International Journal of Biomedicine 12(2) (2022) 242-246
http://dx.doi.org/10.21103/Article12(2)_OA7

ORIGINAL ARTICLE

COVID-19

INTERNATIONAL JOURNAL OF BIOMEDICINE

Oxidative Stress Intensity in Children and Adolescents with a New Coronavirus Infection

Lyubov V. Rychkova, PhD, ScD, Member of the RAS; Marina A. Darenskaya*, PhD, ScD; Natalya V. Semenova, PhD, ScD; Sergey I. Kolesnikov, PhD, ScD, Member of the RAS; Alla G. Petrova, PhD, ScD; Olga A. Nikitina, PhD, ScD; Anastasia S. Brichagina; Lyubov I. Kolesnikova, PhD, ScD, Member of the RAS

Scientific Centre for Family Health and Human Reproduction Problems
Irkutsk, the Russian Federation

Abstract

The aim of our research was to assess the intensity of oxidative stress (OS) in children and adolescents with COVID-19 using the oxidative stress index (OSI).

***Methods and Results*:** The study was conducted between May 2020 and March 2021. The main group included 17 children and adolescents [8(47.1%) boys and 9(52.9%) girls; mean age of 12.35±4.01 years] with diagnosed COVID-19 infection (mild to moderate course) selected as a result of the primary diagnostic examination from among those admitted to hospitalization at the Irkutsk Regional Infectious Diseases Clinical Hospital. The control group included 17 healthy children and adolescents (average age of 12.35±4.01 years) matched by copy-pair type. The obtained data indicated statistically significant differences in a number of parameters between children and adolescents with COVID-19 and the control groups. We found statistically significant higher levels of lipid peroxidation (LPO) products (CDs, $P<0.0001$; KD and CT, $P=0.006$; and TBARs, $P=0.013$) in the study group than in the control group. Among antioxidant defense (AOD) system parameters, the levels of retinol ($P=0.015$) and reduced glutathione ($P=0.048$) and SOD activity ($P<0.0001$) were statistically lower in the study group than in the control group. The OSI level was significantly greater (by 8.5 times, $P=0.028$) in the study group than in the control group, which confirms the development of antioxidant deficiency in COVID-19.

Conclusion: The results of the assessment of OSI in children and adolescents with COVID-19 indicate insufficient activity of some critical components of AOD and a shift of the redox balance toward pro-oxidant factors, which can have extremely negative consequences in the development of the disease. In this regard, we recommend carrying out corrective measures to stabilize LPO/AOD parameters by including drugs with antioxidant properties in the treatment complex.(**International Journal of Biomedicine. 2022;12(2):242-246.**)

Key Words: COVID-19 • oxidative stress index • children • adolescents • polymerase chain reaction

For citation: Rychkova LV, Darenskaya MA, Semenova NV, Kolesnikov SI, Petrova AG, Nikitina OA, Brichagina AS, Kolesnikova LI. Oxidative Stress Intensity in Children and Adolescents with a New Coronavirus Infection. International Journal of Biomedicine. 2022;12(2):242-246. doi:10.21103/Article12(2)_OA7

Abbreviations

AOD, antioxidant defense; **ACE2**, angiotensin-converting enzyme 2; **CDs,** conjugated dienes; **COVID-19**, coronavirus disease 2019; **GSH**, reduced glutathione; **GSSG**, oxidized glutathione; **KD and CT,** ketodienes and conjugated trienes; **LPO,** lipid peroxidation; **OS,** oxidative stress; **OSI,** oxidative stress index; **ROS**, reactive oxygen species; **SARS-CoV-2**, severe acute respiratory syndrome-related coronavirus 2; **SOD,** superoxide dismutase; **TAA**, total antioxidant activity; **TBARs**, thiobarbituric acid reactants.

Introduction

The pandemic of coronavirus infection (COVID-19) is the most devastating disease since the turn of the 21th century, but unfortunately, many of its clinical manifestations, pathogenetic characteristics, and treatments are still unclear. The number of cases of infection worldwide has exceeded 500 million to date, and the rates are still increasing.[1] An important distinguishing

feature of COVID-19 is the different severity of the course depending on the age of the patient. Thus, if the disease is mild or moderate for children and adolescents, for the elderly the course will be more severe, with a high mortality rate, especially in the presence of chronic comorbidities such as diabetes mellitus, arterial hypertension, and cardiovascular diseases.[2]

According to worldwide studies, children and adolescents are significantly less likely to have a new coronavirus infection, usually within 1%-5% of patients with diagnosed clinical cases of COVID-19 and up to 11% of those infected with SARS-CoV-2.[3,4] Moreover, there is a direct correlation between emergency department visits and the vaccination intensity of the population in the region where the child lives. In regions with high vaccination coverage, the data tend to be lower.[5] Schoolchildren and preschool-age children, make up the bulk of infected children.[3] Children are characterized by mild clinical symptoms, with the main symptoms in the form of fever, cough, signs of intoxication, etc.[6] The majority of cases are asymptomatic, while about 10% require hospitalization.[7] There are some cases with a severe course (about 1% of children), especially in children with a burdened pre-morbid and comorbid background and severe comorbid disorders.[4] Overall, no particular changes were found in the structure of morbidity in children in different "waves" of COVID-19. However, some differences concern the so-called "third wave" (May-June 2021): an increase in the number of hospitalized children, early hospital admission from the beginning of the disease, prolongation of the virus release period, reduction of cases with development of multisystem inflammatory syndrome, which characterizes modern features of the course of COVID-19 infection in children.[3] In addition, the pediatric population should receive no less attention than the adult population because of the active participation of children in the spread of the new infection.

Many respiratory infections are accompanied by excessive generation of ROS and insufficient activity of the antioxidant defense (AOD) system.[8] The disproportion between the presence of antioxidants and free radicals or pro-oxidants in the biological system is defined as oxidative stress (OS). Studies show that OS plays an important role in the genesis of coronavirus infections, including COVID-19.[9-12] The integral coefficient evaluating the intensity of OS reactions can characterize the stage of pathological process formation in the body, including in the presence of infectious diseases.[13-16] There is virtually no information on the state of OS reactions in children with coronavirus infection. At the same time, such studies are highly relevant and can improve the effectiveness of preventive and therapeutic measures.

The aim of our research was to assess the OS intensity in children and adolescents with COVID-19 using the oxidative stress index (OSI).

Material and Methods

Design of study

The study was conducted between May 2020 and March 2021. The main group included 17 children and adolescents [8(47.1%) boys and 9(52.9%) girls; mean age of 12.35±4.01 years] with diagnosed COVID-19 infection (mild to moderate course) selected as a result of the primary diagnostic examination from among those admitted to hospitalization at the Irkutsk Regional Infectious Diseases Clinical Hospital. The control group included 17 healthy children and adolescents (average age of 12.35±4.01 years) matched by copy-pair type. Inclusion criteria were the age of subjects, informed consent to participate in the study, and presence of laboratory-confirmed SARS-CoV-2. Exclusion criteria were a severe disease, refusal to participate in the study, failure to meet inclusion criteria, and other reasons. On admission to the hospital, we performed a general clinical examination of patients, analysis of medical records, and questionnaire survey. The questionnaire included information on the presence of a positive PCR test for SARS-CoV-2 RNA (laboratory confirmation of infection), dynamic monitoring of enzyme immunoassay and PCR, the course of the disease, and epidemiological history. We collected data on complications of the underlying disease, need for respiratory support, renal replacement therapy, presence of viral or fungal co-infection, and laboratory findings. The main group of children and adolescents was homogeneous in terms of the nature and duration of the infection and the therapeutic effect.

Biochemical measurements

The OSI [the ratio of the LPO-AOD system indicators in the study group to average indicators in the control group], as integral indicator the OS intensity, was calculated using the formula that was developed and modified in our previous study.[13-16] The formula takes into account not only the accumulation of LPO products at various stages (from primary to final), but also the activity of various parts of the AOD system (enzymatic and non-enzymatic).

Plasma concentrations of primary/secondary/final products of LPO (CDs/KD-CT/ TBARs) were estimated.[17,18] The state of the AOD system was assessed by the content of α-tocopherol and retinol,[19] GSH and GSSG,[20] and the SOD activity.[21]

The measurements were carried out using a Shimadzu RF-1501 spectrofluorophotometer (Japan) and Shimadzu RF-1650 spectrofluorophotometer (Japan).

Statistical analysis was performed using STATISTICA 8.0 software package (Stat-Soft Inc, USA). The normality of distribution of continuous variables was tested by the Kolmogorov-Smirnov test with the Lilliefors correction and Shapiro-Wilk test. The F test for equality of two variances was applied. For descriptive analysis, results are presented as mean±standard deviation (SD), median (Me), interquartile range (IQR; 25th to 75th percentiles). Differences of continuous variables departing from the normal distribution, even after transformation, were tested by the Mann-Whitney *U*-test. A probability value of $P<0.05$ was considered statistically significant.

Ethics approval of research

All participants or their parents signed an informed consent to participate in the study in accordance with the World Medical Association Declaration of Helsinki (1964, 2013 ed.). The study was approved the Biomedical Ethics Committee at the Scientific Centre for Family Health and Human Reproduction Problems, Russia (No. 6/1 dated June 19, 2020).

Results and Discussion

The obtained data indicated statistically significant differences in a number of parameters between children and adolescents with COVID-19 and the control groups. Thus, we found statistically significant higher levels of LPO products (CDs, $P<0.0001$; KD and CT, $P=0.006$; and TBARs, $P=0.013$) in the study group than in the control group. Among AOD system parameters, the levels of retinol ($P=0.015$) and reduced glutathione ($P=0.048$) and SOD activity ($P<0.0001$) were statistically lower in the study group than in the control group (Table 1).

Table 1.

Content of LPO products and AOD components in children and adolescents with COVID-19 (Me, 25%-75%).

Parameters	Control group	Main group
CDs, μmol/L	1.18 (0.84-1.82)	7.03 (5.51-7.58) *
KD and CT, units	0.22 (0.14-0.32)	0.9 (0.43-1.2) *
TBARs, μmol/L	0.86 (0.67-1.36)	1.33 (1.14-1.91) *
SOD activity, units	1.66 (1.6-1.74)	1.01 (0.94-1.14) *
α- tocopherol, μmol/L	7.71 (5.95-11.7)	7.85 (5.17-8.79)
retinol, μmol/L	1.25 (0.59-2.21)	0.85 (0.63-0.99) *
GSH, mmol/L	2.32 (2.08-2.85)	1.79 (1.67-2.45) *

* - *statistically significant differences.*

According to our data, the OSI level was significantly greater (by 8.5 times, $P=0.028$) in the study group than in the control group, which confirms the development of antioxidant deficiency in COVID-19 (Figure 1).

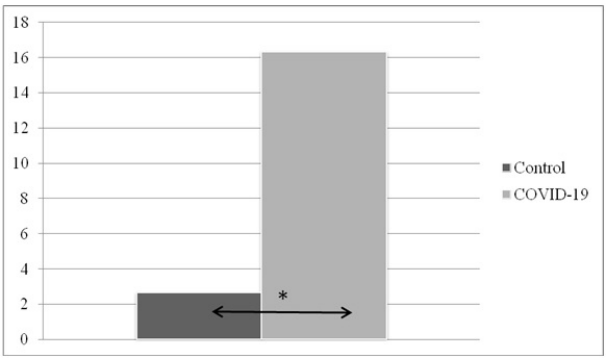

Fig. 1. *The level of OSI in children and adolescents with COVID-19 (* - statistically significant differences between the two groups).*

Currently, there are very few works concerning metabolic responses in the pediatric and adolescent population with a new coronavirus infection. Most of them are theoretical in explaining the reasons for a milder course of infection in this cohort of patients. Possible causes include a number of factors, such as differences in the ACE2 expression, immune response reactivity, the nature of the inflammatory response, melatonin secretion levels, and other metabolic parameters.[22,23] Differences in the distribution, maturation, and function of viral receptors, as well as the likely protective effect of low levels of ACE2 in children, have also been noted.[24] On the other hand, it is well known that some infectious diseases, such as paralytic polio and rubella, are milder in children than in adults.[25] There are suggestions that the more favorable course of infection in children may be due to the high intensity of metabolic reactions.[23,25]

Our analysis of the OSI values indicates the presence of a higher intensity of OS reactions in children and adolescents with COVID-19 relative to healthy children.

Several studies have shown that OS plays an important role in viral infections such as SARS-CoV and SARS-CoV-2.[26,27] Coronavirus contains an S-protein that enables virus access to target cells via the ACE2 receptor. The latter is expressed on the surface of epitheliocytes of the respiratory and digestive tracts, the upper parts of which are the entry gates of infection. Accumulation of intermediate products of viral metabolism is accompanied by the generation of ROS and mitochondrial damage.[12] The infection progresses and descends to the lower parts of the respiratory tract, affecting alveolar type I and type II cells and endotheliocytes, where the expression and subsequent secretion of pro-inflammatory cytokines occurs.[9] When this occurs, alveolar macrophages and infiltrated immune cells are activated, which increases oxygen consumption and aggravates the process of hypoxia.[28] Activated alveolar macrophages release pro-inflammatory cytokines in the alveoli, which then enter the great circle of the circulation. Intense inflammation leads to excessive production of ROS, activation by hypoxia-induced factors (HIF-1α, NF-κB), etc.[29] Experimental studies of coronavirus infections of past decades showed that the pro-inflammatory response was secondary to an impaired AOD system.[25] This conclusion was supported by similar clinical data. A number of papers have also identified low AOD activity as a key component determining the severity of viral infections.[10,12,27] Viral respiratory infections, including respiratory syncytial virus, human metapneumovirus, and influenza virus infections, were shown to suppress the expression and activity of antioxidant enzymes, resulting in reduced antioxidant capacity.[8] Although the exact role of OS in viral virulence is not clear, it may be secondary to the modulation of the immune system caused by oxidative damage.[28,29] Strong evidence for the role of OS comes from studies of ACE2 involvement. ACE2 plays an important role in determining the severity level of SARS-CoV-2 infections because it is not only a condition for SARS-CoV-2 entry into the cell but also acts as a modulator of OS and inflammation.[30]

Viral infection causes increased synthesis of ROS as a result of the lack of appropriate activity of the AOD system components to neutralize toxic metabolites. It is likely that in our study, the increased OSI values in children and adolescents with COVID-19 were associated with the insufficiency of a number of antioxidants. Thus, in particular, the insufficient activity of SOD, GSH, and retinol was noted. SOD is a key enzyme of the first line of defense against ROS, responsible for the innate antioxidant response in aerobic organisms.[31,32] It was noted

that even a slight decrease in the activity of SOD causes a shift of metabolic reactions toward the prevalence of pro-oxidant processes.[33] Glutathione (γ-1-glutamyl-1-cysteinylglycine) is a tripeptide that plays an important role in cellular detoxification through glutathione S-transferase activity, and participates in antioxidant defense, regulates the synthesis and recovery of fat- and water-soluble vitamins, supports "thiol status," and modulates cell proliferation.[26] Lower levels of glutathione are associated with immune dysfunction, which leads to higher susceptibility to viral infections, particularly SARS-CoV-2 infection.[27] Vitamin A and related retinols are involved in modifying the immune system by expressing the key antiviral antibodies.[34] Consequently, retinol deficiency in the blood of children with COVID-19 may adversely affect the course of the disease. Considering the vital role of vitamins as regulators of growth and tissue morphological differentiation, changes in this metabolic link in children and adolescents seem to be highly significant.[35-37]

Conclusion

Thus, the results of the assessment of OSI, the integral index of OS, in children and adolescents with COVID-19 indicate insufficient activity of some critical components of AOD and a shift of the redox balance toward pro-oxidant factors, which can have extremely negative consequences in the development of the disease. In this regard, we recommend carrying out corrective measures to stabilize LPO/AOD parameters by including drugs with antioxidant properties in the treatment complex.

This work was performed with the use of equipment of the collective research center "Centre for the development of progressive personalized health technologies" SC FHHRP, Irkutsk.

Competing Interests

The authors declare that they have no competing interests.

References

1. WHO Coronavirus (COVID-19) Dashboard. https://covid19.who.int/
2. Liu K, Chen Y, Lin R, Han K. Clinical features of COVID-19 in elderly patients: A comparison with young and middle-aged patients. J Infect. 2020 Jun;80(6):e14-e18. doi: 10.1016/j.jinf.2020.03.005.
3. Mazankova LN, Samitova ER, Osmanov IM, Afukov II, Dracheva NA, Malakhov AB, et al. Clinical and epidemiological features of the course of a new coronavirus infection COVID-19 in children during periods of increased incidence in Moscow in 2020-2021. Children's infections. 2021;20(3):5-10.
4. On the state of sanitary and epidemiological well-being of the population in the Russian Federation in 2020: State report. Moscow: Federal Service for Supervision of Consumer Rights Protection and Human Welfare, 2021;256.
5. Siegel DA, Reses HE, Cool AJ, Shapiro CN, Hsu J, Boehmer TK, et al. Trends in COVID-19 Cases, Emergency Department Visits, and Hospital Admissions Among Children and Adolescents Aged 0-17 Years - United States, August 2020-August 2021. MMWR Morb Mortal Wkly Rep. 2021 Sep 10;70(36):1249-1254. doi: 10.15585/mmwr.mm7036e1. Erratum in: MMWR Morb Mortal Wkly Rep. 2021 Sep 24;70(38):1355.
6. Blanchard-Rohner G, Didierlaurent A, Tilmanne A, Smeesters P, Marchant A. Pediatric COVID-19: Immunopathogenesis, Transmission and Prevention. Vaccines (Basel). 2021 Sep 8;9(9):1002. doi: 10.3390/vaccines9091002.
7. Rothan HA, Byrareddy SN. The epidemiology and pathogenesis of coronavirus disease (COVID-19) outbreak. J Autoimmun. 2020 May;109:102433. doi: 10.1016/j.jaut.2020.102433.
8. Khomich OA, Kochetkov SN, Bartosch B, Ivanov AV. Redox Biology of Respiratory Viral Infections. Viruses. 2018 Jul 26;10(8):392. doi: 10.3390/v10080392.
9. Delgado-Roche L, Mesta F. Oxidative Stress as Key Player in Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV) Infection. Arch Med Res. 2020 Jul;51(5):384-387. doi: 10.1016/j.arcmed.2020.04.019.
10. Voronina TA. Antioxidants/antihypoxants: the missing puzzle piece in effective pathogenetic therapy for COVID-19. Infectious Diseases. 2020;18(2):97-102. doi: 10.20953/1729-9225-2020-2-97-102.[Article in Russian].
11. Darenskaya MA, Kolesnikova LI, Kolesnikov SI. [COVID-19: Oxidative Stress and the Relevance of Antioxidant Therapy]. Annals of the Russian Academy of Medical Sciences. 2020;75(4):318–325. doi: 10.15690/vramn1360.[Article in Russian].
12. Cárdenas-Rodríguez N, Bandala C, Vanoye-Carlo A, Ignacio-Mejía I, Gómez-Manzo S, Hernández-Cruz EY, Pedraza-Chaverri J, Carmona-Aparicio L, Hernández-Ochoa B. Use of Antioxidants for the Neuro-Therapeutic Management of COVID-19. Antioxidants (Basel). 2021 Jun 17;10(6):971. doi: 10.3390/antiox10060971.
13. Kolesnikova LI, Semyonova NV, Grebenkina LA, Darenskaya MA, Suturina LV, Gnusina SV. Integral indicator of oxidative stress in human blood. Bull Exp Biol Med. 2014 Oct;157(6):715-7. doi: 10.1007/s10517-014-2649-z. [Article in Russian].
14. Darenskaya MA, Rychkova LV, Kolesnikov SI, Kravtsova OV, Semenova NV, Brichagina AS, et al. Oxidative stress index levels in Asian adolescents with exogenous-constitutional obesity. International Journal of Biomedicine. 2022;12(1):142-146. doi: 10.21103/Article12(1)_OA16.
15. Darenskaya MA, Gavrilova OA, Rychkova LV, Kravtsova OV, Grebenkina LA, Osipova EV, et al. The assessment of oxidative stress intensity in adolescents with obesity by the integral index. International Journal of Biomedicine. 2018;8(1):37-41. doi: 10.21103/Article8(1)_OA5.
16. Kolesnikova LI, Rychkova LV, Kolesnikov SI, Darenskaya MA, Gavrilova OA, Kravtsova OV, et al. [The evaluation of the lipid peroxidation system and antioxidant defense in adolescent boys with exogenously constitutive

***Corresponding author:** Marina A. Darenskaya, PhD, ScD. Scientific Centre for Family Health and Human Reproduction Problems, Irkutsk, the Russian Federation. E-mail: marina_darenskaya@inbox.ru*

obesity with using the coefficient of oxidative stress]. Voprosy pitaniia [Problems of Nutrition]. 2018;87(1):28-34. doi: 10.24411/0042-8833-2018-10003. [Article in Russian].
17. Volchegorskiy IA, Nalimov AG, Yarovinskiy BG, Lifshitz RI. [Comparison of different approaches to the determination of lipid peroxidation products in heptane-isopropanol extracts of blood]. Voprosy Meditsinskoi Khimii. 1989;35(1):127-131. [Article in Russian].
18. Gavrilov VB, Gavrilova AR, Mazhul LM. Analysis of methods for determining the products of lipid peroxidation in blood serum by the test with thiobarbituric acid. Voprosy Meditsinskoi Khimii.1987;1:118-122. [Article in Russian]
19. Chernyauskene RCh, Varskevichene ZZ, Grybauskas PS.]Simultaneous determination of the concentrations of vitamins E and A in blood serum\. Laboratornoe Delo. 1984;6:362–365. [Article in Russian].
20. Hissin PJ, Hilf R. A fluorometric method for determination of oxidized and reduced glutathione in tissues. Anal Biochem. 1976 Jul;74(1):214-26. doi: 10.1016/0003-2697(76)90326-2.
21. Misra HP, Fridovich I. The role of superoxide anion in the autoxidation of epinephrine and a simple assay for superoxide dismutase. J Biol Chem. 1972 May 25;247(10):3170-5.
22. Brodin P. Why is COVID-19 so mild in children? Acta Paediatr. 2020 Jun;109(6):1082-1083. doi: 10.1111/apa.15271.
23. Lee PI, Hu YL, Chen PY, Huang YC, Hsueh PR. Are children less susceptible to COVID-19? J Microbiol Immunol Infect. 2020 Jun;53(3):371-372. doi: 10.1016/j.jmii.2020.02.011.
24. Zhu L, Lu X, Chen L. Possible causes for decreased susceptibility of children to coronavirus. Pediatr Res. 2020 Sep;88(3):342. doi: 10.1038/s41390-020-0892-8.
25. Keles ES. Mild SARS-CoV-2 infections in children might be based on evolutionary biology and linked with host reactive oxidative stress and antioxidant capabilities. New Microbes New Infect. 2020 Jun 24;36:100723. doi: 10.1016/j.nmni.2020.100723.
26. Suhail S, Zajac J, Fossum C, Lowater H, McCracken C, Severson N, Laatsch B, Narkiewicz-Jodko A, Johnson B, Liebau J, Bhattacharyya S, Hati S. Role of Oxidative Stress on SARS-CoV (SARS) and SARS-CoV-2 (COVID-19) Infection: A Review. Protein J. 2020 Dec;39(6):644-656. doi: 10.1007/s10930-020-09935-8.
27. Darenskaya M, Kolesnikova L, Kolesnikov S. The Association of Respiratory Viruses with Oxidative Stress and Antioxidants. Implications for the COVID-19 Pandemic. Curr Pharm Des. 2021;27(13):1618-1627. doi: 10.2174/1381612827666210222113351.
28. Alwazeer D, Liu FF, Wu XY, LeBaron TW. Combating Oxidative Stress and Inflammation in COVID-19 by Molecular Hydrogen Therapy: Mechanisms and Perspectives. Oxid Med Cell Longev. 2021 Oct 4;2021:5513868. doi: 10.1155/2021/5513868.
29. Melekhina EV, Muzyka AD, Soldatova EY, Esakova NV, Voronko OP, Evsyukov RV, et al. [New possibilities of anti-inflammatory therapy in the complex treatment of patients with COVID-19]. Infectious Diseases. 2021;19(2):27-36. [Article in Russian].
30. Ziegler CGK, Allon SJ, Nyquist SK, Mbano IM, Miao VN, Tzouanas CN, et al.; HCA Lung Biological Network. Electronic address: lung-network@humancellatlas.org; HCA Lung Biological Network. SARS-CoV-2 Receptor ACE2 Is an Interferon-Stimulated Gene in Human Airway Epithelial Cells and Is Detected in Specific Cell Subsets across Tissues. Cell. 2020 May 28;181(5):1016-1035.e19. doi: 10.1016/j.cell.2020.04.035.
31. Kolesnikova LI, Darenskaya MA, Grebenkina LA, Osipova EV, Dolgikh MI, Natyaganova LV. [The state of the antioxidant status of children of different ages]. Voprosy Pitaniia. 2013;82(4):27-33. [Article in Russian].
32. Beltrán-García J, Osca-Verdegal R, Pallardó FV, Ferreres J, Rodríguez M, Mulet S, Sanchis-Gomar F, Carbonell N, García-Giménez JL. Oxidative Stress and Inflammation in COVID-19-Associated Sepsis: The Potential Role of Anti-Oxidant Therapy in Avoiding Disease Progression. Antioxidants (Basel). 2020 Sep 29;9(10):936. doi: 10.3390/antiox9100936.
33. Kolesnikova LI, Darenskaya MA, Kolesnikov SI. Free radical oxidation: a pathophysiologist's view. Bulletin of Siberian Medicine. 2017;16(4):16-29. doi: 10.20538/1682-0363-2017-4-16–29. [Article in Russian].
34. Dao DQ, Ngo TC, Thong NM, Nam PC. Is Vitamin A an Antioxidant or a Pro-oxidant? J Phys Chem B. 2017 Oct 12;121(40):9348-9357. doi: 10.1021/acs.jpcb.7b07065. Epub 2017 Sep 28. PMID: 28937764.
35. Zhitnikova LM. [The use of a vitamin antioxidant complex in frequently ill children and children with atopy]. Infectious Diseases. 2011;4:70-74. [Article in Russian].
36. Yerbasskaya AV, Govorova LV, Ivanova VV, Zheleznikova GF. [Free radical oxidation, hormonal and immune status in children with acute respiratory infection and pneumonia]. Infectious diseases. 2012;10(3):29-37. [Article in Russian]
37. Aykac K, Ozsurekci Y, Yayla BCC, Gurlevik SL, Oygar PD, Bolu NB, et al. Oxidant and antioxidant balance in patients with COVID-19. Pediatr Pulmonol. 2021 Sep;56(9):2803-2810. doi: 10.1002/ppul.25549.