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Research Article

## Features of severe forms of new coronavirus infection (COVID-19) in children

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### ABSTRACT

**BACKGROUND:** The problem of the complicated course of COVID-19 and deaths in children with severe comorbid pathology is relevant. Severe forms of the disease are often the cause of critical conditions and deaths, including decompensated respiratory failure, acute respiratory distress syndrome, septic shock, cardiac, hepatic, renal insufficiency, coagulation disorders, damage to the central nervous system.

**AIM:** The aim is to analyze the features of the course of COVID-19 in children who require mandatory hospitalization in specialized hospitals for background pathology, to identify predictors of the development of severe forms of COVID-19 in order to choose the optimal ways of treating this pathology.

**MATERIALS AND METHODS:** Under the supervision of the St. Petersburg State Pediatric Medical University in the department for children with new coronavirus infection COVID-19 with intensive care and intensive care wards in the period 2020–2022 with a confirmed diagnosis of “new coronavirus infection” there were 791 patients aged 0 to 17 years. The diagnosis was made on the basis of clinical and epidemiological data, the results of a comprehensive laboratory and instrumental study. The severity of the disease was determined in accordance with the methodological recommendations of the Ministry of Health of the Russian Federation.

**RESULTS:** The severe form of COVID-19 was diagnosed in 34 patients out of 791 (4.3%). Adverse outcomes were 1.4%. In 27 out of 34 children (79.4%), new coronavirus infection occurred against the background of severe comorbid pathology. Pneumonia was diagnosed in 91.2% of cases. 88.2% of patients needed oxygen therapy.

**CONCLUSIONS:** Severe forms of COVID-19 in children are characterized by high fever with severe intoxication, respiratory tract damage with a significant volume of lung damage (CT-3 and CT-4) with the development of multiple organ failure. Predictors that require mandatory hospitalization in specialized hospitals for background pathology in severe forms of COVID-19 are: primary immunodeficiency conditions, oncohematological pathology with postcytostatic aplasia of hematopoiesis, severe organic lesions of the central nervous system, epilepsy, protein-energy deficiency of 3–4 degrees, bronchopulmonary dysplasia, atypical emolytic uremic syndrome with acute kidney damage. Comprehensive treatment of such patients should be carried out by a multidisciplinary team in a specialized department with extensive diagnostic and therapeutic capabilities.

**Keywords:** COVID-19; severe forms; children; SARS-CoV-2 virus; deaths.

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Научная статья

## Особенности тяжелых форм новой коронавирусной инфекции (COVID-19) у детей

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### АННОТАЦИЯ

**Актуальность.** Проблема осложненного течения COVID-19 и летальных исходов у детей с тяжелой коморбидной патологией является актуальной. Тяжелые формы заболевания нередко становятся причиной критических состояний и летальных исходов, включая декомпенсированную дыхательную недостаточность, острый респираторный дистресс-синдром, септический шок, сердечную, печеночную, почечную недостаточность, нарушения коагуляции, поражение центральной нервной системы.

**Цель** — проанализировать особенности течения COVID-19 у детей, которые требуют обязательной госпитализации в профильные стационары по фоновой патологии, выявить предикторы развития тяжелых форм COVID-19 для выбора оптимальных способов лечения этой патологии.

**Материалы и методы.** Под наблюдением в ФГБОУ ВО «Санкт-Петербургский государственный педиатрический медицинский университет» Минздрава России в отделении для детей с новой коронавирусной инфекцией COVID-19 с палатами реанимации и интенсивной терапии в период 2020–2022 гг. с подтвержденным диагнозом «новая коронавирусная инфекция» находился 791 пациент в возрасте от 0 до 17 лет. Диагноз выставляли на основании клинико-эпидемиологических данных, результатов комплексного лабораторного и инструментального исследования. Степень тяжести заболевания устанавливали в соответствии с методическими рекомендациями Министерства здравоохранения Российской Федерации.

**Результаты.** Тяжелая форма COVID-19 диагностирована у 34 пациентов из 791 (4,3 %). Неблагоприятные исходы составили 1,4 %. У 27 из 34 детей (79,4 %) новая коронавирусная инфекция протекала на фоне тяжелой коморбидной патологии. Пневмония диагностирована в 91,2 % случаев. В оксигенотерапии нуждались 88,2 % пациентов.

**Заключение.** Тяжелые формы COVID-19 у детей характеризуются высокой лихорадкой с выраженной интоксикацией, поражением дыхательных путей со значительным объемом поражения легких (КТ-3 и КТ-4) с развитием полиорганной недостаточности. Предикторами, которые требуют обязательной госпитализации в профильные стационары по фоновой патологии при тяжелых формах COVID-19, являются: первичные иммунодефицитные состояния, онкогематологическая патология с постцитостатической аплазией кроветворения, тяжелые органические поражения центральной нервной системы, эпилепсия, белково-энергетическая недостаточность III–IV степени, бронхолегочная дисплазия, атипичный гемолитико-уремический синдром с острым повреждением почек. Комплексное лечение таких пациентов следует проводить мультидисциплинарной командой в профильном отделении, имеющем широкие диагностические и лечебные возможности.

**Ключевые слова:** COVID-19; тяжелые формы; дети; вирус SARS-CoV-2; летальные исходы.

### Как цитировать

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## BACKGROUND

The complex course and fatal outcomes of COVID-19 in children with severe comorbidities is a crucial issue. In the United States, 17.4% of COVID-19 cases reported to the Centers for Disease Control and Prevention (CDC) occurred in children (data as of September 07, 2022) [17]. Objective data on SARS-CoV-2 infection prevalence in the pediatric population are inconsistent because systematic testing is rare and contact tracing and seroprevalence studies for children with mild COVID-19 are lacking. As of February 2022, approximately 75% of children and adolescents had serologic evidence of COVID-19 [18].

The clinical presentation of the new coronavirus infection (NCI) ranges from mild respiratory manifestations to severe pneumonia with acute respiratory distress syndrome (ARDS) and multiorgan failure. Complicated forms of the disease typically develop in patients with severe comorbidities, whereas severe cases are observed in only approximately 1% of children with COVID-19 [6, 9, 14].

Severe forms of NCI can lead to critical conditions and fatal outcomes, including decompensated respiratory failure; ARDS; septic shock; cardiac, hepatic, and renal failure; coagulation disorders; and central nervous system damage [3, 9–11]. Additionally, children may develop a severe multi-system inflammatory syndrome associated with SARS-CoV-2 [2, 4, 8, 9, 12]. Although SARS-CoV-2 infection, severe disease course, and fatal outcomes due to COVID-19 are less common in children than in adults [1, 15, 16], they can still occur.

A CDC analysis of mortality due to NCI in individuals aged <21 years found that the highest number of cases occurred in children and adolescents with comorbidities. Specifically, 70% of the cases were in patients aged 10–20 years, 20% in children aged 1–9 years, and 10% in patients aged <1 year. The mortality rate was higher among male individuals (63%) and in the 18–20 years age group (41.3%). Additionally, 75% of those who passed away had one concomitant pathology, whereas the remaining individuals had two or more. The common concomitant pathologies were chronic lung diseases (e.g., bronchial asthma), neurological and cardiovascular diseases, obesity, diabetes mellitus, hydronephrotic transformation of the kidneys, oncohematologic pathology, and intestinal intussusception [13, 19].

The pathogenesis and severity of COVID-19 in children remain unclear compared with those in adults. However, the number of hospitalizations in intensive care units for children is comparable to that for adults [20].

*This study aimed* to analyze the characteristics of COVID-19 in children who require hospitalization in specialized hospitals for underlying pathology and identify predictors of severe forms of COVID-19 to determine optimal treatment methods for this pathology.

## MATERIALS AND METHODS

Overall, 791 individuals aged 0–17 years were diagnosed with NCI and hospitalized in the department for children with COVID-19 in the intensive care wards at St. Petersburg State Pediatric Medical University of the Ministry of Health of Russia between 2020 and 2022.

Patients with severe COVID-19 were included. Severity was assessed based on the degree of intoxication and fever syndromes, catarrhal manifestations, lung damage, other organ and system involvement, and changes in laboratory parameters. Disease severity was determined according to the methodological recommendations of the Ministry of Health of Russia [9].

The diagnosis was based on clinical and epidemiological data and laboratory and instrumental examination results, including clinical blood analysis, urinalysis, nasopharyngeal and oropharyngeal mucus culture for SARS-CoV-2 by polymerase chain reaction (PCR), biochemical examination, coagulogram, X-ray and/or multispiral computed tomography of the chest, electrocardiography, lung ultrasound, and cardiac echocardiography.

All patients received comprehensive treatment based on disease severity, premorbid background, and age. Recombinant interferon- $\alpha$ 2b preparations were used as etiotropic agents. Antibacterial, pathogenetic, and symptomatic therapies were administered as indicated.

## RESULTS AND DISCUSSION

The patient age distribution was as follows: 3.1% ( $n = 25$ ), 0–1 month; 15.7% ( $n = 124$ ), 1 month–1 year; 15.0% ( $n = 118$ ), 1–3 years; 16.3% ( $n = 129$ ), 3–7 years; 19.6% ( $n = 155$ ), 7–12 years; 10.2% ( $n = 81$ ), 12–15 years; and 20.1% ( $n = 159$ ), >15 years.

Based on the severity of COVID-19 ( $n = 791$ ), the distribution of cases among children was as follows: 57.4% ( $n = 454$ ), mild; 38.3% ( $n = 303$ ), moderate; and 4.3% ( $n = 34$ ), severe. The fatal outcome rate was 1.4% ( $n = 11$ ).

We analyzed 34 severe NCI cases. Table 1 presents the age distribution of children with severe COVID-19.

Of the children, 29 patients (85.3%) had contact with COVID-19, of whom 14 patients had familial contact and 15 had contact with medical personnel or caregivers. The source of infection was not identified in 14.7% ( $n = 5$ ) of cases.

Upon hospital admission, 20 patients (58.8%) presented with varying degrees of clinical symptoms. Additionally, 14 children (41.2%) were transferred from other hospitals/departments for isolation because of a positive result for SARS-CoV-2 in nasopharyngeal and oropharyngeal smears by PCR. These children did not exhibit clinical signs of the disease at the time of hospitalization but developed symptoms during observation.

**Table 1.** Distribution of children by age with severe form of COVID-19

**Таблица 1.** Распределение детей по возрасту с тяжелой формой COVID-19

Age group / Возрастная группа	Number of children / Количество детей	%
Young children and preschoolers / Дети раннего возраста и дошкольники		
0–1 month / 0–1 мес.	1	2.9
1 month – 1 years / 1 мес. – 1 г.	1	2.9
1–3 years / 1–3 года	4	11.8
3–7 years / 3–7 лет	4	11.8
Total / Всего	10	29.4
School-age children / Дети школьного возраста		
7–12 years / 7–12 лет	9	26.5
12–15 years / 12–15 лет	3	8.8
Over 15 years old / Старше 15 лет	12	35.3
Total / Всего	24	70.6

**Table 2.** Concomitant pathology of children with severe form of COVID-19

**Таблица 2.** Сопутствующая патология у детей с тяжелой формой COVID-19

Concomitant pathology / Сопутствующая патология	Number of children / Количество детей	%
<b>Oncohematological</b> (patients after bone marrow transplantation): aplastic anemia, acute lymphoblastic leukemia, acute myeloblastic leukemia, myelodysplastic syndrome, mucopolysaccharidosis type 1 (Gurler syndrome) / <b>Онкогематологическая</b> (пациенты после трансплантации костного мозга): апластическая анемия, острый лимфобластный лейкоз, острый миелобластный лейкоз, миелодиспластический синдром, мукополисахаридоз 1-го типа (синдром Гурлера)	10	37.1
<b>Endocrine:</b> type 1 diabetes mellitus, type 2 diabetes mellitus + grade III obesity, hyperinsulinism + grade III obesity, hypothyroidism + grade III obesity, chronic adrenal insufficiency / <b>Эндокринная:</b> сахарный диабет 1-го типа, сахарный диабет 2-го типа + ожирение III степени, гиперинсулинизм + ожирение III степени, гипотиреоз + ожирение III степени, хроническая надпочечниковая недостаточность	6	22.2
<b>Pulmonological:</b> bronchial asthma, mucopolipidosis, chronic obstructive pulmonary disease, primary immunodeficiency / <b>Пульмонологическая:</b> бронхиальная астма, муколипидоз, хроническая обструктивная болезнь легких, первичный иммунодефицит	6	22.2
<b>Nephrological:</b> systemic vasculitis (Goodpasture syndrome), hemolytic-uremic syndrome / <b>Нефрологическая:</b> системный васкулит (синдром Гудпасчера), гемолитико-уремический синдром	3	11.1
<b>Surgical:</b> gangrenous appendicitis / <b>Хирургическая:</b> гангренозный аппендицит	1	3.7
<b>Diseases of the newborn period:</b> hemolytic disease of newborns, sepsis / <b>Болезни периода новорожденности:</b> гемолитическая болезнь новорожденных, сепсис	1	3.7
Total / Всего	27	100

Upon admission to the department, 44.1% ( $n = 15$ ) of cases were diagnosed as mild, 23.5% ( $n = 8$ ) as moderately severe, and 32.4% ( $n = 11$ ) as severe.

Among the 34 children, 27 (79.4%) had severe comorbid pathology (Table 2). Additionally, 20.6% ( $n = 7$ ) of patients with severe COVID-19 did not have an aggravated premorbid background or comorbid pathology.

All severe COVID-19 patients exhibited the main clinical syndromes, including fever, intoxication, and catarrhal syndrome, with varying degrees of involvement in the upper and lower respiratory tracts.

Disease severity was primarily attributed to the diagnosis of pneumonia, which was present in 91.2% ( $n = 31$ ) of cases. Upon admission, 58.1% ( $n = 18$ ) of the patients

**Table 3.** The volume of lung damage in children with COVID-19**Таблица 3.** Объем поражения легких у детей при COVID-19

Criteria for lung damage according to multispiral computed tomography (CT) / Критерий поражения легких по данным мультиспиральной компьютерной томографии (КТ)	Number of children / Количество детей	%
CT-0 (no involvement) / КТ-0 (отсутствие вовлечения)	3	8.8
CT-1 (minimum volume, prevalence less than 25% of lung volume) / КТ-1 (минимальный объем, распространенность менее 25 % объема легких)	1	2.9
CT-2 (average volume, 25–50%) / КТ-2 (средний объем, 25–50 %)	2	5.9
CT-3 (significant volume, 50–75%) / КТ-3 (значительный объем, 50–75 %)	22	64.7
CT-4 (subtotal volume, more than 75%) / КТ-4 (субтотальный объем, более 75 %)	6	17.7
Total / Всего	34	100

exhibited varying degrees of lung lesions. During the course of the disease, pneumonia developed in 41.9% ( $n = 13$ ) of children (Table 3). In 8.8% ( $n = 3$ ) of cases, no changes in lung condition were observed throughout the disease period.

In 88.2% (30 of 34) of children with severe disease, oxygen therapy was required. Of the patients, 53.3% ( $n = 16$ ) received oxygen from the first day of hospitalization, with 10 of them using a face mask/cannula and 6 on invasive ventilation. Later in the course of the disease, an additional 14 patients (46.7%) required oxygen therapy, with 6 using noninvasive ventilation via face mask/cannula and 8 on a ventilator.

Hemogram analysis revealed that 73.5% ( $n = 25$ ) had leukopenia, 17.6% ( $n = 6$ ) had leukocytosis, 64.7% ( $n = 22$ ) had anemia, and 47.2% ( $n = 16$ ) had thrombocytopenia. In all the patients, pronounced inflammatory changes in the blood were noted when the disease progressed or the condition worsened.

Biochemical blood analysis ( $n = 34$ ) showed an increase in C-reactive protein levels in all patients. Alanine aminotransferase/aspartate aminotransferase was elevated in 53.0% ( $n = 18$ ) of cases, whereas lactate dehydrogenase was elevated in 32.4% ( $n = 11$ ). Ferritin was increased in 44.1% ( $n = 15$ ) of the cases. Metabolic disorders were detected in all patients. Hypoproteinemia was observed in 41.2% ( $n = 14$ ) of the children, and hypoalbuminemia was noted in 26.5% ( $n = 9$ ). Coagulogram indicated hypocoagulation in 47.1% ( $n = 16$ ) of patients, hypercoagulation in 14.7% ( $n = 5$ ), and increased D-dimer in 73.5% ( $n = 25$ ).

Of the children studied, 23 (67.4%) had a favorable outcome with recovery from COVID-19. Six patients were discharged home with clinical and laboratory recovery, 10 were transferred to another hospital/department for further treatment of concomitant pathology, and 7 were transferred to the pulmonology department with recovery but persisting lung changes.

In 11 of 791 (1.4%) COVID-19 patients, unfavorable outcomes were observed, and severe concomitant pathologies were determined: 6 children had malignant oncohematology

disease after bone marrow transplant, 2 had hemolytic-uremic syndrome, 1 had primary immunodeficiency, 1 had combined pathology (Shereshevsky–Turner syndrome, chronic obstructive pulmonary disease, organic brain damage), and 1 had a pathology of the newborn (bacterial sepsis) [5, 7].

Furthermore, in all the 11 COVID-19 patients with unfavorable outcomes, signs of multiorgan failure were present, including encephalopathy and cardiovascular, renal, and hepatic failure. Severe pneumonia (CT3, CT4) with respiratory failure was noted in 8 patients (72.7%), ARDS was present in 5 patients (45.4%), pulmonary embolism in 4 patients (36.4%), sepsis in 4 patients (36.4%), and septic shock in 3 patients (27.3%). Additionally, 8 children (72.7%) developed coagulation disorders, specifically disseminated intravascular coagulation syndrome.

The study results indicate that severe forms of NCI are accompanied by the classical syndrome complex, which includes high fever, marked intoxication, and upper and lower respiratory tract involvement (CT3, CT4) and respiratory (III–IV degree) and multiorgan failure. The presence of significant lung damage should be considered even in the absence of clinical symptoms of the disease.

Oncohematologic pathology, including aplastic anemia, myeloblast leukemia, and lymphoblast leukemia, and long-term highly toxic cytostatic therapy contribute to the development of marked immunosuppression. This leads to a progressive increase in the severity of NCI (CT1–CT4). The disease often progresses without complications but may be complicated by sepsis of viral, bacterial, or fungal origin and the development of multiorgan failure.

Other studies have confirmed our results, indicating that comorbid pathology significantly complicates the course of COVID-19 in children and, in some cases, leads to unfavorable outcomes [13, 19]. Severe comorbid pathology in children of varying ages is a predictor of a severe course of COVID-19 and contributes to unfavorable prognosis. SARS-CoV-2 infection exacerbates underlying conditions, leading to complications and potentially fatal outcomes.

## CONCLUSIONS

Severe cases of COVID-19 in children are characterized by high fever, respiratory tract involvement resulting in significant lung damage (CT3 and CT4), and multiorgan failure.

Predictors for mandatory hospitalization in specialized hospitals for background pathology in severe forms of COVID-19 include primary immunodeficiency states, oncohematological pathology with postcytostatic aplasia of hematopoiesis, severe organic lesions of the central nervous system, epilepsy, protein-energy deficiency (III–IV degree), bronchopulmonary dysplasia, and atypical hemolytic–uremic syndrome with acute kidney injury. Children with COVID-19 and severe comorbidities (e.g., oncohematologic, endocrine, renal, and primary immunodeficiencies) and severe lesions in the central nervous system and other

systems and organs require complex treatment. The treatment should be performed in a specialized department with extensive diagnostic and therapeutic capabilities and by a trained team of specialist physicians using a multidisciplinary approach.

## ADDITIONAL INFORMATION

**Authors' contribution.** Thereby, all authors made a substantial contribution to the conception of the study, acquisition, analysis, interpretation of data for the work, drafting and revising the article, final approval of the version to be published and agree to be accountable for all aspects of the study.

**Competing interests.** The authors declare that they have no competing interests.

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