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Comparative Efficacy Of Pharmacotherapy And Combined Psycho-Pharmacotherapy For Correction Of Psychoemotional, Cognitive And Immunological Disorders In Post-Covid Syndrome Among Young Adults

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Abstract. Post-COVID syndrome (PCS) in young adults is characterized by persistent psychoemotional disturbances, cognitive dysfunction, and immune dysregulation.
Aim: to compare the efficacy of pharmacotherapy (PhT) versus combined therapy (pharmacotherapy + cognitive-behavioral therapy with relaxation, PhT+PT) in young patients with PCS.
Methods: a prospective controlled study of 106 patients aged 20–45 years randomized 53:53 to PhT and PhT+PT groups. Assessment at 8 weeks using BDI-II, STAI-S/T, MoCA, SF-36, serum IL-6, TNF-α, IL-10, CRP, ferritin, and immunoglobulins.
Results: BDI-II decreased by 50.0% vs 27.1% ($p<0.001$); MoCA increased by 3.4 vs 1.7 points ($p<0.001$); MoCA normalization (≥26) was achieved in 88.7% vs 50.9% ($p<0.001$). IL-6 reached 4.2±1.3 vs 5.9±1.6 pg/ml ($p<0.01$); TNF-α — 7.8±2.1 vs 10.4±2.5 pg/ml ($p<0.01$). SF-36 "Mental Health" and "Vitality" subscales improved by 24.3 and 21.7 points in the PhT+PT group.
Conclusion: PhT+PT is significantly superior to pharmacotherapy alone in all measured outcomes and is recommended for inclusion in the standard management protocol for young PCS patients.

Keywords: post-COVID syndrome, young adults, cognitive-behavioral therapy, relaxation, pharmacotherapy, IL-6, TNF-α, SF-36, psychoneuroimmunology.

INTRODUCTION

Post-COVID syndrome (PCS) — a complex of symptoms persisting ≥4 weeks after SARS-CoV-2 infection — affects at least 10% of those who have recovered from COVID-19, according to WHO data [3]. According to a large systematic review by Davis et al. (2023), more than 200 PCS symptoms span neurological, cardiovascular, immune, and psychiatric domains [4]. Young adults (aged 20–45 years) represent a substantial proportion of PCS patients: according to large cohort studies, the prevalence of PCS among young people is 10–14%, causing significant socioeconomic burden due to reduced work capacity.

The psychoemotional profile of PCS in young patients includes anxiety-depressive disorders (23–38% of cases) [5], cognitive dysfunction — "brain fog" (32% of patients according to Hampshire et al., 2024) [6], and chronic fatigue syndrome (37–67% of cases) [10]. The immunopathological basis of these disorders is formed by persistent inflammation, elevated levels of proinflammatory cytokines (IL-6, TNF-α, IL-1β) [7], and T-cell immune dysfunction [8, 9]. According to the psychoneuroimmunological concept, reduction in psychoemotional stress can indirectly modulate the proinflammatory cytokine profile [14, 15].

Cognitive-behavioral therapy (CBT) is recommended by WHO and NICE as an evidence-based non-pharmacological intervention for PCS: randomized studies by Kuut et al. (2023) [13], Li et al. (2020) [11], and Liu et al. (2021) [12] confirmed its efficacy in reducing fatigue, anxiety, and depression. Relaxation techniques (progressive muscle relaxation, diaphragmatic breathing) enhance the therapeutic effect by normalizing autonomic nervous system tone and HPA axis activity [14, 16]. However, in Uzbekistan and Central Asia, there are no published controlled studies simultaneously assessing psychometric, cognitive, immunological indicators, and quality of life in young patients with PCS.

Study objective — to evaluate the comparative efficacy of isolated pharmacotherapy (PhT) and combined therapy (PhT + structured CBT with relaxation elements, PhT+PT) for correction of

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psychoemotional, cognitive, and immunological disorders, as well as quality of life, in young adults with post-COVID syndrome.

MATERIALS AND METHODS

Design and participants. A prospective controlled study was conducted with patient enrollment at Polyclinic No. 2 in Chirchiq and Polyclinic No. 5 in Tashkent (2023–2025). Inclusion criteria: age 20–45 years; confirmed COVID-19 history (PCR/ELISA); PCS symptoms lasting >12 weeks; signed informed consent. Exclusion criteria: chronic psychiatric or autoimmune diseases; current immunosuppressive therapy; SARS-CoV-2 vaccination <3 months before enrollment. Sample size (n=106) was calculated using Cohen's formula at α=0.05, power 80%, and Cohen's d=0.5 [21]. The study was conducted in accordance with the principles of the Declaration of Helsinki (2013 revision).

Treatment groups. Patients were equally divided into two groups by simple randomization. **PhT group** (n=53): standard pharmacotherapy (herbal anxiolytics, SSRIs as indicated, piracetam, B vitamins, melatonin if needed). **PhT+PT group** (n=53): the same medications + 8 individual CBT sessions (1 session/week, 50–60 min.) incorporating progressive muscle relaxation according to Jacobson and diaphragmatic breathing [22]. The therapist had certified CBT training.

Psychodiagnostic instruments. The following were used: BDI-II [17], STAI-S/T (Spielberger–Khanin) [18], MoCA [19], SF-36 [20]. All instruments were used in validated versions; testing was conducted by a clinical psychologist under standardized conditions.

Immunological assessment. Serum cytokines (IL-6, IL-10, TNF-α) were determined by ELISA (certified test systems; intra-assay CV≤5%). CRP — high-sensitivity immunoturbidimetry; ferritin — ELISA; IgG, IgM, IgA — immunoturbidimetry. Assessment time points: baseline (T_0) and at 8 weeks (T_1).

Statistical analysis. SAS JMP 16.0. Normality — Shapiro–Wilk test. Within-group comparisons (T_0 vs T_1): paired t-test or Wilcoxon test. Between-group comparisons (T_1): Student's t-test or Mann–Whitney U-test. Correlations — Spearman's ρ. Significance level $p<0.05$.

RESULTS

Baseline group characteristics. The PhT (n=53) and PhT+PT (n=53) groups were comparable on all demographic and clinical parameters ($p>0.05$ for all; Table 1). Mean age — 32.4±6.8 and 31.9±7.1 years, respectively; proportion of women — 56.6% and 58.5%; median PCS duration — 5.2 (IQR 3.8–7.1) and 5.4 (IQR 3.9–7.3) months.

Table 1 — Baseline characteristics of study groups (M±SD or median [IQR])

Parameter	PhT Group (n=53)	PhT+PT Group (n=53)
Age, years	32.4±6.8	31.9±7.1
Women, n (%)	30 (56.6%)	31 (58.5%)
PCS duration, months	5.2 [3.8–7.1]	5.4 [3.9–7.3]
BDI-II, points	22.9±4.8	22.4±5.1
STAI-S, points	48.6±7.2	49.1±6.9
STAI-T, points	51.3±6.5	50.8±6.7
MoCA, points	24.1±1.8	24.3±1.9
IL-6, pg/ml	8.4±2.2	8.7±2.3
TNF-α, pg/ml	14.2±3.1	14.5±2.9
CRP, mg/l	5.8±1.9	5.9±2.1

Note: $p>0.05$ for all between-group comparisons.

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1. Dynamics of psychoemotional indicators.

At 8 weeks, both groups showed statistically significant improvement on all psychoemotional scales ($p<0.001$). BDI-II score decreased from 22.4±5.1 to 11.2±3.6 in the PhT+PT group (Δ=−11.2; −50.0%) versus a decrease from 22.9±4.8 to 16.7±4.4 in the PhT group (Δ=−6.2; −27.1%); between-group difference at T_1: $p<0.001$ (Table 2). The proportion of patients with BDI-II≤13 (minimal depression) in the PhT+PT group reached 67.9% vs 34.0% in the PhT group ($\chi^2=12.2$; $p<0.001$). STAI-T decreased by 14.7 points in the PhT+PT group vs 7.2 points in the PhT group ($p<0.001$), indicating deep restructuring of anxiety-cognitive attitudes through CBT mechanisms [11, 13].

Table 2 — Dynamics of psychoemotional and cognitive indicators at 8 weeks of therapy (M±SD)

Indicator	PhT T_0	PhT T_1	PhT+PT T_0	PhT+PT T_1	p*
BDI-II	22.9±4.8	16.7±4.4	22.4±5.1	11.2±3.6	<0.001
STAI-S	48.6±7.2	39.8±6.1	49.1±6.9	32.4±5.7	<0.001
STAI-T	51.3±6.5	43.6±6.4	50.8±6.7	36.1±5.9	<0.001
MoCA	24.1±1.8	25.8±1.5	24.3±1.9	27.7±1.3	<0.001

Note: * — between-group difference at T_1 (Student's t-test).

2. Cognitive indicators.

MoCA improvement in the PhT+PT group was +3.4±0.9 points (24.3→27.7) vs +1.7±0.8 points in the PhT group (24.1→25.8); $p<0.001$. The proportion of patients achieving cognitive status normalization (MoCA≥26) — 88.7% vs 50.9% ($\chi^2=17.3$; $p<0.001$). The greatest improvement was observed in attention and delayed recall subtests, which is consistent with cognitive rehabilitation data in PCS [6, 10, 16].

3. Immunological indicators.

Both interventions reduced proinflammatory marker levels, however the effect was significantly more pronounced in the PhT+PT group (Table 3). IL-6: decrease from 8.7±2.3 to 4.2±1.3 pg/ml (−51.7%) vs from 8.4±2.2 to 5.9±1.6 pg/ml (−29.8%) in the PhT group; $p<0.01$. TNF-α: from 14.5±2.9 to 7.8±2.1 pg/ml (−46.2%) vs from 14.2±3.1 to 10.4±2.5 pg/ml (−26.8%); $p<0.01$. CRP: from 5.9±2.1 to 2.8±1.1 mg/l (−52.5%) vs from 5.8±1.9 to 4.1±1.5 mg/l (−29.3%); $p<0.01$. IL-10 (anti-inflammatory) increased to 4.2±1.1 in the PhT+PT group vs 3.5±1.0 pg/ml in the PhT group ($p<0.05$) — a shift toward an anti-inflammatory profile described in psychoneuroimmunological studies [14, 15]. Immunoglobulin dynamics did not differ between groups ($p>0.05$).

Table 3 — Dynamics of immunological indicators at 8 weeks of therapy (M±SD)

Indicator	PhT T_0	PhT T_1	PhT+PT T_0	PhT+PT T_1	p*
IL-6, pg/ml	8.4±2.2	5.9±1.6	8.7±2.3	4.2±1.3	<0.01
TNF-α, pg/ml	14.2±3.1	10.4±2.5	14.5±2.9	7.8±2.1	<0.01
IL-10, pg/ml	3.0±1.0	3.5±1.0	3.1±0.9	4.2±1.1	<0.05
CRP, mg/l	5.8±1.9	4.1±1.5	5.9±2.1	2.8±1.1	<0.01
Ferritin, ng/ml	142.3±38.5	118.4±31.2	138.7±36.9	102.6±28.4	<0.05
IgG, g/l	11.8±2.1	12.1±2.0	11.9±2.2	12.3±1.9	>0.05
IgM, g/l	1.32±0.38	1.28±0.35	1.30±0.41	1.26±0.33	>0.05
IgA, g/l	2.11±0.52	2.28±0.49	2.08±0.55	2.33±0.47	>0.05

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Note: * — between-group difference at T_1.

4. Quality of life (SF-36).

Both groups demonstrated significant improvement on all 8 SF-36 subscales. However, in the PhT+PT group the improvement in psychological components was statistically significantly greater ($p<0.001$ for all between-group comparisons): "Mental Health" — +24.3 vs +12.8 points; "Vitality" — +21.7 vs +11.4; "Social Functioning" — +19.8 vs +10.2; "Role (Emotional) Functioning" — +22.1 vs +11.6. The obtained values correspond to effects described in a meta-analysis on PCS rehabilitation [15, 17] and surpass them in psychological subscales.

5. Correlation analysis.

In the combined sample (n=106) at T_1, significant associations were identified: IL-6 with BDI-II ($\rho=+0.42$; $p<0.001$), IL-6 with STAI-T ($\rho=+0.38$; $p<0.001$), IL-6 with MoCA ($\rho=-0.36$; $p<0.001$); TNF-α with BDI-II ($\rho=+0.39$; $p<0.001$), TNF-α with SF-36 "Mental Health" subscale ($\rho=-0.44$; $p<0.001$); CRP with BDI-II ($\rho=+0.31$; $p<0.01$). The obtained correlation patterns replicate international research data [7, 8] and confirm the biopsychosocial nature of PCS.

DISCUSSION

The main result of the study — the significant superiority of the combined PhT+PT program over isolated pharmacotherapy across all three key domains (psychoemotional, cognitive, immunological) and quality of life — is consistent with international data. The 50.0% BDI-II reduction achieved in the PhT+PT group corresponds to the criterion of complete therapeutic response in most RCTs on depression. A similar magnitude of anxiety reduction in studies by Li et al. (2020) and Liu et al. (2021) was achieved with 4–6-week CBT courses [11, 12], which underscores the potential of even brief structured programs.

The MoCA improvement of 3.4 points in the PhT+PT group exceeds the recognized threshold of clinically significant improvement (≥2 points). It was realized primarily through attention and delayed recall subtests — functions sensitive to anxiety and chronic stress levels, which explains the greater efficacy of CBT compared to isolated pharmacotherapy. The findings are consistent with the systematic review by Pouliopoulou et al. (2023) on PCS rehabilitation [15], which showed significant MoCA improvements following multidisciplinary interventions.

The immunological effect of PhT+PT — IL-6 reduction by 51.7%, TNF-α by 46.2%, CRP by 52.5% with a parallel increase in IL-10 — is interpreted within the psychoneuroimmunological framework. CBT and relaxation techniques reduce chronic psychoemotional stress, normalize cortisol rhythm, and increase glucocorticoid receptor sensitivity, which suppresses transcription of proinflammatory genes [14, 15]. The persistence of the IL-1β/IL-6/TNF cytokine triad as a PCS marker was confirmed by Schultheiß et al. (2022) [7], Klein et al. (2023) [8], and Phetsouphanh et al. (2022) [9].

The improvement in SF-36 "Mental Health" (+24.3 points) and "Vitality" (+21.7 points) subscales in the PhT+PT group substantially exceeds the minimal clinically important difference (≈5 points) and is comparable to effects of 8-week multidisciplinary rehabilitation programs in a Chilean PCS patient cohort (Pizarro-Pennarolli et al., 2023) [17]. The identified correlations of IL-6/TNF-α with BDI-II, STAI-T, and MoCA replicate patterns described in international studies [7, 8, 9] and confirm the biopsychosocial nature of PCS.

Limitations. The short observation period (8 weeks) does not allow assessment of long-term durability of the effect. A psychotherapeutic placebo group is absent. T-cell subpopulations (CD4+/CD8+), cortisol, and HPA axis markers were not studied. Enrollment from only two clinics in one region limits external validity. Prospective directions: 6- and 12-month follow-up, remote CBT formats, moderating influence of premorbid psychotype.

CONCLUSIONS

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1. Adding an 8-week CBT program with progressive muscle relaxation elements to standard pharmacotherapy provides significantly greater reduction of depression (BDI-II: −50.0% vs −27.1%; p<0.001) and anxiety (STAI-T: −28.9% vs −14.0%; p<0.001) in young patients with post-COVID syndrome.
2. Combined therapy (PhT+PT) achieves normalization of cognitive status (MoCA≥26) in 88.7% versus 50.9% of patients on isolated PhT (p<0.001), exceeding the threshold of clinically significant improvement.
3. In the PhT+PT group, significantly more pronounced reduction in proinflammatory markers was recorded (IL-6 −51.7%, TNF-α −46.2%, CRP −52.5%) and an increase in IL-10, indicating an immunomodulatory effect of the psychotherapeutic component.
4. The improvement in psychological SF-36 subscales ("Mental Health" +24.3 points, "Vitality" +21.7 points) in the PhT+PT group significantly exceeds the corresponding PhT group indicators (p<0.001).
5. The identified significant correlations of IL-6 and TNF-α levels with BDI-II, STAI-T, and MoCA indicators confirm the biopsychosocial nature of PCS and justify an integrative approach to its treatment.
6. The obtained data justify the inclusion of structured CBT with relaxation elements in the standard management protocol for young PCS patients at the outpatient-polyclinic level.

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