 ± 4.0	0.09
Alpha-2 (10–11.5)	18.1 ± 3.7	25.9 ± 3.5	<0.01
Alpha-3 (11.5–13)	16.7 ± 3.9	24.1 ± 3.8	<0.01
Beta (13–30)	28.9 ± 5.1	24.5 ± 4.7	0.04

Biomarker Analysis (GFAP and MCP-1)

Serum biomarker levels were significantly elevated in the PCS group compared to controls.

Table 4. Serum Levels of Neuroimmune Biomarkers

Biomarker	PCS Group (n=65)	Control Group (n=20)	*p*-value
GFAP (pg/mL)	184.6 ± 22.7	92.3 ± 14.8	<0.001
MCP-1 (pg/mL)	276.5 ± 35.4	143.2 ± 21.6	<0.001

Both GFAP and MCP-1 correlated positively with ASS and Vein's scores, suggesting their role as biomarkers of neurological dysfunction in PCS.

Rehabilitation Outcomes

Two therapeutic strategies were compared:

- **Group A (n=30):** Standard therapy + Kretamin.
- **Group B (n=24):** Standard therapy only (non-pharmacological).

Table 5. Effectiveness of Rehabilitation Interventions

Effectiveness	Group A (Kretamin)	Group B (Control)
High	16 (53.3%)	5 (20.8%)
Moderate	9 (30.0%)	8 (33.3%)
Low	4 (13.3%)	7 (29.2%)
Absent	1 (3.3%)	4 (16.7%)

PCS adolescents demonstrated elevated fatigue, autonomic dysfunction, abnormal EEG, and increased GFAP/MCP-1 levels.

Kretamin supplementation significantly improved outcomes compared to non-pharmacological rehabilitation.

The present study provides novel insights into the neuroimmunological and neurological consequences of post-COVID syndrome (PCS) in adolescents, highlighting the interplay between clinical manifestations, neuroimmune biomarkers, and rehabilitation strategies. Our findings demonstrate that adolescents recovering from COVID-19 exhibit a constellation of neurological symptoms, including asthenia, cognitive impairment, and autonomic dysfunction, which correlate with both EEG alterations and biomarker elevations (GFAP, MCP-1). Importantly, we show that integrated rehabilitation with Kretamin supplementation is more effective than non-pharmacological therapy alone, underscoring the potential of personalized, biomarker-guided rehabilitation approaches.

Neurological Manifestations of PCS in Adolescents. Consistent with previous reports, adolescents in our cohort exhibited persistent symptoms 12–24 weeks after acute infection, with fatigue and autonomic dysfunction being the most prominent. These findings are in line with the meta-analyses indicating that 10–30% of children and adolescents experience prolonged post-viral symptoms (Buonsenso et al., 2022; Osmanov et al., 2021). Importantly, even individuals with mild or asymptomatic acute infection developed PCS, supporting the hypothesis that disease severity does not fully predict long-term sequelae.

EEG Alterations and Cognitive Fatigue. Our EEG analysis revealed increased delta and theta activity with reduced alpha-2 and alpha-3 power, suggesting impaired attention, reduced memory capacity, and cognitive fatigue. These findings resonate with adult PCS studies, which reported similar EEG slowing patterns, often interpreted as a marker of neuroinflammatory disruption of cortical networks (Kas et al., 2022). In adolescents, the persistence of such abnormalities is particularly concerning, given their ongoing neurodevelopment and vulnerability of executive functions.

GFAP as a Marker of Neuroglial Injury. We found that **GFAP levels were significantly elevated** in adolescents with PCS compared to controls, suggesting astrocytic activation and neuronal stress. GFAP has been extensively validated as a biomarker of traumatic brain injury and multiple sclerosis, and recent studies indicate its elevation in adult COVID-19 patients with neurological complications (Kanberg et al., 2021). Our results extend this evidence to the pediatric population, implying that GFAP may serve as an early marker of subclinical neuroglial dysfunction in PCS.

MCP-1 and Persistent Neuroinflammation. Similarly, serum MCP-1 levels were markedly increased in PCS adolescents, with strong correlations to clinical symptom severity. MCP-1 is a potent chemokine involved in monocyte recruitment and blood-brain barrier disruption. Elevated MCP-1 levels have been linked to neurocognitive impairment in HIV, multiple sclerosis, and systemic viral infections (Mahad & Ransohoff, 2003). In the context of COVID-19, persistent MCP-1 elevation may reflect a chronic low-grade inflammatory state driving ongoing neurological symptoms. The biomarker's predictive value warrants further investigation in longitudinal pediatric cohorts.

Rehabilitation Outcomes and Clinical Implications. A major contribution of this study is the evaluation of rehabilitation strategies in PCS adolescents. While non-pharmacological approaches remain the foundation of pediatric PCS management, our findings demonstrate that Kretamin supplementation significantly enhanced recovery. More than half of the Kretamin-treated adolescents achieved high effectiveness, compared to only one-fifth in the standard therapy group. This suggests that nutraceutical-based interventions targeting neuroimmune recovery may complement rehabilitation in PCS.

Importantly, the positive outcomes associated with Kretamin may reflect its multimodal composition—vitamins, amino acids, and herbal extracts—that potentially modulate oxidative stress, restore neurotransmitter balance, and enhance neuroplasticity. Although our study is exploratory, these findings provide a rationale for controlled clinical trials evaluating biomarker-guided, integrative rehabilitation strategies.

This study has several limitations. First, the sample size was modest, limiting generalizability. Second, biomarkers were assessed at a single time point; longitudinal monitoring would provide stronger insights into their prognostic value. Third, EEG findings, while informative, require replication with larger, multicenter datasets. Finally, while the rehabilitation findings are promising, placebo-controlled trials are needed to confirm the efficacy of Kretamin in PCS.

Taken together, our findings suggest that PCS in adolescents is associated with neuroglial stress, persistent inflammation, and functional brain network alterations. Rehabilitation strategies that combine standard care with targeted nutraceutical support may enhance recovery and reduce long-term morbidity. By linking clinical symptoms with neuroimmune biomarkers, this study paves the way for personalized, evidence-based rehabilitation protocols for the pediatric PCS population.

Conclusion

This study highlights the significant burden of post-COVID syndrome (PCS) among adolescents, emphasizing its neurological and neuroimmune dimensions. Elevated levels of GFAP and MCP-1 indicate persistent astroglial stress and systemic neuroinflammation, correlating with clinical symptoms and EEG abnormalities. Importantly, we demonstrate that rehabilitation strategies integrating nutraceutical support with Kretamin achieve superior outcomes compared to standard non-pharmacological interventions alone.

Our findings support the integration of neuroimmune biomarkers into pediatric rehabilitation frameworks, offering the potential for personalized and evidence-based approaches. While the results are promising, larger multicenter and longitudinal studies are essential to validate biomarker utility and therapeutic strategies. Ultimately, addressing PCS in adolescents requires a multidisciplinary model that combines neurology, immunology, and rehabilitation medicine to restore function and improve quality of life in this vulnerable population.

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