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THE CONDITION OF THE VASCULAR ENDOTHELIUM IN CHILDREN WITH COVID-19 AND BRONCHO-OBSTRUCTIVE SYNDROME

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Abstract

Introduction: The impact of SARS-CoV-2 infection on the human organism has proven to be more diverse than that of previously known viral infections. However, the full spectrum of the long-term consequences of the disease, especially in children, has not been thoroughly studied. One key area of concern is the development of broncho-obstructive syndrome (BOS) as a post-COVID-19 complication, which involves airway inflammation and hyperreactivity. This study investigates the relationship between endothelial dysfunction and BOS in pediatric patients following SARS-CoV-2 infection.

Objective: To explore the endothelial status in children with SARS-CoV-2 infection and its association with the development of BOS, and to assess the role of endothelial dysfunction markers—circulating endothelial cells (CECs), endothelin-1, and nitric oxide metabolites—in this context.

Methods: A retrospective study was conducted between 2020 and 2022, involving 486 children. The study included two primary groups: (1) Control: Healthy children with no history of SARS-CoV-2 infection or BOS; children with SARS-CoV-2 infection but no BOS, and (2) Main: Children with BOS but no SARS-CoV-2 infection; children with SARS-CoV-2 infection followed by the development of BOS. Endothelial function was assessed by measuring levels of CECs, endothelin-1, and nitric oxide metabolites.

Results: The study found significantly elevated CECs and endothelin-1 levels, along with decreased nitric oxide metabolites, in children who developed BOS following SARS-CoV-2 infection. The highest levels of endothelial dysfunction markers were observed in this group, suggesting a synergistic effect of SARS-CoV-2 infection and BOS on endothelial damage. Notably, 64.3% of children in this group exhibited elevated CEC levels, reflecting severe endothelial dysfunction. Endothelin-1 levels were also significantly higher in children with BOS after SARS-CoV-2 infection (0.46 ± 0.02 fmol/mL) compared to healthy controls and children with BOS without a history of SARS-CoV-2 infection. These findings highlight the critical role of endothelial dysfunction in the pathogenesis of post-COVID-19 respiratory complications.

Conclusion: SARS-CoV-2 infection contributes to significant endothelial dysfunction in children, particularly in those who develop BOS. The combination of SARS-CoV-2 infection and BOS exacerbates endothelial damage, which likely plays a critical role in the pathogenesis of post-COVID-19 respiratory complications. These findings suggest the need for further research into therapeutic strategies aimed at correcting endothelial dysfunction, potentially improving outcomes for pediatric patients suffering from long-term respiratory sequelae following COVID-19.

Keywords: SARS-CoV-2, Endothelial Dysfunction, Circulating Endothelial Cells (CECs), Broncho-Obstructive Syndrome (BOS), Pediatric COVID-19, Endothelin-1, Nitric Oxide Metabolites, Post-COVID-19 Complications, Vascular Endothelium, Respiratory Complications.

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Резюме

СОСТОЯНИЕ СОСУДИСТОГО ЭНДОТЕЛИЯ У ДЕТЕЙ С COVID-19 И БРОНХООБСТРУКТИВНЫМ СИНДРОМОМ

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Введение: Воздействие инфекции SARS-CoV-2 на человеческий организм оказалось более разнообразным, чем у ранее известных вирусных инфекций. Однако полный спектр долгосрочных последствий заболевания, особенно у детей, еще не был тщательно изучен. Одной из ключевых проблем является развитие бронхообструктивного синдрома (БОС) как постковидного осложнения, которое включает воспаление дыхательных путей и гиперреактивность. Это исследование направлено на изучение связи между эндотелиальной дисфункцией и БОС у детей после инфекции SARS-CoV-2, и на определение роли маркеров эндотелиальной дисфункции - циркулирующих эндотелиальных клеток (ЦЭК), эндотелина-1 и метаболитов оксида азота - в этом контексте.

Методы: Ретроспективное исследование было проведено в период с 2020 по 2022 год и охватило 486 детей. Исследование включало две основные группы: (1) Контрольная группа: здоровые дети, не имеющие истории инфекции SARS-CoV-2 или БОС; дети с инфекцией SARS-CoV-2, но без БОС, и (2) Основная группа: дети с БОС, но без инфекции SARS-CoV-2; дети с инфекцией SARS-CoV-2, за которой последовало развитие БОС. Функция эндотелия оценивалась путем измерения уровней ЦЭК, эндотелина-1 и метаболитов оксида азота.

Результаты: Исследование показало значительное повышение уровней ЦЭК и эндотелина-1, а также снижение метаболитов оксида азота у детей, развивших БОС после инфекции SARS-CoV-2. Наибольшие уровни маркеров эндотелиальной дисфункции были обнаружены в этой группе, что свидетельствует о синергетическом эффекте инфекции SARS-CoV-2 и БОС на повреждение эндотелия. Особенно важно, что 64,3% детей в этой группе продемонстрировали повышенные уровни ЦЭК, что отражает тяжелую эндотелиальную дисфункцию. Уровни эндотелина-1 также были значительно выше у детей с БОС после инфекции SARS-CoV-2 ($0,46 \pm 0,02$ фмоль/мл) по сравнению с здоровыми детьми и детьми с БОС без истории инфекции SARS-CoV-2. Эти результаты подчеркивают важнейшую роль эндотелиальной дисфункции в патогенезе респираторных осложнений после COVID-19.

Выводы: Инфекция SARS-CoV-2 способствует значительной эндотелиальной дисфункции у детей, особенно у тех, кто развивает БОС. Сочетание инфекции SARS-CoV-2 и БОС усугубляет повреждение эндотелия, что, вероятно, играет ключевую роль в патогенезе респираторных осложнений после COVID-19. Эти данные подчеркивают необходимость дальнейших исследований терапевтических стратегий, направленных на коррекцию эндотелиальной дисфункции, что может улучшить исходы лечения педиатрических пациентов, страдающих от долгосрочных респираторных последствий после COVID-19.

Ключевые слова: SARS-CoV-2, эндотелиальная дисфункция, циркулирующие эндотелиальные клетки (ЦЭК), бронхообструктивный синдром (БОС), детский COVID-19, эндотелин-1, метаболиты оксида азота, постковидные осложнения, сосудистый эндотелий, респираторные осложнения.

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Түйіндеме

COVID-19 ЖӘНЕ БРОНХООБСТРУКТИВТІ СИНДРОМЫ БАР БАЛАЛАРДА ТАМЫР ЭНДОТЕЛИІНІҢ ЖАҒДАЙЫ

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Кіріспе: SARS-CoV-2 инфекциясының адам организміне әсері бұрын белгілі вирустық инфекцияларға қарағанда әртүрлірек болып шықты. Дегенмен, аурудың ұзақ мерзімді салдары, әсіресе балаларда, толық зерттелген жоқ. Негізгі мәселелердің бірі – бронхообструктивті синдромның (БОС) постковидтік асқыну ретінде дамуы, оған тыныс жолдарының қабынуы және гиперреактивтілік кіреді. Бұл зерттеу SARS-CoV-2 инфекциясынан кейінгі балаларда эндотелиалды дисфункция мен БОС арасындағы байланысты, сонымен қатар эндотелиалды дисфункция маркерлерінің – айналымдағы эндотелиалды клеткалар (АЭК), эндотелин-1 және азот оксидінің метаболиттерінің ролін анықтауға бағытталған.

Әдістері: 2020-2022 жылдар аралығында ретроспективті зерттеу жүргізіліп, 486 бала қамтылды. Зерттеу екі негізгі топты қамтыды: (1) Бақылау тобы: SARS-CoV-2 инфекциясы немесе БОС анамнезі жоқ дені сау балалар; SARS-CoV-2 инфекциясы бар, бірақ БОС-ы жоқ балалар, және (2) Негізгі топ: SARS-CoV-2 инфекциясы жоқ, бірақ БОС-ы бар балалар; SARS-CoV-2 инфекциясынан кейін БОС дамыған балалар. Эндотелий функциясы АЭК, эндотелин-1 және азот оксидінің метаболиттері деңгейін анықтау арқылы бағаланды.

Нәтижелер: Зерттеу SARS-CoV-2 инфекциясынан кейін БОС дамыған балаларда ЦЭК және эндотелин-1 деңгейінің айтарлықтай жоғарылағанын, ал азот оксидінің метаболиттерінің төмендегенін көрсетті. Эндотелиалды дисфункция маркерлерінің ең жоғары деңгейі осы топта байқалды, бұл SARS-CoV-2 инфекциясы мен БОС-тың эндотелийге зақым келтірудегі синергетикалық әсерін көрсетеді. Ерекше маңыздысы, осы топтағы балалардың 64,3%-ында АЭК деңгейінің жоғарылауы байқалды, бұл эндотелиалды дисфункцияның ауыр түрін көрсетеді. SARS-CoV-2 инфекциясынан кейін БОС дамыған балаларда эндотелин-1 деңгейі де дені сау балаларға және SARS-CoV-2 инфекциясы анамнезі жоқ БОС-ы бар балаларға қарағанда айтарлықтай жоғары болды ($0,46 \pm 0,02$ фмоль/мл). Бұл нәтижелер COVID-19-дан кейінгі респираторлық асқынулар патогенезінде эндотелиалды дисфункцияның маңызды рөлін атап өтеді.

Қорытынды: SARS-CoV-2 инфекциясы балаларда, әсіресе БОС дамығандарда, эндотелиалды дисфункцияның айтарлықтай дамуына ықпал етеді. SARS-CoV-2 инфекциясы мен БОС-тың бірігуі эндотелий зақымдануын шиеленістіреді, бұл COVID-19-дан кейінгі респираторлық асқынулар патогенезінде маңызды рөл атқарады. Бұл деректер эндотелиалды дисфункцияны түзетуге бағытталған терапиялық стратегияларды одан әрі зерттеу қажеттілігін көрсетеді, бұл COVID-19-дан кейінгі ұзақ мерзімді респираторлық салдарларға шалдыққан балалардың емдеу нәтижелерін жақсартуы мүмкін.

Түйін сөздер: SARS-CoV-2, эндотелиалды дисфункция, айналымдағы эндотелиалды клеткалар (АЭК), бронхообструктивті синдром (БОС), балалардағы COVID-19, эндотелин-1, азот оксидінің метаболиттері, постковидтік асқынулар, қан тамырлары эндотелийі, респираторлық асқынулар.

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Introduction

The impact of SARS-CoV-2 infection on the human organism has proven to be more diverse than that of previously known viral infections [1-3]. However, the full spectrum of the long-term consequences of the disease, especially in children, has not been thoroughly studied. The delayed development (or detection) of widespread morbidity has resulted in a shorter observation period, a limited number of patients, and a restricted range of clinical examinations [4]. Although the study of COVID-19 incidence in children and its consequences began in mid-2020, many aspects remain unexplored.

One of the key areas in studying the pathophysiology of COVID-19 is the identification of its impact on the vascular endothelium [5]. The endothelium, which is widely distributed throughout the body and performs a variety of functions, has been shown to be significantly affected by SARS-CoV-2. Endothelial dysfunction has been implicated in the outcomes of various diseases, leading some authors to conclude that COVID-19 often manifests due to severe endothelial dysfunction [6]. Specifically, endothelial dysfunction is thought to play a crucial role in post-viral complications such as broncho-obstructive syndrome, a condition involving airway inflammation and hyperreactivity that can result from viral infections.

However, the specific effects of endothelial dysfunction on the development of organ pathology in children, particularly those unrelated to the cardiovascular system, remain poorly understood. Additionally, there is a lack of information regarding the role of endothelial dysfunction in

the development of BOS in children who have recovered from COVID-19.

The aim of this study is to determine the characteristics of vascular endothelial conditions in children with SARS-CoV-2 infection, particularly focusing on the relationship between SARS-CoV-2 infection and the development of broncho-obstructive syndrome. By assessing key markers of endothelial dysfunction—circulating endothelial cells, endothelin-1, and nitric oxide metabolites—the study seeks to identify how endothelial injury contributes to the pathogenesis of broncho-obstructive syndrome in children post-SARS-CoV-2 infection.

Materials and Methods

Study Design

This retrospective study was conducted at the Private Multidisciplinary Clinic Institution "Venera" in Semey, Republic of Kazakhstan, from 2020 to 2022. The study was approved by the local ethics committee on October 22, 2022 (Protocol No. 1).

Inclusion Criteria

Children aged 2–18 years were eligible for inclusion if they had a history of recurrent broncho-obstructive syndrome (BOS) or if BOS was identified during the study. The study population included children with a history of SARS-CoV-2 infection or asymptomatic SARS-CoV-2 infection, confirmed by either a positive PCR test or the detection of diagnostic IgG antibodies to SARS-CoV-2. Written informed consent from parents or legal guardians was obtained for participation and the anonymous use of study data.

Exclusion Criteria

Children were excluded if they were younger than 2 years or older than 18 years, had severe congenital bronchopulmonary or cardiovascular diseases, or had immunodeficiencies. Additionally, children under 5 years with clinically verified bronchial asthma were excluded from the study. Children whose legal guardians did not provide written consent or who withdrew consent at any stage of the study were also excluded.

Study Population

A total of 486 children were enrolled in the study and categorized into a main group (259 children) and control group (227 children), based on the presence of bronchial obstruction syndrome (BOS) and the history of SARS-CoV-2 infection:

• Main Groups:

○ BOS without SARS-CoV-2 infection: 198 children diagnosed with BOS but with no history of SARS-CoV-2 infection.

○ BOS after SARS-CoV-2 infection: 61 children who developed BOS following SARS-CoV-2 infection.

• Control Groups:

○ Healthy Control: 120 children without BOS and without a history of SARS-CoV-2 infection, confirmed by detailed anamnesis and repeated analysis for the presence of antibodies.

○ SARS-CoV-2 Control: 107 children who had SARS-CoV-2 infection but did not develop BOS. This group included children who had clinically symptomatic COVID-19 (confirmed by PCR or clinical symptoms) as well as those

who tested positive for SARS-CoV-2 antibodies (diagnostic IgG titers) without exhibiting clinical symptoms.

Methods for Studying Vascular Endothelial State

Vascular endothelial function was assessed using blood test results, which included the following parameters: Circulating Endothelial Cells, Endothelin-1, Nitric Oxide Metabolites.

Statistical Analysis

Data were analyzed using nonparametric tests due to the nature of the distributions. Comparisons between independent groups were performed using the Mann-Whitney U test. A p-value of less than 0.05 was considered statistically significant.

Results

The analysis of vascular endothelial markers revealed significant differences in endothelial dysfunction across the study groups, with particular emphasis on circulating endothelial cells (CECs), endothelin-1, and nitric oxide (NO) metabolites.

Circulating Endothelial Cells (CECs)

The levels of CECs varied significantly across the study groups (Figure 1). In the healthy control group, the average CECs count was 1.2 ± 0.1 per 10^3 platelets. In children with a history of SARS-CoV-2 infection but no BOS, the CECs count increased to 1.8 ± 0.1 per 10^3 platelets. The main group with persistent BOS without prior SARS-CoV-2 infection had a lower CECs level of 1.4 ± 0.1 per 10^3 platelets. The highest CECs level was observed in children who developed BOS following SARS-CoV-2 infection (3.3 ± 0.2 per 10^3 platelets).

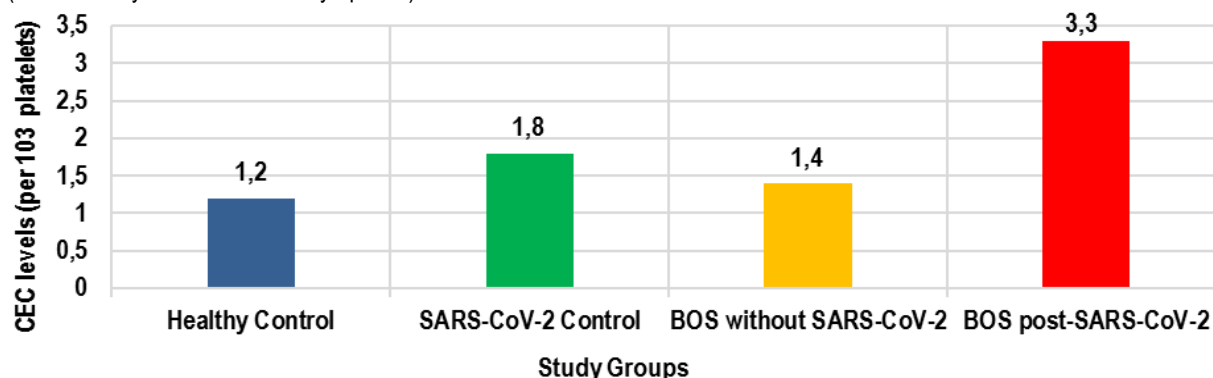


Figure 1. Levels of Circulating Endothelial Cells in Children Across Study Groups.

The graph shows the mean CECs levels (per 10^3 platelets) across two study groups: Control (healthy control and SARS-CoV-2 control) and Main Group (BOS without SARS-CoV-2 and BOS after SARS-CoV-2).

Figure 2 presents the distribution of CECs levels across the study groups. The proportion of children with higher CECs levels increased in groups with a history of SARS-CoV-2 infection and BOS development. In the healthy control group, most children had CEC levels below 1.5 per 10^3 platelets, with only a small fraction exceeding this threshold. In contrast, BOS post-SARS-CoV-2 group had the highest percentage of children with CECs levels exceeding 2.5 per 10^3 platelets, indicating significant endothelial dysfunction.

Endothelin-1 Levels

Endothelin-1 concentrations were assessed across both control and main study groups (Figure 3). The healthy control group had an average endothelin-1 level of 0.32 ± 0.02 fmol/mL. In the SARS-CoV-2 control group, the endothelin-1 level was slightly higher at 0.35 fmol/mL. In the

main groups, children with BOS without a history of SARS-CoV-2 infection had endothelin-1 levels of 0.39 ± 0.01 fmol/mL, while the highest levels were observed in the group of children who developed BOS following SARS-CoV-2 infection, with an average of 0.46 ± 0.02 fmol/mL.

Figure 4 illustrates the gradation of endothelin-1 concentrations among the groups. The distribution of endothelin-1 levels shifted towards higher values in children with BOS, particularly in those with a prior SARS-CoV-2 infection. The healthy control group primarily had endothelin-1 concentrations below 0.40 fmol/mL, whereas in the BOS post-SARS-CoV-2 group, more than half of the children had endothelin-1 levels exceeding 0.50 fmol/mL. This trend highlights the potential role of endothelial dysfunction in the pathogenesis of BOS following SARS-CoV-2 infection.

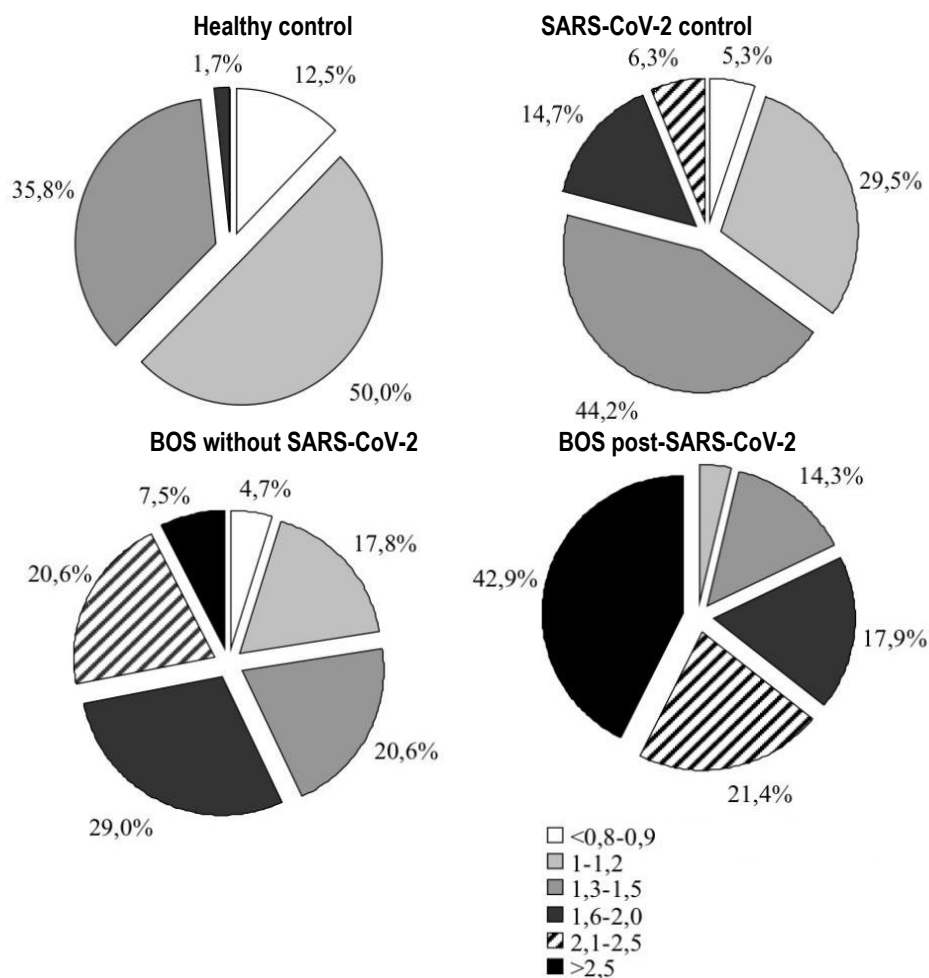


Figure 2. Distribution of Circulating Endothelial Cell Levels Across Study Groups.

Figure illustrates the distribution of CECs levels among the study groups: Control (healthy control and SARS-CoV-2 control) and Main Group (BOS without SARS-CoV-2 and BOS after SARS-CoV-2). The color gradients correspond to specific concentration ranges: <0,8-0,9 per10⁹ platelets, 1-1,2 per10³ platelets, 1,3-1,5 per10³ platelets, 1,6-2,0 per10³ platelets, 2,1-2,5 per10³ platelets, >2,5 per10³ platelets.

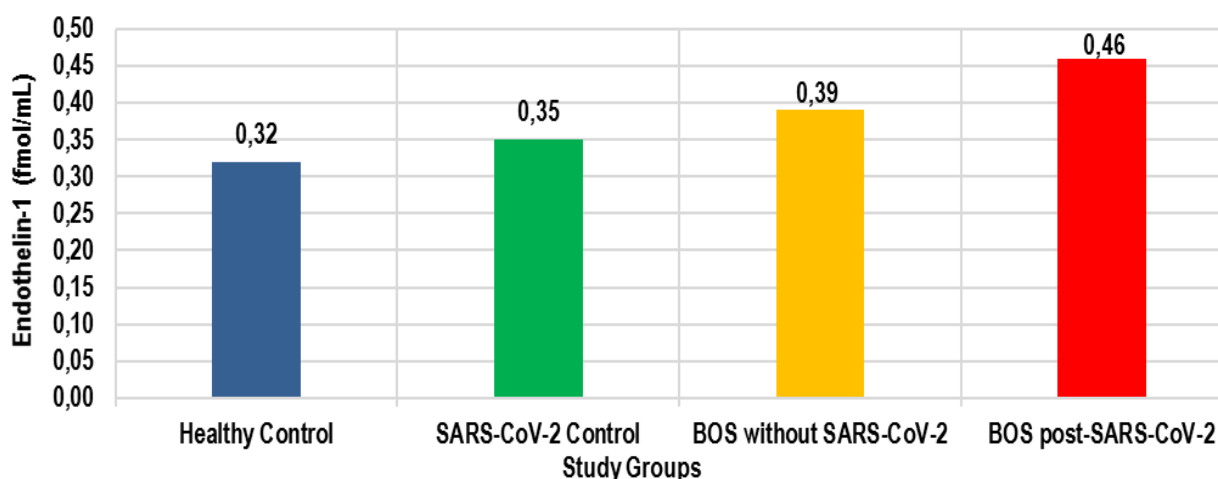


Figure 3. Levels of Endothelin-1 in Children Across Study Groups.

The graph illustrates the mean endothelin-1 concentrations (fmol/mL) in children from the study groups: Control (healthy control and SARS-CoV-2 control), BOS without SARS-CoV-2 infection, and BOS post-SARS-CoV-2 infection.

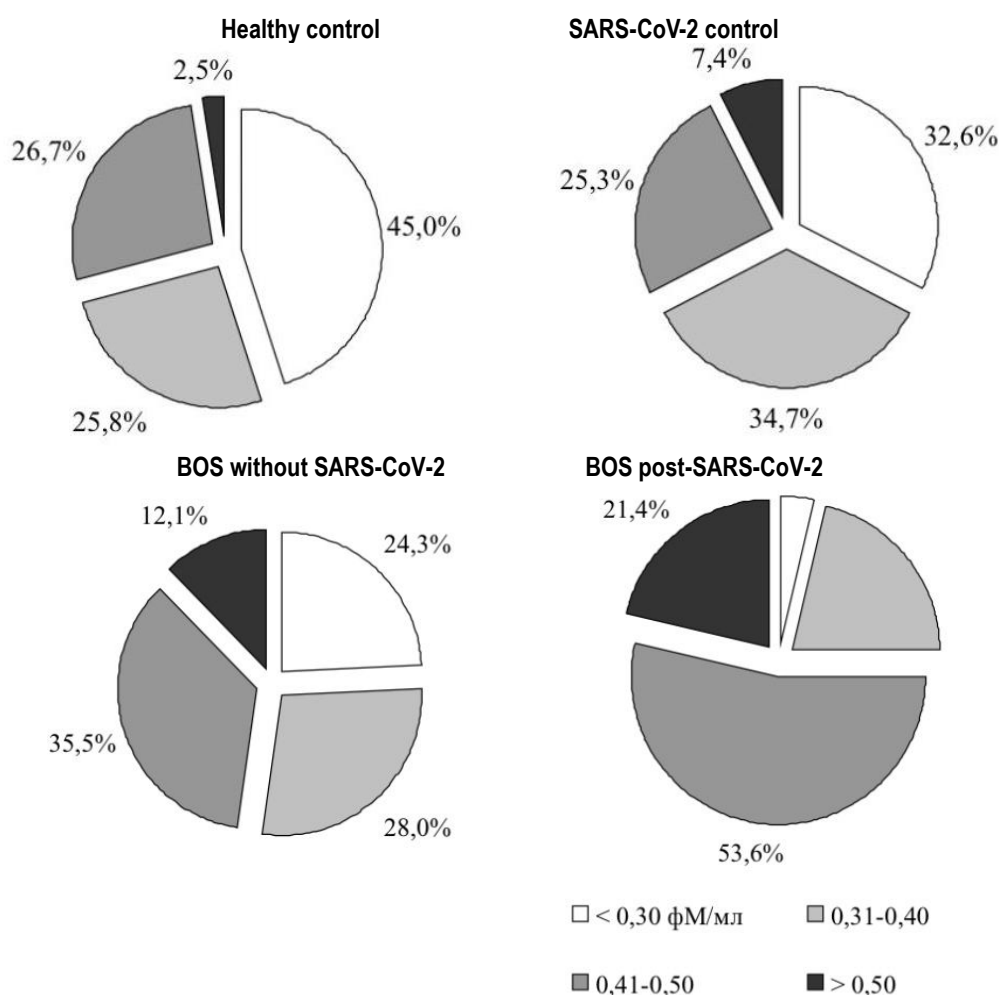


Figure 4. Distribution of Endothelin-1 Concentrations Across Study Groups.

Figure shows the gradation of endothelin-1 concentrations among the study groups: Control (healthy control and SARS-CoV-2 control) and Main Group (BOS without SARS-CoV-2 and BOS after SARS-CoV-2). The color gradient corresponds to specific concentration ranges: < 0.30 fmol/mL, 0.31–0.40 fmol/mL, 0.41–0.50 fmol/mL, > 0.50 fmol/mL.

Nitric Oxide (NO) Metabolites

The levels of NO metabolites varied across the different study groups (Figure 5). The healthy control group had an average NO metabolite level of 3.3 ± 0.2 μ M/L. The SARS-CoV-2 control group, which included children with a history of SARS-CoV-2 infection but no BOS, showed a slightly lower average of 3.2 ± 0.2 μ M/L.

In the main groups, the children with BOS but no history of SARS-CoV-2 infection had a NO metabolite level of 3.1 ± 0.3 μ M/L, while the lowest level was observed in the group with BOS post-SARS-CoV-2 infection, which had an average of 2.2 ± 0.1 μ M/L.

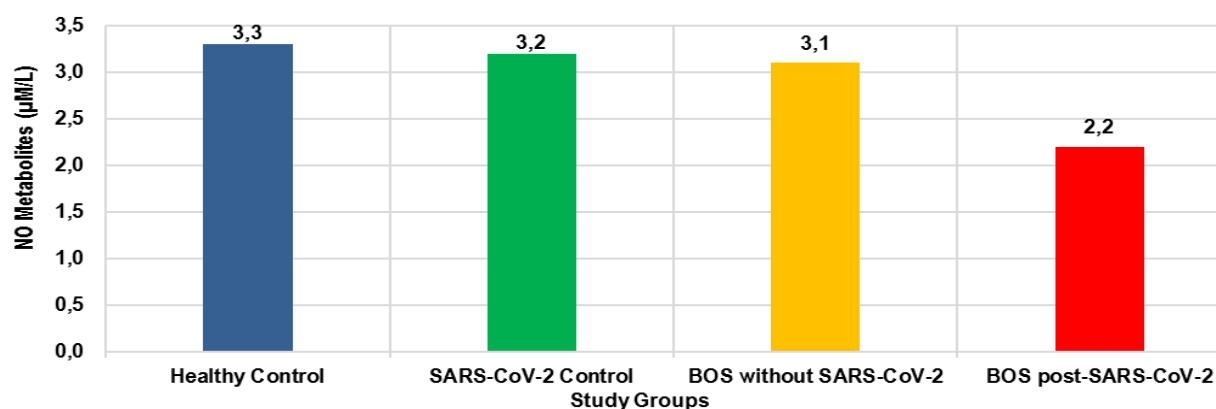


Figure 5. Levels of Nitric Oxide Metabolites in Children Across Study Groups.

The graph illustrates the mean NO metabolite levels (μ M/L) in children from the control (healthy control and SARS-CoV-2 control) and main groups (BOS without SARS-CoV-2 and BOS after SARS-CoV-2).

Figure 6 shows the distribution of NO metabolite levels among the study groups. The majority of children in the healthy control and SARS-CoV-2 control groups had NO metabolite levels between 3.0–3.5 $\mu\text{M/L}$. However, in children with BOS, particularly those with a

history of SARS-CoV-2 infection, NO levels shifted downward, with a higher proportion of individuals having concentrations below 2.5 $\mu\text{M/L}$. This reduction suggests impaired endothelial function and nitric oxide bioavailability in these patients.

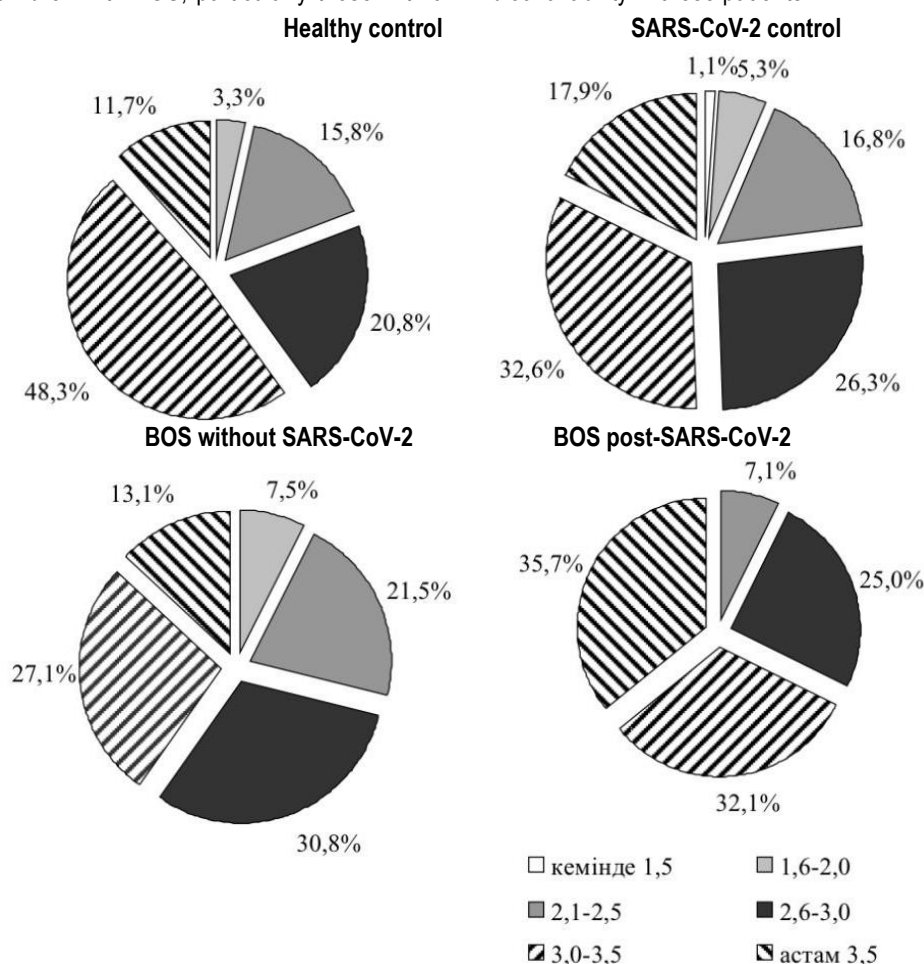


Figure 6. Distribution of Nitric Oxide Metabolite Levels Across Study Groups.

Figure illustrates the distribution of NO metabolite levels among the study groups: Control (healthy control and SARS-CoV-2 control) and Main Group (BOS without SARS-CoV-2 and BOS after SARS-CoV-2). The color gradient corresponds to specific concentration ranges: < 1,5 $\mu\text{M/L}$, 1,6-2,0 $\mu\text{M/L}$, 2,1-2,5 $\mu\text{M/L}$, 2,6-3,0 $\mu\text{M/L}$, 3,0-3,5 $\mu\text{M/L}$, > 3,5 $\mu\text{M/L}$.

Thus, the data demonstrate that SARS-CoV-2 infection (especially when followed by the development of BOS) leads to significant endothelial dysfunction, as reflected by increased levels of CECs and endothelin-1, alongside decreased levels of NO metabolites. These changes are most pronounced in children who developed BOS post-SARS-CoV-2 infection, suggesting a synergistic effect of the infection and the development of BOS on endothelial damage.

Discussion. The SARS-CoV-2 pandemic has been associated with a variety of negative health outcomes, some of which persist long after recovery. One of the most significant findings in adults is the development of endothelial dysfunction, which plays a central role in the pathogenesis of cardiovascular and systemic complications [8-11]. The endothelium is particularly vulnerable to SARS-CoV-2 due to the virus's binding to the angiotensin-converting enzyme 2 (ACE2) receptor, which is widely expressed on endothelial cells [12]. However, much less is known about the impact of COVID-19 on endothelial function in children, particularly with respect to post-

infection syndromes like broncho-obstructive syndrome (BOS).

Endothelial dysfunction is recognized for its involvement in regulating vascular tone, hemostasis, and the repair of damaged blood vessels, all of which are crucial for maintaining cardiovascular health [13,14]. This dysfunction, when it occurs, disrupts normal vascular homeostasis, potentially leading to a cascade of pathophysiological consequences. In adults, endothelial dysfunction has been implicated in various organ systems, including the kidneys, lungs, and gastrointestinal tract [16-20]. However, research on how endothelial dysfunction affects children after SARS-CoV-2 infection, especially in the context of BOS, remains limited.

Our study highlights the significant role that endothelial dysfunction plays in pediatric patients post-COVID-19, particularly in those who develop BOS. The findings show that children with COVID-19 who subsequently developed BOS had markedly higher levels of circulating endothelial cells (CECs) and endothelin-1, alongside reduced nitric oxide (NO) metabolites. Specifically, CECs were elevated to

3.3 ± 0.2 per 10^3 platelets, endothelin-1 levels were increased to 0.46 ± 0.02 fmol/mL, and NO metabolites were reduced to 2.2 ± 0.1 μ M/L. These changes in endothelial markers point to a disruption in endothelial function, which may contribute to the development of post-COVID-19 complications, including BOS.

Interestingly, children who had SARS-CoV-2 infection but did not develop BOS exhibited moderate endothelial dysfunction, with elevated CECs (1.8 ± 0.1 per 10^3 platelets). However, the combination of SARS-CoV-2 infection and BOS led to a much more pronounced effect on endothelial health. This group showed the highest levels of CECs and endothelin-1, paired with the lowest levels of NO metabolites. This finding suggests that SARS-CoV-2 infection and BOS may act synergistically, amplifying endothelial damage and worsening post-viral complications. This aligns with previous findings in adults, where endothelial dysfunction has been linked to the severity of COVID-19 outcomes [8-11]. Notably, this study is one of the first to demonstrate these effects in children, specifically in relation to BOS.

The elevated CEC levels observed in children with BOS post-SARS-CoV-2 infection (64.3% prevalence) further support the notion of significant endothelial dysfunction in this group. These findings are consistent with the endothelial damage observed in adults with COVID-19, reinforcing the idea that endothelial injury is central to the clinical severity of post-viral complications. Additionally, the reduction in NO metabolites in children with BOS suggests that impaired nitric oxide production is contributing to vasoconstriction, inflammation, and thrombosis. This could help explain the increased risk of severe respiratory complications in these children, as impaired NO synthesis compromises vascular tone and immune function.

Moreover, the elevated endothelin-1 levels in children with BOS post-SARS-CoV-2 infection suggest a link between endothelial dysfunction and bronchial hyperreactivity and airway obstruction. Endothelin-1 is a potent vasoconstrictor and is known to play a role in airway remodeling and inflammation. Our data support the hypothesis that endothelial dysfunction exacerbates these processes, contributing to the development and worsening of BOS.

These findings underscore the potential for targeting endothelial dysfunction as a therapeutic strategy in children who develop BOS following SARS-CoV-2 infection. Future research should focus on exploring interventions aimed at restoring endothelial function to mitigate long-term health consequences and improve clinical outcomes in this vulnerable population.

Limitations of the study.

This study has several limitations that should be considered when interpreting the findings.

One notable limitation is the absence of longitudinal follow-up data. Without tracking the children over an extended period, it is challenging to assess the long-term effects of endothelial dysfunction. It remains uncertain whether the observed endothelial changes persist or resolve with time.

Additionally, while the study carefully categorized participants based on SARS-CoV-2 infection status and the presence of BOS, there may be unmeasured confounding factors that could influence the results. Factors such as pre-existing respiratory conditions, genetic predispositions, or

environmental exposures could contribute to endothelial dysfunction and the development of BOS.

Conclusion.

SARS-CoV-2 infection results in significant endothelial dysfunction in children, particularly in those who develop BOS. The presence of BOS post-SARS-CoV-2 infection leads to exacerbated endothelial damage, as evidenced by elevated levels of circulating endothelial cells and endothelin-1, alongside reduced nitric oxide metabolites. These alterations in endothelial function suggest that the combination of BOS and SARS-CoV-2 infection may synergistically worsen endothelial injury.

The observed endothelial dysfunction is likely to contribute to bronchial hyperreactivity, inflammation, and airway obstruction, emphasizing its role in the pathophysiology of BOS. This dysfunction could be an important factor in the long-term respiratory complications experienced by children who have had COVID-19.

Given these findings, further studies are needed to explore the underlying mechanisms of endothelial dysfunction in pediatric COVID-19 and develop potential therapeutic strategies to mitigate the long-term effects of endothelial injury and improve clinical outcomes for affected children.

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