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ABSTRACT

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CLINICAL AND LABORATORY CHARACTERISTICS OF POST-COVID SYNDROME IN CHILDREN AGED 5–12 YEARS IN RELATION TO IGG LEVELS TO SARS-COV-2

Coronavirus infection caused by SARS-CoV-2 is a risk factor for the development of post-Covid syndrome in pediatric patients. The clinical presentation of pediatric post-COVID syndrome is highly heterogeneous. The identified associations between clinical, inflammatory, and coagulation parameters highlight potential mechanisms underlying prolonged post-COVID manifestations and may contribute to the development of improved monitoring strategies in pediatric practice.

Aim of the study. To investigate the clinical and laboratory characteristics of post-COVID syndrome in children aged 5–12 years, with a focus on inflammatory, immune, and coagulation markers, and to determine the correlations between clinical manifestations and laboratory parameters.

Materials and methods. A prospective open cohort study was conducted involving 110 children aged 5–12 years, including 80 patients with post-COVID syndrome and 30 children without a history of SARS-CoV-2 infection (control group). Clinical symptoms, complete blood count, coagulation profile, levels of IgG to SARS-CoV-2, C-reactive protein (CRP), fibrinogen, and electrocardiographic findings were assessed.

Statistical analysis included calculation of means, standard deviations, medians, 95% confidence intervals, and Pearson or Spearman correlation coefficients. Statistical significance was set at $p < 0.05$.

Results. Most children with post-COVID syndrome exhibited asthenic, neurological, respiratory, and gastrointestinal manifestations: fatigue (91.3%), fever (96.3%), headache (57.5%), sleep disturbances (72.5%), and attention deficit (63.8%).

The mean hemoglobin level was 130.4 ± 14.9 g/L, erythrocyte sedimentation rate (ESR) – 18.6 ± 12.4 mm/h, and fibrinogen – 3.86 ±

1.14 g/L. Elevated CRP (>10 mg/L) was observed in more than half of the patients, indicating persistent low-grade inflammation. A significant positive correlation was found between fibrinogen and IgG to SARS-CoV-2 (r = 0.27; *p* = 0.017), confirming the association between humoral immune activation and ongoing inflammatory response.

Coagulation parameters demonstrated a tendency toward hypercoagulability, while ECG findings revealed predominantly functional changes, such as sinus arrhythmia (28.8%) and incomplete right bundle branch block (23.8%).

Conclusions. Post-COVID syndrome in children is a multisystem condition characterized by sustained inflammation, activation of the coagulation cascade, and endothelial dysfunction. Identified clinical and laboratory correlations highlight the contribution of immunoinflammatory mechanisms in the development of post-COVID alterations and emphasize the need for dynamic monitoring and long-term follow-up of affected children.

Keywords: Post-COVID syndrome, SARS-CoV-2, multisystem inflammatory syndrome (MIS-Co), C-reactive protein, endothelial dysfunction, clinicopathological correlations, immunoinflammatory cascade.

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РЕЗЮМЕ

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КЛІНІКО-ЛАБОРАТОРНА ХАРАКТЕРИСТИКА ПОСТКОВІДНОГО СИНДРОМУ У ДІТЕЙ 5-12 РОКІВ ЗАЛЕЖНО ВІД РІВНЯ IGG ДО SARS-COV-2

Перенесена коронавірусна інфекція викликана SARS-CoV-2 є фактором ризику розвитку постковідного синдрому у пацієнтів дитячого віку. Особливості перебігу стану, який вкладається в постковідний синдром варіабельні. Виявлені кореляційні зв'язки між IgG та клініко-лабораторними даними можуть бути використані для створення клінічних предикторів ризику затяжного перебігу постковідного синдрому й оптимізації програм реабілітації у педіатричній практиці.

Мета роботи – Вивчити клініко-лабораторні особливості перебігу постковідного синдрому у дітей віком 5–12 років із визначенням запальних, імунних та коагуляційних маркерів, а також встановити взаємозв'язки між лабораторними показниками та клінічними проявами.

Матеріали і методи. Проведено проспективне відкрите когортне дослідження, до якого включено 110 дітей віком 5–12 років, із них 80 пацієнтів із постковідним синдромом та 30 дітей контрольної групи без ознак перенесеної SARS-CoV-2-інфекції. Оцінювалися клінічні прояви, показники загального аналізу крові, коагулограми, рівень IgG до SARS-CoV-2, С-реактивного білка (СРБ), фібриногену, а також результати електрокардіографії. Статистичний аналіз включав визначення середніх значень, стандартного відхилення, медіани, 95% довірчих інтервалів та кореляційних коефіцієнтів Пірсона або Спірмена ($p < 0,05$ вважали статистично значущим).

Результати. У більшості дітей із постковідним синдромом спостерігалися астенічні, неврологічні, респіраторні та

гастроінтестинальні прояви: слабкість (91,3%), лихоманка (96,3%), головний біль (57,5%), порушення сну (72,5%) і концентрації уваги (63,8%). Середні значення гемоглобіну становили 130,4 ± 14,9 г/л, ШОЕ — 18,6 ± 12,4 мм/год, фібриногену — 3,86 ± 1,14 г/л. У більшості дітей відзначалося підвищення СРБ (>10 мг/л) та тривале збереження системної запальної реакції. Встановлено достовірну позитивну кореляцію між рівнем фібриногену та IgG до SARS-CoV-2 (r = 0.27; *p* = 0.017), що підтверджує участь гуморального імунітету в механізмах постінфекційного запалення. Показники коагулограми свідчать про тенденцію до гіперкоагуляції, а ЕКГ — про наявність переважно функціональних змін (синусова аритмія — 28,8%, неповна блокада правої ніжки пучка Гіса — 23,8%).

Висновки. Постковідний синдром у дітей має мультисистемний характер і супроводжується персистенцією запалення, активацією коагуляційного каскаду та ендотеліальною дисфункцією. Виявлені клініко-лабораторні взаємозв'язки підтверджують роль імунозапальних механізмів у формуванні постковідних змін та підкреслюють необхідність динамічного моніторингу таких пацієнтів.

Ключові слова: постковідний синдром, SARS-CoV-2, мультисистемний запальний синдром (MIS-Co), С-реактивний протеїн, ендотеліальна дисфункція, коагуляційні порушення, імунозапальний каскад.

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INTRODUCTION

Post-COVID-19 syndrome (post-acute sequelae of SARS-CoV-2, PASC) in children is increasingly recognized as a distinct multisystem condition characterized by symptoms persisting for 4–12 weeks or longer after acute SARS-CoV-2 infection. According to multicenter cohort studies, school-aged children most commonly present with asthenia, sleep and attention disturbances, headaches, and reduced exercise tolerance, while a subset predominantly exhibits respiratory and gastrointestinal manifestations [1–4, 10]. At the same time, the spectrum and duration of symptoms in the pediatric population demonstrate considerable heterogeneity, depending on age, severity of the primary infection, and individual host-related factors [3, 4].

The immunopathogenesis of pediatric PASC is thought to involve prolonged low-grade inflammatory activity, dysregulation of innate and adaptive immune responses, post-infectious endothelial dysfunction, and alterations in vascular homeostasis [5–8, 13, 14]. Alongside clinical manifestations, laboratory evidence of ongoing inflammatory and endothelial activation has been reported, including elevated C-reactive protein (CRP), increased erythrocyte sedimentation rate (ESR), hyperfibrinogenemia, coagulation abnormalities, and shifts in leukocyte profiles toward neutrophilia [2, 6, 9, 15, 16]. However, the relationships between clinical symptoms and laboratory markers in children aged 5–12 years remain insufficiently characterized, and published data are often inconsistent or derived from heterogeneous pediatric cohorts [3, 7, 11].

Growing attention has been directed toward the coagulation component of PASC. Pediatric case series and cohort studies suggest that a proportion of children demonstrate persistent signs of endothelial activation and secondary hypercoagulability, including elevated fibrinogen levels, variability in aPTT and PT, and increased soluble fibrin–monomer complexes, which may contribute to microcirculatory disturbances and cardiovascular complaints [6, 8, 17, 18]. In contrast, the clinical relevance of the humoral immune response—specifically IgG antibodies to SARS-CoV-2—beyond their role as markers of prior infection and immune memory remains uncertain. In particular, the prognostic value of IgG levels and their relationship to inflammatory and coagulation parameters in pediatric post-COVID-19 syndrome has not been clearly established [7, 11–13].

Cardiac manifestations of PASC in children are generally functional and transient, including rhythm variability, sinus arrhythmia, and incomplete right bundle branch block, and are believed to reflect

autonomic imbalance and temporary involvement of the endothelium and myocardium in the context of post-infectious immune dysregulation [2, 8, 19–24]. Despite increasing recognition of these features, standardized approaches to risk stratification and long-term monitoring remain limited, largely due to the paucity of studies that comprehensively evaluate clinical symptoms, inflammatory and hemostatic markers, humoral immune responses, and electrocardiographic findings within a single cohort of younger school-aged children.

In this context, a comprehensive clinical and laboratory assessment of children aged 5–12 years with post-COVID-19 syndrome is of particular clinical relevance. Such an approach may (1) identify informative routine biomarkers reflecting low-grade inflammation and endothelial activation, and (2) clarify the relationships between clinical manifestations, hematological and coagulation parameters, and humoral immune responses. This integrated evaluation is essential for improving diagnostic stratification and developing evidence-based follow-up strategies in pediatric post-COVID-19 care [1, 5, 6, 9–12, 25–34]

Aim of the study. To investigate the clinical and laboratory characteristics of post-COVID syndrome in children aged 5–12 years, with a focus on inflammatory, immune, and coagulation markers, and to determine the correlations between clinical manifestations and laboratory parameters.

MATERIALS AND METHODS

According to the study design, a non-randomized, open-label, prospective cohort observation was conducted among pediatric patients with post-COVID-19 syndrome at the Municipal Children's Hospital No. 5 of the Zaporizhzhia City Council. A total of 110 participants were enrolled and divided into two groups based on serum IgG levels to SARS-CoV-2. The first group included 80 children diagnosed with post-COVID-19 syndrome, while the second (control) group consisted of 30 children without post-COVID-19 manifestations and with negative IgG to SARS-CoV-2 infection. The groups were matched by age and sex within the inclusion criteria. Parents or legal guardians of all participants provided written informed consent and were fully informed about the study objectives and procedures.

The inclusion criteria were as follows: age between 5 and 12 years; hospitalization with clinical manifestations consistent with post-COVID-19 syndrome occurring between 4 and 12 weeks after acute SARS-CoV-2 infection; documented previous SARS-CoV-2 infection confirmed either by positive PCR testing during the acute phase or by the presence of IgG antibodies to the SARS-CoV-2 spike protein, measured quantitatively and expressed in binding antibody units per milliliter (BAU/mL) in accordance with World Health Organization (WHO) standards; and provision of written informed consent by parents or legal guardians. Children included in the main group were hospitalized with fever, symptoms of systemic intoxication, and clinical signs of involvement of one or more organ systems with varying degrees of severity.

To minimize the potential influence of confounding factors on inflammatory markers (CRP and ESR), children with clinically apparent chronic inflammatory conditions or active infectious diseases unrelated to SARS-CoV-2 were not included in the study. All participants underwent routine clinical examination at admission, and no signs of active chronic inflammation were identified.

Clinical parameters were evaluated, including patient and parental complaints, body temperature, fatigue, headache, dizziness, cough, chest pain, abdominal pain, nausea, vomiting, diarrhea, as well as sleep and attention disturbances. Laboratory assessments comprised a complete blood count (erythrocyte sedimentation rate [ESR], leukocytes, platelets, lymphocytes), biochemical tests (coagulation profile), and immunoassays (C-reactive protein and IgG antibodies to SARS-CoV-2). Electrocardiography (ECG) was performed to assess cardiac rhythm. Statistical analysis was carried out to determine correlations between serum IgG levels to SARS-CoV-2 and the clinical and laboratory manifestations of post-COVID-19 syndrome.

General clinical health indicators were assessed through physical examination, medical history collection, and evaluation of patient and parental complaints. All general laboratory and biochemical analyses, including the determination of IgG antibodies to SARS-CoV-2, were performed at the Clinical Diagnostic Laboratory of the Municipal Children's Hospital No. 5, Zaporizhzhia City Council.

The statistical analysis was based on testing the normality of data distribution using the Shapiro–Wilk test. When appropriate, nonparametric approaches were applied alongside parametric methods. Group comparisons were performed using the independent two-sample t-test in cases where normality was confirmed by the Shapiro–Wilk test and homogeneity of variances by Levene's test. If these assumptions were violated, the Mann–Whitney U test was used. For single-factor parameters, analysis of variance (ANOVA) was employed, and in cases of non-normal distribution, the Kruskal–Wallis test was applied. Post hoc comparisons were conducted using Dunn's method with Bonferroni correction or the Tukey test to assess intergroup differences.

To summarize the results, arithmetic means with corresponding standard deviations were calculated, and the standard error of the mean was evaluated with the

construction of 95% confidence intervals. The level of statistical significance was set at $p < 0.05$, in accordance with international standards for statistical data processing.

The strength of the relationships between independent quantitative variables was assessed using correlation analysis, applying Pearson's correlation coefficient, and, when appropriate, Spearman's rank correlation coefficient.

All computations and statistical algorithms were implemented as custom macros using SPSS version 16, Microsoft Excel 2015, and Statistica for Windows version 13 (StatSoft Inc., license No. JPZ804I382130ARCN10-J).

All participating children and their parents or legal guardians were fully informed about the purpose and procedures of the study and provided written informed consent prior to inclusion.

RESULTS

Gender and age characteristics of the study sample were analyzed. Among all 110 participants, there were 55 boys and 55 girls. In the first group, the ratio was 37 boys to 43 girls, while in the control group of 30 children, there were 18 boys and 12 girls.

The mean age of the study population was 9.5 ± 2.69 years. The average age among boys was 9.27 ± 2.69 years, whereas among girls it was 9.85 ± 2.66 years.

The results of the study revealed that clinical manifestations of post-COVID-19 syndrome in children of primary school age exhibit considerable variability and include both symptoms of general asthenia and signs of involvement of the respiratory, gastrointestinal, and cardiovascular systems.

In the group of 80 patients with confirmed post-COVID-19 syndrome, the predominant symptoms were general weakness (91.3%; 95% CI 83.9–95.8), fever (96.3%; 95% CI 90.5–98.8), and headache (57.5%; 95% CI 46.2–68.0). These manifestations reflect the systemic response of the body to the sequelae of SARS-CoV-2 infection and correlate with laboratory indicators of inflammation, particularly elevated levels of C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR).

Among respiratory disorders, cough was reported in 55.0% of children (95% CI 43.6-65.9) and difficulty breathing in 61.3% (95% CI 50.1-71.4). In most cases, respiratory symptoms persisted after clinical recovery, consistent with data from *Radtke T, 2023 Palacios S. and Behnood SA*, which indicate prolonged post-infectious broncho-obstruction in children.

Chest pain was observed in 22.5% of children (95% CI 14.8–32.5) and was more frequently associated with shortness of breath, which may indicate functional or inflammatory alterations of the vascular endothelium and myocardium.

Among gastrointestinal symptoms, abdominal pain was found in 68.8% (95% CI 57.6-78.0), nausea in 46.3%, vomiting in 10.0%, and diarrhea in isolated cases (1.3%). These disorders are confirmed by data from *Nehme M. et al. 2022* on post-infectious changes in the digestive tract associated with microcirculation dysregulation and reactive changes in the microbiota.

Sleep disturbances (72.5%) and impaired concentration (63.8%) were observed in the majority of patients, suggesting the involvement of central regulatory mechanisms and the autonomic nervous system. These symptoms showed associations with the duration of fever and IgG levels to SARS-CoV-2, consistent with existing data on the role of post-infectious neuroinflammation. (*Taquet M et al.,2022*).

Among cardiac manifestations, muffled heart sounds were detected in 68.8% of children, while a systolic murmur was observed in 55.0%. These findings were more frequent in patients with elevated levels of inflammatory markers and fibrinogen, which may indicate transient inflammatory involvement of the myocardium or endothelium. (*Usachova O.2022, Guner Ozenen G*).

None of the patients exhibited persistent loss of taste or smell, which is consistent with data from European cohort studies *(Ludvigsson, 2021),* where such symptoms were reported as rare among children (*Fig. 1*).

Thus, the clinical presentation of post-COVID-19 syndrome in children is characterized by the predominance of systemic asthenic, neurological, and inflammatory manifestations, with frequent involvement of the respiratory and gastrointestinal systems. Most patients exhibited a combination of three or more symptoms, confirming the multisystem nature of the pathological process.

The complete blood count parameters in children of the main group indicated signs of systemic inflammatory response and activation of immune reactivity. The mean hemoglobin level was 130.4 ± 14.9 g/L with a median of 131 g/L, which is at the lower limit of the age-specific norm; however, mild anemia was detected in 17.5% of patients. In the control group, the mean hemoglobin level was 134.8 ± 13.6 g/L, with no statistically significant difference between the groups ($p > 0.05$).

The erythrocyte count in children of the main group ranged from 3.4×10^{12}/L to 5.8×10^{12}/L (mean 4.57 ± 0.59×10^{12}/L, median 4.6×10^{12}/L). In 9.3% of cases, a tendency toward a moderate decrease in red blood cell count was noted, which may be considered a manifestation of delayed post-infectious anemia previously described in pediatric patients following COVID-19 (*Boyarchuk O et al.; Maddux AB et al., 2022*).

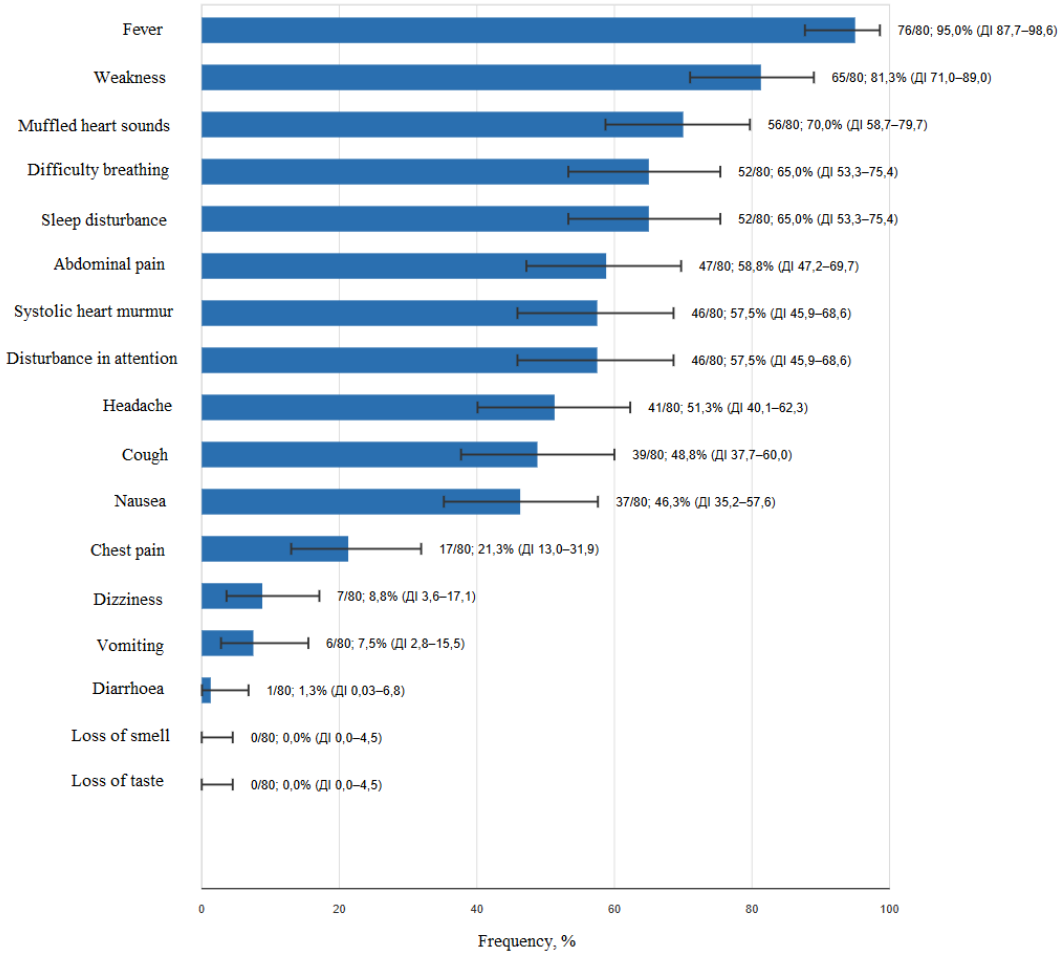


Figure 1. Incidence of major clinical symptoms in children with post-covid syndrome (column chart with 95% CI, n=80, %)

The mean leukocyte count was 8.2 ± 3.9 × 10⁹/L, exceeding the age-specific norm in 28% of children, with 14% of patients demonstrating leukocytosis above 11 × 10⁹/L, which correlated with more severe clinical manifestations and elevated CRP levels. These findings are consistent with literature reports *(Maddux AB et al., Zimmermann P et al.)* indicating sustained activation of the inflammatory response during the convalescent period in children. The erythrocyte sedimentation rate (ESR) in children with post-COVID-19 syndrome was significantly elevated — 18.6 ± 12.4 mm/h, with a median of 16 mm/h and maximum values reaching 52 mm/h. In the control group, the mean ESR was 7.4 ± 3.1 mm/h ($p < 0.001$). Elevated ESR values were observed in 40% of participants and showed a direct correlation with CRP levels ($r = 0.32$; $p < 0.01$), confirming the presence of systemic inflammation. (*Zabeida A et al.*) (*Fig. 2*).

The mean platelet count was 274 ± 88 × 10⁹/L; however, 11.3% of children demonstrated thrombocytosis exceeding 400 × 10⁹/L. This finding reflects activation of the megakaryocytic pathway, which is typical for children during the post-inflammatory recovery phase. (*Kaushik S et al, Boyarchuk O et al*).

Segmented neutrophils predominated in the leukocyte formula, with a mean value of 41 ± 13%, while the proportion of band cells was 19.6 ± 10.8%, exceeding the age-specific norm in approximately one-third of the children. A positive correlation was found between the proportion of band neutrophils and peak body temperature ($r = 0.25$; $p = 0.029$), indicating neutrophil activation during the acute phase of inflammation. In 62.5% of children, a relative decrease in lymphocytes to 28.3 ± 9.7% was observed, which is likely associated with post-infectious redistribution within the cellular components of the immune system**.** Monocytosis was detected in 9.8% of patients, which is consistent with the alterations described in the studies by *Yong SJ. ,2022* (*Fig. 2*).

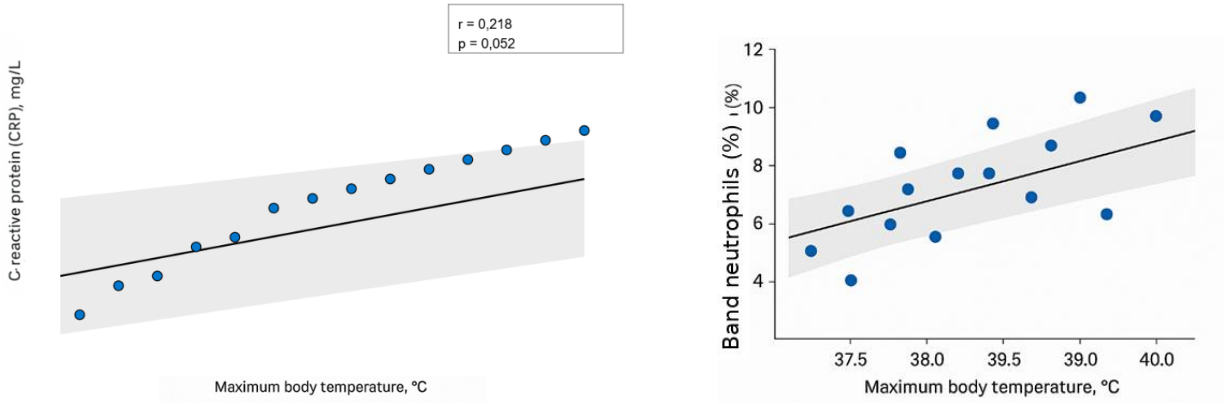


Figure 2. Correlation between maximum body temperature and C-reactive protein (CRP) levels in children with post-covid syndrome; Correlation between maximum body temperature and band neutrophils (%, *r* = 0.25; *p* < 0.05)

Thus, the results of hematological studies indicate the persistence of inflammatory response markers in most children following SARS-CoV-2 infection, manifested by neutrophilia, lymphopenia, and elevated erythrocyte sedimentation rate (ESR). These findings support the hypothesis of ongoing low-grade inflammation during the post-COVID period, which may contribute to the development of clinical manifestations of the syndrome.

At the same time, correlation analysis did not reveal significant associations between ESR and leukocyte parameters, including total white blood cell count, band neutrophils, and lymphocytes (*Fig. 3*), suggesting heterogeneity of cellular inflammatory responses in children with post-COVID-19 syndrome.

The mean Activated Partial Thromboplastin Time (aPTT) was 29.1 ± 9.5 seconds, with a median of 30.0 seconds (IQR 23.5–36.0). Prolonged aPTT (>36 seconds) was observed in 27% of patients, whereas shortened aPTT (<25 seconds) was found in 18%. This variability indicates the coexistence of both hypocoagulable and hypercoagulable responses, which may reflect different phases of endothelial function recovery following systemic inflammation.

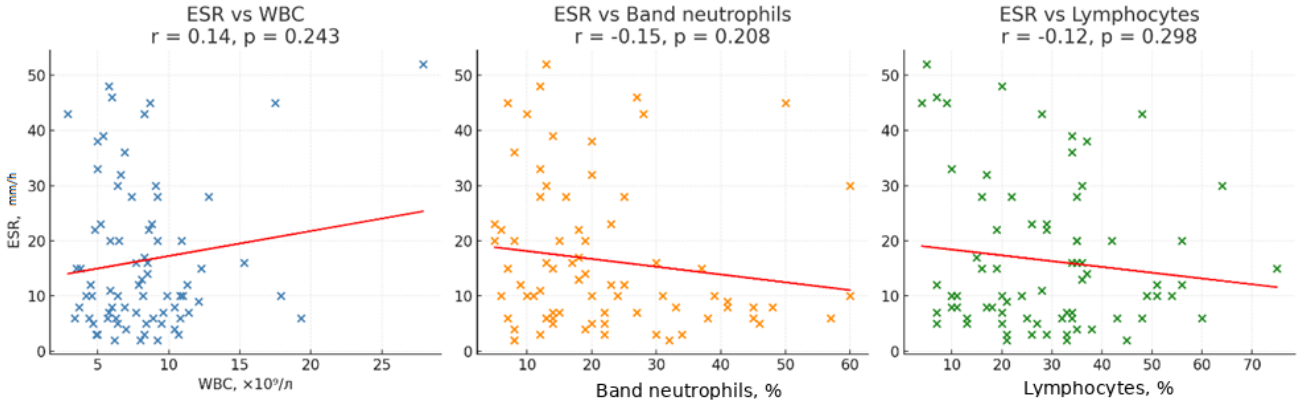


Figure 3 – Scatter plots illustrating the relationships between erythrocyte sedimentation rate (ESR) and leukocyte parameters (WBC, band neutrophils, and lymphocytes)

The Prothrombin Time (PT) ranged from 62% to 112%, with a mean value of 85.7 ± 11.8% and a median of 86.0%. A decrease in PT (<80%) was recorded in 22% of children, suggesting a moderate prolongation of prothrombin time, likely associated with elevated fibrinogen levels.

The mean fibrinogen level was 3.86 ± 1.14 g/L, with a median of 3.69 g/L (IQR 2.56–4.84). Hyperfibrinogenemia (>4.5 g/L) was detected in 35% of patients, indicating an acute-phase inflammatory response. A significant positive correlation was established between fibrinogen levels and IgG concentrations to SARS-CoV-2 (r = 0.27; p = 0.017), which may reflect activation of the humoral immune response during the convalescent phase (*Sinha P, Matthay M.2022*).

The mean thrombin time (TT) was 20.3 ± 9.1 seconds, with a median of 18.0 seconds (IQR 15.0–21.0). In 18% of children, TT exceeded the upper limit of normal (>25 seconds), which may indicate a delayed conversion of fibrinogen to fibrin.

An increase in soluble fibrin–monomer complex (SFMC) levels was observed in some patients and correlated with clinical signs of endothelial dysfunction, such as muffled heart sounds, dyspnea, and chest pain.

Thus, children with post-COVID-19 syndrome exhibited a range of hemostatic alterations characterized by a predominance of hypercoagulability, activation of fibrinogenesis, and mild prolongation of thrombin time. These findings confirm the involvement of endothelial inflammation and dysregulation of the coagulation cascade in the pathogenesis of post-COVID cardiovascular complications. The obtained results are consistent with the data reported by *Zabeida A et al, Kaushik S,* which emphasize the role of persistent hemostatic disturbances in children following COVID-19 (*Fig. 4*).

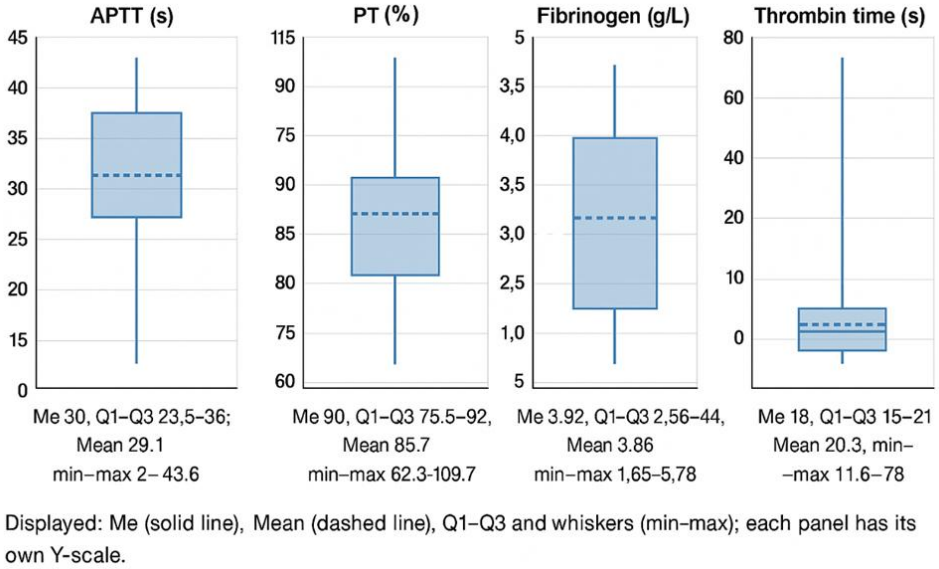


Figure 4. Box-plot of the main indicators of the coagulogram in children with post-covid syndrome (aPTT, PT, fibrinogen, PT; median, interquartile range, whiskers - min-max; dotted - average value)

The analysis of systemic inflammatory markers revealed that most children with post-COVID-19 syndrome exhibited signs of ongoing or low-grade inflammation, manifested by elevated levels of C-reactive protein (CRP) and an increased erythrocyte sedimentation rate (ESR).

The mean C-reactive protein (CRP) level was 32.4 ± 22.8 mg/L, with a median of 26 mg/L (IQR 12–42 mg/L), ranging from 6 mg/L to 95 mg/L. In 58.7% of patients, CRP levels exceeded 10 mg/L, confirming the presence of residual inflammatory activity during the convalescent period. These findings are consistent with the reports of *Zabeida A et al, Kaushik S ., Boyarchuk O 2023),* in which children with post-COVID manifestations also demonstrated prolonged CRP elevation as a marker of immune-inflammatory activation.

Statistical analysis revealed a weak positive trend between CRP levels and maximum body temperature; however, this association did not reach statistical significance (r = 0.22; p = 0.052) (Fig. 5A). Therefore, no definitive correlation between the intensity of the febrile response and systemic inflammatory activity can be concluded.

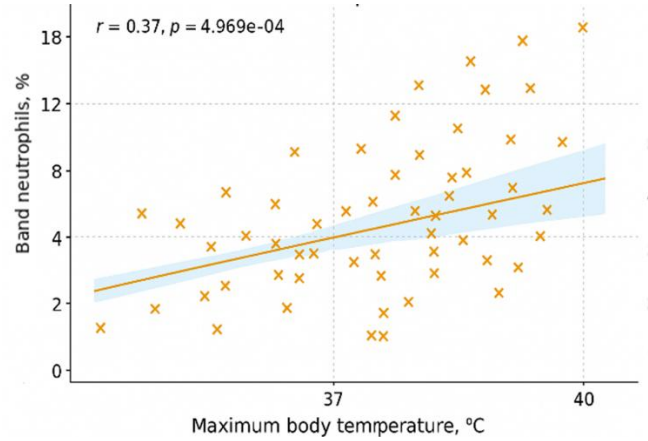
In contrast, a statistically significant positive correlation was confirmed between CRP and ESR (r = 0.32; p = 0.0037) (Fig. 2), indicating a coordinated acute-phase response. Such patterns are characteristic of the post-viral convalescent period in children, during which low-grade inflammation may persist, potentially maintained by cytokine-mediated mechanisms (Davis HE, 2022).

The mean peak body temperature among the studied children was 38.4 ± 0.9 °C, with 47.5% of patients exhibiting fever above 38.5 °C.

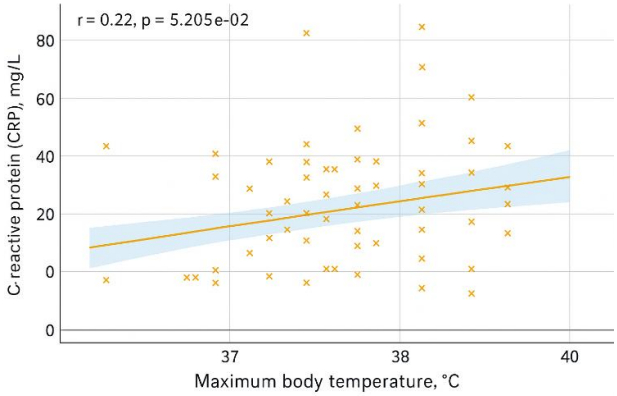
Significant correlations were identified between elevated body temperature and increased levels of CRP, ESR, and the proportion of band neutrophils ($r = 0.25$; $p = 0.029$), confirming the systemic nature of the inflammatory response. The obtained results indicate that CRP remains the most sensitive laboratory marker of inflammatory activity in children with post-COVID-19 syndrome, showing significant correlations with other indicators of systemic inflammation (*Fig. 5B*).

These findings are consistent with the results reported by *Maddux AB et al 2023.* which demonstrate the persistence of low-grade inflammation in 40–60% of children within 1–3 months after recovery from COVID-19.

The level of IgG antibodies to SARS-CoV-2 was determined in all children in the main group and was used to confirm prior infection and to assess the intensity of the humoral immune response. The mean IgG concentration in children with post-COVID-19 syndrome was 7.68 ± 3.12 BAU/mL, with a median of 8.6 BAU/mL (IQR 5.2–9.3). High antibody levels (>10 BAU/mL), consistent with a stable post-infectious immune response, were observed in 23.7% of children, whereas low IgG levels (<4 BAU/mL) were detected in 18.8% of cases, potentially indicating an insufficient humoral response or antibody production exhaustion following immune system hyperactivation. These findings are consistent with previous reports demonstrating variability in the persistence of IgG antibodies in children depending on the severity of the primary SARS-CoV-2 infection.



5A



5B

Figure 5A. Trend between maximum body temperature and C-reactive protein (CRP, mg/L) levels in children with post-COVID-19 syndrome (r = 0.22; p = 0.052; linear regression with 95% confidence interval).

Figure 5B. Correlation between maximum body temperature and erythrocyte sedimentation rate (ESR, mm/h) (*r* = 0.32; *p* = 0.0037; significant positive correlation)

Correlation analysis showed no significant associations between IgG levels and systemic inflammatory markers, including C-reactive protein (CRP) (r = 0.08; p = 0.495) and erythrocyte sedimentation rate (ESR) (r = −0.10; p = 0.386). These results indicate that the magnitude of the humoral immune response was not directly related to the level of ongoing systemic inflammation in children with post-COVID-19 syndrome.

An important finding of the present study was the identification of a moderate but statistically significant association between IgG levels to SARS-CoV-2 and fibrinogen concentration (Fig. 6). In contrast to the absence of significant correlations between IgG levels and classical inflammatory markers such as CRP and ESR, the observed relationship with fibrinogen suggests a distinct pathophysiological link between humoral immune activation and the coagulation–endothelial axis.

Fibrinogen is a well-recognized acute-phase reactant and a key mediator of coagulation and endothelial function. Its association with IgG levels may reflect persistent low-grade endothelial activation or dysregulation of the hemostatic system in the post-infectious period, rather than ongoing systemic inflammation. This finding supports the concept that post-COVID-19 syndrome in children may involve prolonged immune–endothelial interactions, even in the absence of overt inflammatory activity as measured by CRP or ESR.

The moderate strength of this association indicates that IgG-related immune activity is likely one of several contributing factors in the complex pathogenesis of post-COVID-19 syndrome, rather than a sole determinant. Nevertheless, the observed IgG–fibrinogen relationship highlights the potential role of coagulation-related pathways in mediating post-infectious sequelae and aligns with emerging evidence on endothelial involvement in pediatric post-COVID conditions.

Thus, children with post-COVID-19 syndrome demonstrated heterogeneity in their immune response — ranging from high post-infectious activity to a tendency toward antibody production exhaustion. The identified correlations between IgG and fibrinogen confirm that immune activation is closely linked to

coagulation and cardiac alterations. This underscores the key role of the endothelial–inflammatory cascade in the pathogenesis of post-COVID-19 syndrome in children.

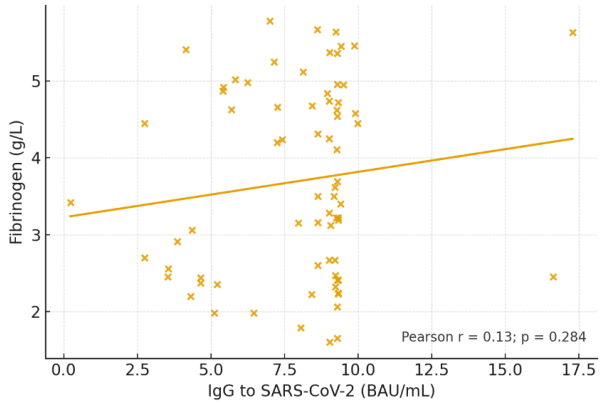


Figure 6. Correlation between IgG to SARS-CoV-2 and fibrinogen (g/L) (r = 0.27; p = 0.017)

The analysis of electrocardiographic (ECG) findings in children aged 5–12 years with post-COVID-19 syndrome revealed functional alterations in cardiac rhythm and conduction, which may result from inflammatory–endothelial myocardial involvement and autonomic nervous system dysregulation.

Among the 80 children in the main group, rhythm or conduction abnormalities were detected in 42 patients (52.5%). The most common finding was sinus arrhythmia, observed in 23 children (28.8%; 95% CI 20.0–39.5), characterized by variability in R–R intervals without other ECG abnormalities. According to the literature *(Taquet M et al., Buonsenso D)*, this type of arrhythmia is considered a manifestation of autonomic imbalance or increased parasympathetic activity that persists following viral involvement.

The second most frequent finding was incomplete right bundle branch block (IRBBB), observed in 19 children (23.8%; 95% CI 15.8–34.2). Such conduction abnormalities were generally asymptomatic but, in some cases, were accompanied by muffled heart sounds or transient complaints of chest pain.

The occurrence of IRBBB likely reflects edema or inflammation within the ventricular conduction system, consistent with the findings of *Bilyi D et al., Patel T et al.,* where similar changes are interpreted as post-inflammatory transient repolarization disturbances (*Fig. 7*).

Overall, more than half of the children exhibited mild yet clinically relevant rhythm or conduction abnormalities, indicating the need for dynamic cardiological follow-up in such patients.

Thus, in children with post-COVID-19 syndrome, moderate transient rhythm and conduction disturbances are frequently observed. Although these changes are typically not accompanied by significant clinical symptoms, they may serve as markers of autonomic imbalance or endothelial activation of the myocardium.

These findings confirm the multisystem nature of post-COVID-19 syndrome, in which the cardiovascular system plays a key role in the clinical manifestation of the disorder.

The clinical and laboratory findings in children aged 5–12 years with post-COVID-19 syndrome demonstrated the multisystem nature of the condition, encompassing residual inflammatory, immunological, coagulation, and cardiac alterations. The most common clinical manifestations included general weakness (91.3%), fever (96.3%), headache (57.5%), sleep disturbances (72.5%), and impaired concentration (63.8%), reflecting both astheno-neurotic and inflammatory components of the post-infectious process. The high prevalence of respiratory (cough, shortness of breath) and gastrointestinal symptoms (abdominal pain, nausea) further supports the multi-organ nature of post-COVID-19 syndrome in children.

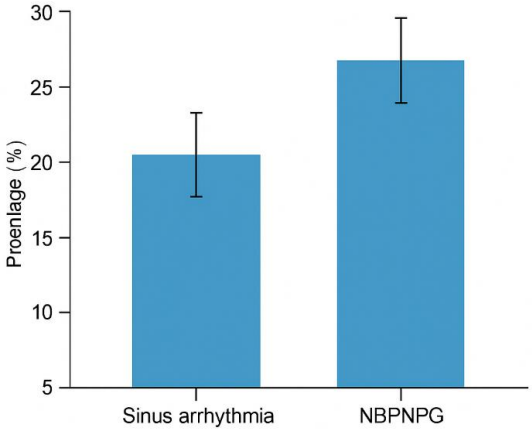


Figure 7. Incidence of major ECG changes in children with post-covid syndrome (sinus arrhythmia, IRBBB, % with 95% CI)

Hematological parameters in most children revealed a moderate increase in ESR (18.6 ± 12.4 mm/h), leukocytosis with a predominance of band neutrophils (19.6 ± 10.8%), and a reduction in lymphocytes (28.3 ± 9.7%), indicating the persistence of the inflammatory response even several weeks after infection. Elevated C-reactive protein (CRP) levels above 10 mg/L in more than half of the patients, along with a significant correlation between CRP and ESR ($r = 0.32$; $p < 0.01$), confirm the presence of low-grade

systemic inflammation, as previously reported by *Maddux AB et al.*

The coagulation profile demonstrated a tendency toward hypercoagulability, with elevated fibrinogen levels (3.86 ± 1.14 g/L), moderate shortening of APTT, and decreased PT in some children. These alterations indicate endothelial activation and an acute-phase response, as evidenced by a positive correlation between fibrinogen and IgG to SARS-CoV-2 (r = 0.27; p = 0.017). Thus, children with post-COVID-19 syndrome develop a secondary hypercoagulable state that may increase the risk of microcirculatory disturbances and warrants long-term monitoring of hemostatic parameters *(Sinha et al., 2022).*

IgG levels in most children indicated a stable post-infectious humoral response (7.68 ± 3.12 BAU/mL); however, in some patients with pronounced clinical symptoms, hyperactivation of humoral immunity was observed, accompanied by elevated fibrinogen levels. This suggests that enhanced humoral activity may sustain endothelial inflammation and contribute to functional myocardial overload, which aligns with the hypotheses proposed by *Guner Ozenen G et al.*

In more than half of the children (52.5%), ECG revealed minimal yet clinically significant changes—predominantly sinus arrhythmia (28.8%) and incomplete right bundle branch block (23.8%). Such abnormalities were more frequently observed in patients with elevated fibrinogen levels, which may indicate post-inflammatory dysfunction of autonomic regulation.

No persistent arrhythmias or structural myocardial lesions were detected; however, the findings highlight the necessity of long-term cardiologic monitoring in children with post-COVID-19 syndrome.

In summary, among children aged 5–12 years who have recovered from COVID-19, post-COVID-19 syndrome predominantly exhibits a systemic inflammatory and neurovegetative nature, with endothelial activation, humoral immune response, and microcirculatory disturbances playing key roles. Correlation analyses demonstrated close interrelations between IgG, fibrinogen, and NT-proBNP levels, confirming the involvement of immunoinflammatory mechanisms in the development of cardiovascular alterations.

The obtained data are consistent with recent international studies *Patel T et al., Guner Ozenen G et al.* and contribute to a deeper understanding of the pathogenesis of post-COVID-19 syndrome in children.

DISCUSSION

The obtained results demonstrate that post-COVID-19 syndrome in children aged 5–12 years is characterized by multisystem involvement, with inflammatory, immune, hemostatic, and cardiac alterations contributing to its clinical presentation. Importantly, these changes persist beyond the acute phase of SARS-CoV-2 infection and remain evident despite apparent clinical recovery.

The findings indicate that a substantial proportion of children continue to exhibit signs of low-grade systemic inflammation and functional dysregulation in the post-infectious period. Clinically, this is manifested by a combination of asthenic symptoms, neurovegetative disturbances, and mild cardiac abnormalities, supporting the concept of a prolonged post-infectious condition rather than residual effects of acute disease.

The predominance of symptoms such as general weakness, sleep disturbances, impaired concentration, and headache suggests the involvement of central regulatory mechanisms and dysregulation of the autonomic nervous system. Similar clinical patterns were reported by Radtke T et al. (2021), who described the development of post-COVID-19 manifestations in children 4–12 weeks after acute infection, predominantly presenting with fatigue, reduced cognitive performance, and emotional lability.

Our results are consistent with these observations, as more than 70% of patients in the present cohort exhibited neurological or behavioral symptoms even after normalization of routine somatic parameters. This finding underscores the dissociation between subjective clinical complaints and standard clinical recovery markers, highlighting the need for comprehensive post-infectious follow-up in pediatric patients.

The high prevalence of fever, cough, and shortness of breath, together with gastrointestinal manifestations such as abdominal pain and nausea, reflects the multisystem nature of post-COVID-19 syndrome in children. Comparable clinical patterns have been reported by Bilyi D et al. (2022), who described combined involvement of the respiratory, cardiovascular, and gastrointestinal systems in pediatric patients with post-COVID-19 syndrome, particularly in the presence of endothelial dysfunction.

The persistence of elevated CRP and ESR levels 4–8 weeks after acute infection indicates ongoing low-grade inflammatory activity. This observation is consistent with previous reports by Kaushik S et al. (2021) and Zabeida A et al. (2023), who described similar inflammatory profiles in children with multisystem inflammatory syndrome (MIS-C). In the present study, a significant association was observed between CRP and ESR (r = 0.32; $p < 0.01$), supporting the coordinated activation of acute-phase inflammatory responses. In contrast, the relationship between CRP levels and febrile response demonstrated only a weak, non-significant positive trend, suggesting that residual inflammatory activity may persist independently of overt fever in the post-infectious period.

Hematological findings, including an increased proportion of band neutrophils (19.6 ± 10.8%) and a reduced relative lymphocyte count (28.3 ± 9.7%), indicate a leftward shift in the leukocyte differential, which is characteristic of prolonged or resolving inflammation. However, correlation analysis did not reveal significant associations between ESR and leukocyte parameters, highlighting the heterogeneity of cellular inflammatory responses in children with post-COVID-19 syndrome. Similar patterns were described by Maddux AB et al. (2021), who reported that neutrophil predominance during post-infectious recovery may reflect cytokine-mediated immune activation rather than ongoing acute inflammation.

The coagulation abnormalities identified in this cohort suggest a tendency toward a hypercoagulable state, supporting the hypothesis proposed by Sinha P. and Matthay M.A. (2020) regarding persistent endothelial activation following SARS-CoV-2 infection. Elevated fibrinogen levels were detected in 35% of children, and the observed positive association between fibrinogen concentration and IgG levels ($r = 0.27$; $p = 0.017$) indicates a link between humoral immune activity and acute-phase protein synthesis. Notably, variability in activated partial thromboplastin time (aPTT), including both prolongation and shortening across patients, reflects instability of the coagulation balance, which may predispose susceptible individuals to microcirculatory disturbances in the post-infectious period.

The detected IgG concentration (7.68 ± 3.12 BAU/mL) indicates an adequate humoral immune response in most children. However, variability in IgG levels was observed across the cohort, and higher antibody concentrations were more frequently detected in patients with more pronounced clinical manifestations. While this observation may reflect heterogeneity of the post-infectious immune response, the absence of associations between IgG levels and systemic inflammatory markers suggests that humoral immune memory is dissociated from ongoing inflammatory activity in the post-COVID period.

The presence of sinus arrhythmia (28.8%) and incomplete right bundle branch block (23.8%) reflects functional and predominantly transient alterations of cardiac rhythm and conduction. These findings are consistent with previous reports describing autonomic imbalance and altered heart rate variability in children following SARS-CoV-2 infection, likely related to dysregulation of autonomic control rather than structural myocardial damage.

Integrating the clinical and laboratory findings, a pathogenetic model can be proposed in which SARS-CoV-2–induced endothelial dysfunction initiates cytokine-mediated responses and coagulation disturbances, contributing to autonomic and cardiac manifestations in the post-infectious period. Importantly, within this framework, IgG antibodies represent markers of prior infection and immune memory but do not serve as reliable predictors of inflammatory activity or clinical course in children with post-COVID-19 syndrome.

In contrast, coagulation-related parameters, particularly fibrinogen, appear to be more closely linked to post-infectious pathophysiological processes, supporting the concept of an immune–endothelial–coagulation axis underlying multisystem manifestations. This interpretation is consistent with the concept proposed by Ludvigsson JF (2023), emphasizing the role of endothelial activation and coagulation dysregulation in pediatric post-COVID conditions.

Overall, post-COVID-19 syndrome in children aged 5–12 years appears to be a polyetiological and multifactorial condition, in which endothelial dysfunction, prolonged low-grade inflammatory signaling, and immune dysregulation collectively contribute to clinical manifestations. The combined alterations observed in inflammatory markers, hemostatic parameters, and cardiac conduction suggest a unified cascade of post-infectious responses rather than isolated organ-specific pathology. Further longitudinal studies with dynamic follow-up are required to refine diagnostic criteria and to develop effective monitoring and management strategies for pediatric post-COVID-19 syndrome.

CONCLUSIONS

Post-COVID-19 syndrome in children aged 5–12 years is characterized by multisystem manifestations, with predominance of asthenic, neurological, respiratory, and gastrointestinal symptoms. In most patients, a combination of three or more clinical features was observed, confirming the systemic nature of the post-infectious condition.

The hematological profile was marked by signs of persistent low-grade inflammatory activity, including elevated C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR), neutrophilia, and mild lymphopenia, indicating sustained activation of inflammatory pathways beyond clinical recovery. Alterations in hemostatic parameters revealed a tendency toward a hypercoagulable state, manifested by increased fibrinogen levels and variability in aPTT and PT values, reflecting endothelial activation and acute-phase responses.

Immunological assessment demonstrated heterogeneity of the humoral immune response. Importantly, IgG antibody levels to SARS-CoV-2 were not associated with classical inflammatory markers,

indicating that humoral immune memory does not reflect the intensity of ongoing systemic inflammation and cannot be considered a reliable predictor of disease activity or clinical course in pediatric post-COVID-19 syndrome. At the same time, a moderate but statistically significant association between IgG levels and fibrinogen concentration ($r = 0.27$; $p = 0.017$) suggests involvement of immune–endothelial–coagulation interactions in post-infectious pathophysiology.

Electrocardiographic changes, including sinus arrhythmia (28.8%) and incomplete right bundle branch block (23.8%), were predominantly functional and transient but may represent early manifestations of autonomic imbalance and endothelial-related myocardial dysfunction.

Overall, the identified clinical and laboratory features indicate that post-COVID-19 syndrome in children is driven by a complex inflammatory–endothelial process involving low-grade inflammation, coagulation dysregulation, and functional cardiovascular alterations, underscoring the need for targeted monitoring strategies during the recovery period.

PROSPECTS FOR FUTURE RESEARCH

The obtained results highlight the variability in the severity of post-COVID-19 syndrome among children, which appears to be independent of the severity of the acute SARS-CoV-2 infection. Longitudinal observation of pediatric patients recovering from COVID-19 may facilitate the development of diagnostic algorithms for cardiovascular dysfunction and allow for the identification of prognostically unfavorable indicators associated with the severity and expression of post-COVID-19 manifestations.

In the future, considering the demonstrated significance of the detected alterations, it will be important to investigate inflammatory and cardiovascular biomarkers such as NT-proBNP and D-dimer in children with post-COVID-19 syndrome. Further analysis of their correlations with clinical, laboratory, and instrumental findings could enhance understanding of their diagnostic value and support the establishment of effective monitoring and management strategies for pediatric patients.

The findings of this study emphasize the necessity for dynamic follow-up of children who have recovered from COVID-19, with regular assessment of inflammatory markers, hemostatic parameters, and cardiovascular function. The revealed correlations may serve as a basis for identifying clinical predictors of prolonged post-COVID-19 syndrome and for optimizing pediatric rehabilitation and follow-up programs.

AUTHOR CONTRIBUTIONS

The author confirms sole responsibility for the following: study conception and design, data collection, analysis and interpretation of results, and manuscript preparation.

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CONFLICT OF INTEREST

The authors have no conflict of interest to declare.

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