

PEDIATRICS

CLINICAL AND HEMOSTATIC FEATURES IN CHILDREN WITH VARYING SEVERITY OF COVID-19 IN IRKUTSK

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RESUME

Introduction. As pediatric COVID-19 is often asymptomatic or mild, investigating hemostatic and clinical features in these cases is vital for assessing complication risks, especially since existing research prioritizes severe manifestations.

The aim. Analysis of clinical and hemostatic features in children with varying severity of COVID-19 in Irkutsk.

Materials and methods. This retrospective study analyzed 164 medical records of children hospitalized with COVID-19 at the Ivano-Matreninskaya City Children's Clinical Hospital and the Irkutsk Regional Infectious Diseases Hospital between March 2021 and February 2022. The participants were divided into two groups: the first group included 85 children with mild disease severity, and the second group comprised 79 children with moderate severity. Severe course was observed in 3 patients who were transferred to the Irkutsk Regional Infectious Diseases Hospital. We assessed clinical features and basic coagulogram parameters (5 clotting tests and D-dimer). Statistical analysis was performed using Microsoft Office 2019 and Statistica Basic Academic 13.

Results. Among children with COVID-19, children aged 5–15 years were predominant, with no gender differences between the groups. The disease was predominantly mild to moderate in severity. Moderate disease severity was associated with a significant increase in fibrinogen and D-dimer levels, which correlated with the duration of fever and the presence of thoracalgia syndrome. A shortening of APTT in children with a moderate disease course correlated with the presence of shortness of breath.

Conclusions. Despite the predominantly mild-to-moderate course of COVID-19 in children, monitoring coagulogram parameters is essential. A significant number of children with moderate severity show elevated D-dimer and fibrinogen levels, as well as shortened APTT, indicating a risk of hemostatic complications and correlating with more severe clinical symptoms. Further research is needed to understand how COVID-19 severity affects hemostasis and to prevent serious complications.

Keywords: hemostasis, clinical features, children, COVID-19, coagulogram, D-dimer

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КЛИНИКО-ГЕМОСТАЗИОЛОГИЧЕСКИЕ ОСОБЕННОСТИ У ДЕТЕЙ ПРИ РАЗЛИЧНОЙ СТЕПЕНИ ТЯЖЕСТИ COVID-19 В ИРКУТСКЕ

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РЕЗЮМЕ

Введение. У детей COVID-19 обычно протекает бессимптомно или в легкой форме, реже в среднетяжелой. В связи с этим изучение клинико-гемостазиологических особенностей гемостаза при легком и среднетяжелом течении COVID-19 у детей важно для оценки риска развития осложнений, так как существующие исследования в основном посвящены тяжелым случаям у взрослых и детей.

Цель исследования. Проанализировать клинико-гемостазиологические особенности у детей при различных степенях тяжести COVID-19 в Иркутске.

Материалы и методы. Ретроспективно проанализировано 164 карты детей, госпитализированных с COVID-19 в ОГАУЗ «ГИМДКБ» и ОГБУЗ «ИОИКБ» в период с марта 2021 г. по февраль 2022 г, которым проводили исследование коагулограммы. Пациентов разделили на 2 группы: первая группа включала 85 детей с легкой степенью тяжести, вторая – 79 детей со среднетяжелой. Тяжелое течение – у 3 пациентов, которых перевели в ГБУЗ «ИГОДКБ». В работе анализировались клинические особенности и данные базовой коагулограммы, включающей 5 клоттинговых показателей и D-димер. Для статистической обработки применялись программы Microsoft Office 2019, Statistica Basic Academic 13.

Результаты. Среди детей с COVID-19 преобладали дети 5–15 лет без гендерных различий между группами. В основном заболевание имело легкую и среднюю степень тяжести. Среднетяжелое течение ассоциировалось с достоверным повышением фибриногена и D-димера, коррелирующим с лихорадкой и синдромом торакалгии. Укорочение АПТВ у детей со среднетяжелым течением коррелировало с одышкой.

Заключение. Несмотря на преобладание у детей легкой и средней степени тяжести COVID-19, важно контролировать коагулограмму, так как у значительной части детей со среднетяжелым течением выявленные высокие уровни D-димера и фибриногена, а также укорочение АПТВ, могут свидетельствовать о риске развития осложнений гемостаза и коррелируют с более выраженными клиническими симптомами. Очевидна необходимость дальнейших наблюдений и исследований влияния различных степеней тяжести COVID-19 на гемостаз для профилактики тяжелых осложнений.

Ключевые слова: гемостаз, клинические особенности, дети, COVID-19, коагулограмма, D-димер

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INTRODUCTION

In 2020, the COVID-19 became a global public health challenge [1–3]. The novel coronavirus infection spread rapidly, causing a significant impact on both public health and the economy of countries [2, 3].

It has been established that children and adolescents account for 2.0–7.8 % of all confirmed cases of COVID-19 [4–6]. Moreover, clinical manifestations in children vary depending on age, with gastrointestinal symptoms (diarrhea, vomiting) more common in younger children and respiratory manifestations and fever predominating in adolescents [4, 7]. Children aged 11–17 years appear to be most susceptible to the virus. Most cases of the infection are either asymptomatic or mild [8–10]. However, moderate forms are characterized by prolonged fever and frequent combination of respiratory and abdominal syndromes [8].

In April 2020, there was a report of the development of a multisystem inflammatory syndrome in some children who had COVID-19. This condition was accompanied by significant hemostatic abnormalities [11–13]. These abnormalities manifested as a COVID-19-associated coagulopathy with prothrombotic changes, similar to those seen in adult patients with more severe forms of the illness [14–16]. Moreover, patients with prolonged fever and multisystem involvement were at a significantly increased risk for developing hemostatic issues [17].

According to most studies, the primary mechanism of hemostatic abnormalities in patients with COVID-19 likely relates to the tropism of the novel coronavirus for the vascular endothelium, resulting in endotheliitis and coagulopathy, with a risk of thrombosis [16, 18]. In children with COVID-19, the hypercoagulable syndrome includes increased thrombin and D-dimer levels, prolonged prothrombin time, and decreased fibrinolysis [8, 19]. Currently, mechanisms of hypercoagulation in COVID-19 include hyperinflammatory responses, activation of neutrophil extracellular traps and platelets, elevated levels of von Willebrand factor, and coagulation factor VIII [20, 21].

Despite a significant number of studies on hemostasis in COVID-19, most research focuses on laboratory changes in adult patients and children with severe forms of the disease. At the same time, clinical and hemostatic features in children with mild and moderate infection remain poorly understood.

Optimal clinical and diagnostic criteria, as well as therapeutic approaches for the prevention and treatment of thromboinflammation, which plays a crucial role in the pathogenetic mechanism of COVID-19, are of significant interest.

AIM

To analyze clinical and hemostatic features in children with varying degrees of severity of COVID-19 infection in Irkutsk.

MATERIALS AND METHODS

A retrospective analysis was performed on the medical records of 164 children who were hospitalized with COVID-19 and received inpatient treatment at the Ivano-Matreninskaya City Children's Clinical Hospital and Irkutsk Regional Infectious Diseases Clinical Hospital from March 2021 to February 2022. The study included patients who had mild or moderate COVID-19 based on the WHO Clinical Progression Scale, with clinical and laboratory evidence of COVID-19 confirmed by detection of SARS-CoV-2 in a nasopharyngeal swab using PCR, as well as results from coagulation tests. The age of the children ranged from 1 month to 18 years. This study protocol was approved by the Ethics Committee of the Ivano-Matreninskaya City Children's Clinical Hospital (Protocol No. 4 dated January 20, 2021) and complied with the principles of the Declaration of Helsinki.

The exclusion criteria were presence of any concomitant somatic conditions, chronic and autoimmune pathology, oncological diseases, use of anticoagulant or antiplatelet agents, as well as the absence of coagulation test results and laboratory evidence of infection.

Coagulograms from 164 patients were analyzed. The following parameters were included in the analysis: activated partial thromboplastin time (APTT), Quick prothrombin time (Quick PT), international normalized ratio (INR), thrombin time (TT), fibrinogen, and D-dimer. Clotting parameters of the coagulogram were measured using an automated coagulation analyzer STA-R Evolution (Roche Diagnostics, Switzerland) and Sysmex CS-5100 (Sysmex Corp., Japan). D-dimer levels were measured using a coagulometer with monoclonal antibodies on latex. Assessment of coagulogram parameters was performed by comparing them with reference values for the corresponding age groups and internal standards of diagnostic laboratories, based on current clinical guidelines (APTT normal 28–40 sec; Quick PT 70–140 %; INR 1.0; TT 14–21 sec; fibrinogen 2–4 g/L; and D-dimer < 250 ng/mL) [22].

Children with clinical manifestations of the disease and coagulogram changes were divided into 2 groups. Group 1 included 85 children with mild COVID-19, comprising 43 males (50.6 %) and 42 females (49.4 %), with a mean age of 12 ± 2.1 years. Group 2 included 79 children with moderate severity of the disease, comprising 41 males (51.9 %) and 38 females (48.1 %), with a mean age of 11 ± 1.8 years.

Statistical analysis of the collected data was conducted using Microsoft Office 2019 and Statistica Basic Academic 13 software. At the outset of the study, a required random sample size was determined. To assess correlations between qualitative variables, the Pearson's chi-square test (χ^2) with Yates' correction was employed, and the Fisher's exact test was used for small samples. For intergroup analysis of quantitative parameters, both parametric and non-parametric methods were used: the Student's *t*-test for independent samples and the Mann – Whitney U-test. The effect of parameters

was assessed using a 95 % confidence interval (95% CI). The results of the analysis are presented as medians (Me) and first and third quartiles in the format of $[Q_{0.25}; Q_{0.75}]$. The Spearman's correlation coefficient (r) was used to assess the association between coagulation parameters and clinical indicators. The odds ratio (OR) with 95% confidence interval was calculated using binary logistic regression. The differences between groups were considered to be statistically significant at $p \leq 0.05$ [23].

RESULTS

No statistically significant differences by sex were found between the study groups ($p = 0.72$). The median age and corresponding quartiles of children in both groups were 12 [6;15] and 11 [5;15] years, respectively, with the difference between groups being statistically insignificant ($p = 0.30$). Among children with hemostatic disorders, 53 % had a mild course of the disease, 45 % had a moderate course, and 2 % had a severe course.

The study results revealed significant differences in the clinical presentation of COVID-19 among children, depending on the severity of the disease (Table 1). In Group 2, fever was significantly more common (78.0 % [65–88]) compared to Group 1 (61.0 % [49–71]) ($p_{1-2} = 0.02$). Analysis of respiratory symptoms showed that cough occurred in 51.0 % [41–63] of children in Group 2 compared to 37.0 % [28–49] in Group 1 ($p_{1-2} = 0.0001$). The frequency of dyspnea in Group 2 was 2.5 times higher than in Group 1 (33.0 % [24–45] versus 13.0 % [6–21]) ($p_{1-2} = 0.0001$) (Table 1).

Notably, there were differences in the frequencies of rhinitis and thoracalgia syndrome between the groups. In Group 2, rhinitis was observed in 34.0 % [25–46] of patients compared to 23.0 % [14–33] in Group 1 ($p_{1-2} = 0.04$). Thoracalgia syndrome was noted exclusively in Group 2 (5.0 % [1–11]) ($p = 0.03$). In contrast to these symptoms, the frequency of gastrointestinal manifestations, skin manifestations, and anosmia

did not have statistically significant differences between the two groups ($p > 0.05$) (Table 1).

The median values and quartiles of coagulation parameters and D-dimer levels in children with mild and moderate COVID-19 from Irkutsk are presented in Table 2. The table shows that the median D-dimer level in Group 2 was significantly higher than in Group 1 ($p = 0.002$). There were no statistically significant differences in other coagulation parameters between the two groups.

Analysis of the frequency of changes in clotting parameters of the coagulogram in children with COVID-19 revealed the following: in Group 2, APTT shortening was observed in 10.7 % [4.1; 20.5] of cases, which was higher than in Group 1 (3.5 % [0.5; 11]) ($p_{1-2} = 0.15$) (Table 3). There was a comparable frequency of APTT prolongation in both groups (18.0 % [10.3; 30.1] versus 15.0 % [8.6; 28.2]) ($p_{1-2} = 0.68$). It should be noted that APTT shortening in Group 2 had a statistically significant correlation with the presence of dyspnea in children ($p = 0.03$).

No significant differences in Quick PT changes were observed between the study groups ($p_{1-2} = 0.88$).

The TT was prolonged with a slightly higher frequency in Group 2, in 23.5 % [11.2; 64.1], while in Group 1, it was in 21.5 % [10.3; 61.2] ($p_{1-2} = 1.0$).

The most significant intergroup differences were observed in fibrinogen and D-dimer levels. In Group 2, fibrinogen levels were higher in 14.2 % [7.3; 25.6] compared to 8.6 % [3.6; 19.7] in Group 1 ($p_{1-2} = 0.05$). This was associated with the presence of fever (OR = 1.9; 95% CI: 1.1–3.3).

Additionally, D-dimer concentrations were increased in 27.0 % [14.4; 42.2] of children in Group 2 compared to 6.0 % [0.9; 18.1] in Group 1 ($p_{1-2} = 0.01$). This demonstrated correlations with both fever (OR = 2.1; 95% CI: 1.2–3.8) and the thoracalgia syndrome (OR = 3.2; 95% CI: 1.5–6.7).

Three patients with multisystem inflammatory syndrome associated with COVID-19 showed a marked

TABLE 1

PREVALENCE OF CLINICAL SYMPTOMS IN CHILDREN WITH MILD AND MODERATE SEVERITY OF COVID-19

Symptom	Group 1, % [95% CI] (n=85)	Group 2, % [95% CI] (n=79)	p-value
Fever	61 [49–71] (n=52)	78 [65–88] (n=62)	0.02
Cough	37 [28–49] (n=31)	51 [41–63] (n=40)	0.0001
Dyspnea	13 [6–21] (n=11)	33 [24–45] (n=26)	0.0001
Rhinitis	23 [14–33] (n=20)	34 [25–46] (n=27)	0.04
Thoracalgia syndrome	0	5 [1–11] (n=4)	0.03
Gastrointestinal symptoms	16 [8–25] (n=14)	17 [11–28] (n=13)	0.65
Exanthema	6 [2–12] (n=5)	7 [3–17] (n=6)	0.42
Anosmia	4 [1–9] (n=3)	5 [2–13] (n=4)	0.51

Note. Group 1 – children with mild COVID-19; Group 2 – children with moderate COVID-19; n – group size; p – statistical significance of differences between Group 1 and Group 2 (χ^2 test with Yates' correction).

increase in fibrinogen up to 5.9 g/L and D-dimer up to 1903.2 ng/mL, which correlated with gastrointestinal symptoms and fever [11, 24, 25].

DISCUSSION

Among all COVID-19 cases, only a small proportion occur in children and adolescents [4, 21]. Most children experience the novel coronavirus infection asymptotically or with mild or moderate symptoms, and only a minority develop multisystem inflammatory syndrome [11, 12, 25]. A similar distribution of COVID-19 severity was observed in our study of children in Irkutsk.

Studies by scientists from many countries have established that COVID-19 in children most often develops at the age of 7–13 years [4, 8, 9]. In our study, the majority of participants were between the ages of 5–15 years.

This difference may be due both to regional features and to the different epidemiological situation during the study period.

The clinical presentation of COVID-19 in the children under study varied depending on the severity of the disease. Most cases of COVID-19 among children in Irkutsk were mild or moderate, which is in line with data from other studies that found that more than 90 % of patients had asymptomatic, mild, or moderate symptoms [8, 9, 22]. In mild cases, catarrhal symptoms were predominant, including rhinitis and cough, with no signs of respiratory failure. In moderate cases, respiratory symptoms were more pronounced. Fever occurred more frequently in the moderate group, consistent with scientific evidence of a prolonged febrile response in moderate to severe forms of the disease [8]. Of particular note is the increased frequency of dyspnea and thoracalgia in moderate cases, which are important clinical markers of disease progression in children [7, 26].

TABLE 2

CLOTTING PARAMETERS OF HEMOSTASIS AND D-DIMER IN CHILDREN WITH MILD AND MODERATE SEVERITY OF COVID-19

Parameter	[Q _{0.25} ; Q _{0.75}]		p-value
APTT, sec	Group 1 (n=84) 35.10 [31.3–37.4]	Group 2 (n=75) 33.6 [31.5–38.2]	0.52
Quick PT, %	Group 1 (n=59) 78.85 [65.2–90.4]	Group 2 (n=48) 85.3 [64.9–99.7]	0.34
INR	Group 1 (n=79) 1.1 [1.05–1.3]	Group 2 (n=70) 1.1 [1–1.2]	0.3
TT, sec	Group 1 (n=27) 18.5 [17.7–19.6]	Group 2 (n=25) 18.45 [16.9–19.4]	1.1
Fibrinogen, g/L	Group 1 (n=82) 2.78 [2.6–3.8]	Group 2 (n=77) 2.81 [2.5–3.7]	0.98
D-dimer, ng/mL	Group 1 (n=54) 76.7 [30.2–146.5]	Group 2 (n=55) 148.1 [75.1–269.1]	0.002

Note. Group 1 – children with mild COVID-19; Group 2 – children with moderate COVID-19; n – number of patients with available data; p – statistical significance of differences between Group 1 and Group 2 (Mann – Whitney U-test).

TABLE 3

PREVALENCE OF CHANGES IN COAGULATION CLOTTING PARAMETERS AND THEIR ASSOCIATION WITH CLINICAL MANIFESTATIONS IN CHILDREN WITH MILD TO MODERATE COVID-19

Parameter change	Group 1, % [95% CI] (n=85)	Group 2, % [95% CI] (n=79)	p-value
Shortened APTT	3.5 [0.5; 11]	10.7 [4.1; 20.5]	0.15
Prolonged APTT	18 [10.3; 30.1]	15 [8.6; 28.2]	0.68
Decreased Quick PT	26 [15.3; 42.7]	23 [11.2; 40.8]	0.88
Prolonged TT	23.5 [11.2; 64.1]	21.5 [10.3; 61.2]	1.0
Increased fibrinogen	8.6 [3.6; 19.7]	14.2 [7.3; 25.6]	0.05
Increased D-dimer	6 [0.9; 18.1]	27 [14.4; 42.2]	0.01

Note. Group 1 – children with mild COVID-19; Group 2 – children with moderate COVID-19; n – group size; p – statistical significance of differences between Group 1 and Group 2 (Mann–Whitney U-test, χ^2 test).

During the course of the pandemic, a number of studies on hemostasis in adult patients have been conducted, revealing that mild cases are characterized by normal values, whereas moderate and severe cases show various alterations depending on the severity of the disease (prolonged or shortened APTT, prolonged or normal PT and TT, elevated fibrinogen, and D-dimer levels) [19, 26].

Studies on hemostatic function in COVID-19 among children are less numerous than in adults, and have primarily focused on multisystem inflammatory syndromes [22, 25].

In our study, an analysis of coagulation parameters in the basic coagulation profile revealed significant differences between the groups. In children with mild COVID-19, the parameters were within the normal range, which is in line with the results of other scientific studies [8, 18, 27]. One third of children with moderate COVID-19 in Irkutsk had elevated fibrinogen and D-dimer levels, which correlated with fever and thoracalgia syndrome. These data support the link between an intense inflammatory response and activation of the coagulation system in COVID-19, which undoubtedly constitutes a risk factor for severe complications, including hemostatic ones [19, 27]. According to most studies, approximately 50 % of patients with COVID-19 have elevated D-dimer values and increased fibrinogen levels, both among intensive care patients and those with non-severe disease [9, 10, 18, 28].

In our study, APTT shortening, detected in 10.7 % of patients with moderate disease severity, correlated with dyspnea, which may indicate early signs of coagulation activation. While most researchers have not identified changes in the APTT, there are some studies reporting prolongation of the APTT in both severe and mild disease, with no significant difference between the groups. However, other authors have observed more pronounced prolongation of APTT in severe disease [26, 29, 30].

Several authors have reported that in patients with prolonged and severe symptoms of COVID-19, significantly lower values of the Quick PT were recorded compared to those with mild symptoms (53 % versus 36 %). Other coagulation parameters did not show significant differences in these studies [18, 26]. In our patient population, the Quick PT was shortened in 26 % of cases, without a correlation with the clinical manifestations. The TT in most studies on COVID-19 in children has not changed, as was the case in our study.

In three children with severe COVID-19 and multisystem inflammatory syndrome who were admitted to the Irkutsk Regional Children's Clinical Hospital, significant hypercoagulation alterations were observed: marked increases in fibrinogen levels (5.9 g/L) and D-dimer levels (1903.2 ng/mL), consistent with data from other studies [9, 16, 24, 27]. These patients develop endotheliopathy, thrombocytopathy, and COVID-19-associated coagulopathy ("thromboinflammation" or "immunothrombosis"), characterized

by elevated D-dimer, fibrinogen, and frequently thrombocytopenia [27, 29, 30].

Therefore, in our study, the most prominent clinical manifestations and significant alterations in screening parameters for the basic coagulation profile and D-dimer were observed among children with moderate forms of COVID-19.

CONCLUSION

The COVID-19 pandemic has undoubtedly affected children's health, despite their lower morbidity and mortality compared to adults. Unfortunately, the number of publications concerning hemostasis in mild and moderate COVID-19 in children is limited.

In most cases, the novel coronavirus infection in children of Irkutsk has a mild severity and is not accompanied by changes in the basic coagulogram. In moderate severity, one third of children in Irkutsk have prothrombotic changes (increased fibrinogen levels, increased D-dimer concentration). These changes are associated with fever and thoracalgia syndrome, which emphasizes their potential role as markers of complication risk, including those from hemostasis. In multisystem inflammatory syndrome associated with COVID-19, pronounced thrombotic and hemorrhagic changes may be observed.

In conclusion, it should be emphasized that our study is important for understanding COVID-associated hemostatic disorders in pediatric practice. The identified clinical and hemostatic features in mild and moderate COVID-19 in children contribute to more effective prediction and prevention of thrombotic complications in children.

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Conflicts of interest

The authors declare no conflicts of interest.

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