UDC 616.9:053.2-07

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Clinical and paraclinical manifestation COVID-19 in different age children

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Modern Pediatrics. Ukraine. (2022). 7(127): 15-20. doi 10.15574/SP.2022.127.15

For citation: Kharchenko YuP, Zaretska AV, Prokopova TM, Il'ina-Stohnienko VYu. (2022). Clinical and paraclinical manifestation COVID-19 in different age children. Modern Pediatrics. Ukraine. 7(127): 15-20. doi 10.15574/SP.2022.127.15.

COVID-19 is an infectious disease caused by a new coronavirus first discovered in 2019. The infection has spread rapidly throughout the world and affects people of all ages. Thus, 12.7% of all SARS-CoV-2 patients are children.

Purpose — to establish the clinical and paraclinical manifestations of the course of COVID-19 in children, depending on age to predict the severity of the disease's manifestation.

Materials and methods. The 60 children aged from 3 months to 17 years old with laboratory-confirmed SARS-CoV-2 were examined. All patients underwent general clinical, laboratory, and instrumental examinations and received therapy according to Ukrainian National protocol. SARS-CoV-2 infection was confirmed by real-time PCR.

Results. Thus, in young children COVID-19 begins acutely (90.0%) with intoxication (75.0%), fever (65.0%), nasal congestion (25.0%), rhinorrhea (20.0%), dry cough (60.0%), increased ESR and C-reactive protein (55.0%). The course of COVID-19 in children 4–6 years is accompanied by acute onset (85.71%), fever (85.71%), pharyngitis (85.71%), lymphopenia (28.56%), and no CT signs of lesions (71.43%). In children 7–12 years old, COVID-19 causes intoxication (88.89%), fever (83.33%), pharyngitis (55.56%), dry cough (77.78%), lymphocytosis (16.67%) with accelerated ESR (38.89%) and pneumonia (38.89%). The course of COVID-19 in children was older than 13 years old characterized by fever (73.33%), pharyngitis (66.67%), dry cough (73.33%), olfactory loss (20.0%), leukopenia (20.0%), ESR acceleration (20.0%), and a decrease in prothrombin (13.33%) without pulmonary lesions (73.33%).

Conclusions. These data suggest that the severity and duration of clinical and laboratory manifestations of COVID-19 depend on the child's age. The course of COVID-19 in children of all age groups is mostly of moderate severity with a favorable prognosis ((56.67%) hospitalized children did not have any complications). Only children from 7 to 12 years old need additional attention due to the severe manifestations of intoxication (88.89%) and the risk of complications with pneumonia (38.89%).

The research was carried out in accordance with the principles of the Helsinki Declaration. The study protocol was approved by the Local Ethics Committee of the participating institution. The informed consent of the patient was obtained for conducting the studies.

No conflict of interests was declared by the authors.

Keywords: children, COVID-19, SARS-CoV-2.

Клінічні та параклінічні прояви COVID-19 у дітей різного віку

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COVID-19 — інфекційне захворювання, викликане новим коронавірусом, уперше виявленим у 2019 р. Інфекція швидко поширилася по всьому світу та уражує людей будь-якого віку. Так, 12,7% усіх хворих на SARS-CoV-2 становлять діти.

Мета — встановити клінічні та параклінічні прояви перебігу COVID-19 у дітей залежно від віку для прогнозування тяжкості захворювання.

Матеріали та методи. Обстежено 60 дітей віком від 3 місяців до 17 років із лабораторно підтвердженим SARS-CoV-2. Усім пацієнтам проведено загальноклінічне, лабораторне та інструментальне обстеження і лікування відповідно до національного протоколу. Інфікування SARS-CoV-2 підтверджено з використанням полімеразної ланцюгової реакції.

Результати. Встановлено, що в дітей раннього віку COVID-19 починається гостро (90,0%) з інтоксикації (75,0%), гарячки (65,0%), закладеності носа (25,0%), ринореї (20,0%), сухого кашлю (60,0%), підвищення швидкості осідання еритроцитів (ШОЕ) та С-реактивного білка (55,0%). У дітей віком 4–6 років перебіг COVID-19 супроводжується гострим початком (85,71%), лихоманкою (85,71%), фарингітом (85,71%), лімфопенією (28,56%), відсутністю КТ-ознак ураження легень (71,43%). А в дітей віком 7–12 років COVID-19 викликає інтоксикацію (88,89%), лихоманку (83,33%), фарингіт (55,56%), сухий кашель (77,78%), лімфоцитоз (16,67%) із прискореною ШОЕ (38,89%) та пневмонію (38,89%). При цьому перебіг COVID-19 у дітей віком від 13 років характеризується гарячкою (73,33%), фарингітом (66,67%), сухим кашлем (73,33%), втратою нюху (20,0%), лейкопенією (20,0%), прискоренням ШОЕ (20,0%) та зниженням протромбіну (13,33%) без легеневих уражень (73,33%).

Висновки. За отриманими даними, тяжкість і тривалість клініко-лабораторних проявів COVID-19 залежать від віку дитини. Перебіг COVID-19 у дітей усіх вікових груп переважно середньої тяжкості зі сприятливим прогнозом (56,67±6,39% госпіталізованих дітей не мали жодних ускладнень). Лише діти віком 7–12 років потребують додаткової уваги у зв'язку з вираженими проявами інтоксикації (88,89%) і ризиком ускладнення пневмонією (38,89%).

Дослідження виконано відповідно до принципів Гельсінської декларації. Протокол дослідження ухвалено Локальним етичним комітетом зазначеної в роботі установи. На проведення досліджень отримано інформовану згоду батьків, дітей.

Автори заявляють про відсутність конфлікту інтересів.

Ключові слова: діти, COVID-19, SARS-CoV-2.

In December 2019, a new infectious disease was discovered in the Chinese city of Wuhan, Hubei Province (a novel coronavirus — COVID-19). This new disease was rapidly spread around the globe, and on March 11, 2020, the World Health Organization (WHO) declared a global pandemic [8].

According to J. She et al., COVID-19 infection mainly affects adults, with a very low incidence among children [1]. Thus, the number of children

infected with COVID-19 is not more than 12.7% of the total amount [4].

The messages about the first confirmed cases of COVID-19 infection in children were registered in January 2020 in Shenzhen [6]. Thus, by the end of January, 74 infected children were registered, and only by mid-February, their number had reached three hundred [14]. To date July 2021, since the beginning of the pandemic, approximately 4.06 million children worldwide have been registered with a positive COVID-19 test [1,4].

As far as we know, commonly previous research has investigated mainly adults. Thus, numerous studies shed light on the symptoms and characterize the course of the disease in adults with COVID-19, and fewer of them include small groups of children in their study [3,13].

Prior researchers suggest that the transmission path of COVID-19 is airborne. However, despite reports that viral RNA is found in stool samples from children with COVID-19, to date, there is no evidence of a fecal-oral route of transmission [6]. W. Wang, Y. Xu and others refute the vertical transmission of the virus from mother to child. Moreover, they are emphasizing the low viremia of COVID-19 in pregnant women (less than 1%) and suspect neonatal infection with sick parents and caregivers [12].

The data of some authors has also concluded that the course of coronavirus infections in children, including SARS, MERS, and COVID-19, is usually mild with a favorable prognosis [9,10].

The incubation period, according to the Chinese Centers for Disease Control (CDC), is mostly 3 to 7 days but can reach 12–14 days [11].

Recent data have revealed that the most common symptoms of COVID-19 infection in children are fever and cough. Also, the disease may be accompanied by weakness, myalgia, nasal congestion, runny nose, sneezing, sore throat, headache, nausea and abdominal pain [5]. At the same time, there were reported cases in children with SARS-CoV-2 without fever, only with cough or diarrhea [1]. Moreover, according to Y. Dong, Y. Lifen etc., some children have atypical manifestations of SARS-CoV-2, in the form of vomiting, diarrhea, and other gastrointestinal symptoms, asthma, and difficulty breathing [2,7].

Despite the presence of thousands of cases of COVID-19 in children worldwide, the features of the clinical course remain unclear. Thus, despite the rapid emergence of new data on COVID-19, the prevalence of the disease in children, clinical manifestations and many other questions remain unanswered.

The purpose — to study the features of clinical and laboratory courses on SARS-CoV-2 in children to predict the severity of the disease's manifestation.

Materials and methods of the study

The study was performed based on Odessa city infectious diseases hospital from April — to September 2020.

To achieve the goal, 60 patients with COVID-19 have been divided into 4 groups depending on their age with laboratory-confirmed SARS-CoV-2. The Group 1 includes 20 (33.33±6.08%) children under 3 years old, included 8 (13.33±4.39%) children under 1 year old, the Group 2 — 7 (11.67±4.14%) from 4 to 6 years old, the Group 3 — 18 (30.0±5.92%) from 7 up to 12 years old and the Group 4 — 15 (25.0±5.59%) from 13 years to 17 years 11 months and 29 days old.

There were 28 (46.67±6.44)% boys and 32 (53.33±6.44)% girls.

Inclusion criteria: age to 17 years 11 months and 29 days; the presence of the clinical symptoms of COVID-19; laboratory-confirmed SARS-CoV-2.

Exclusion criteria: age over 18 years old; absence of the clinical symptoms of COVID-19; laboratory negative SARS-CoV-2.

All 60 patients were examined (general clinical, laboratory, and instrumental examinations) and received appropriate therapy according to Ukrainian National protocol. SARS-CoV-2 infection was confirmed by real-time PCR («Abbott» USA), IgM, and IgG antibodies to SARS-CoV-2.

The research was conducted by the principles of bioethics set out in the WMA Declaration of Helsinki — «Ethical principles for medical research involving human subjects» and «Universal Declaration on Bioethics and Human Rights» (UNESCO). Informed consent of the patients (children's parents or their guardians, children) was obtained for the research.

Statistical analysis was performed by using the computer program Microsoft Excel using parametric and non-parametric methods. The arithmetic mean and standard deviation M (SD) is used for normal distribution to describe the group's features. The Student's t-test has been used to compare them. The assessment of the statistical significance of relative indicators has been performed using Pearson's chi-squared (χ^2) test. The critical value of the statistical significance

Table

Comparative characteristics of clinical manifestations of COVID-19 depending on the age of children

Clinical sign	Total number SARS-CoV-2 (n=60)		0–3 years old	4–6 years old	7–12 years old	13-17 years old
			(n=20)	(n=7)	(n=18)	(n=15)
	n	%	%	%	%	%
Acute onset	50	83.33±4.81	90.0±6.71	85.71±13.23	77.78±9.79	80.0±10.3
Intoxication	43	71.67±5.82	75.0±9.68	57.14±18.7	88.89±7.41*	53.33±12.88*
Headache	4	6.67±3.22	–	–	16.67±8.78	6.67±6.44
Smell lost	3	5.0±2.81	–	–	–	20.0±10.3
Fever:	44	73.33±5.71	65.0±10.66	85.71±13.23	83.33±8.78	73.33±11.42
— Subfebrile	23	38.33±6.28	30.0±10.25	57.14±18.7	38.89±11.49	46.67±12.88
— Febrile	17	28.33±5.82	30.0±10.25	28.56±17.07	33.33±11.11	20.0±10.3
— High	4	6.67±3.22	5.0±4.87	–	11.11±7.41	6.67±6.44
Fever longevity: — 3 days	26	43.33±6.39	40.0±10.95	42.86±18.7	50.0±11.78	46.67±12.88
— 7 days	12	20.0±5.16	15.0±7.98	42.86±18.7	27.7±9.79	6.67±6.44
— 10 days	6	10.0±3.87	–	–	16.67±8.78	20.0±10.3
Pharyngitis	32	53.33±6.44	30.0±10.25**	85.71±13.23	55.56±11.71**	66.67±12.17**
Nose congestion	8	13.33±4.39	20.0±8.94	14.28±13.23	5.56±5.4	13.33±8.78
Cough	40	66.67±6.08	60.0±10.95	42.86±18.7	77.78±9.79	73.33±11.42
Diarrhea	3	5.0±2.81	–	14.28±13.23	11.11±7.41	–
Rash	1	1.67±1.65	–	14.28±13.23	–	–
Mild severity	12	20.0±5.16	25.0±9.68	14.28±13.23	11.11±7.41	26.67±11,42
Moderate severity	48	80.0±5.16	75.0±9.68	85.71±13.23	88.89±7.41	73.33±11.42

Notes: * — the difference between groups 7–12 and 13–17 years old are significant ($p<0.05$); ** — the difference between groups 0–3 years and 7–12 years old and 0–3 years and 13–17 years old are significant ($p<0.05$).

level (p) for all kinds of analysis has been taken as $p<0.05$ (<0.5%).

Results

The working hypothesis was based on the fact that the course of COVID-19 in children of different ages has features.

The majority 34 (56.67±6.34%) of children were infected with COVID-19 in the family. At the same time, 12 (20.0±5.16%) children — in children's groups, and 14 (23.33±5.46%) outbreak failed.

In most children, COVID-19 infection occurred in the form of multiple catarrhs of the respiratory tract 34 (56.67±6.32%) and pneumonia 18 (30.0±5.92%). Concomitant diseases included bronchial asthma 1 (1.67%), atopic dermatitis 2 (3.33%), and acute cytomegalovirus infection 1 (1.67%).

We have not seen any complications of COVID-19 in the children under our care.

The general condition in most 48 (80.0±5.16%) children was regarded as moderate, in 12 (20.0±5.16%) as mild, and there were no patients with severe disease under our observation.

SARS-CoV-2 in 50 (83.33±4.81%) children commonly began acutely (Table), with fever 44 (73.33±5.71%), intoxication 43 (71.67±5.82%), catarrhal phenomena 39 (65.0±5.92%), pharyngitis 32 (53.33±6.44%), dry nonproductive cough 40 (66.67±6.08%), nasal congestion 10 (16.67±4.81%) and rhinorrhea 8 (13.33±4.39%).

Our results demonstrated that the intensity and duration of clinical manifestations of COVID-19 were different in children and depend on age. Thus, signs of intoxication in the form of lethargy, weakness, fatigue, sleep disturbances, loss of appetite, and muscle and joint pain were observed in 16 (88.89±7.41%) of children aged 7 to 12 years old, in 15 (75.0±9.68%) of children under 3 years old and only in 4 (57.14±18.7%) of children from 4 to 6 years old and 8 (53.33±12.88%) of children from 13 to 17 years old ($p<0.05$). At the same time, the headache was not a characteristic of children with COVID-19, it has complained only in 3 (16.67±8.78%) children aged 7 to 12 years old and 1 (6.67±3.22%) child from 13 to 17 years old.

Fever was accompanied by the course of the disease in 44 (73.33±5.71%) of children of all groups, of which sub febrile in 23 (38.33±6.27%), febrile — in 17 (28.33±5.82%) and high in 4 (6.67±3.22%). Also, the course of the disease without fever was observed in 16 (26.67±5.71%) of cases. The duration of the fever ranged from 1 to 10 days, an average of 3.81±2.4 days. Thus, the duration of fever of fewer than 3 days was observed in 26 (43.33±6.39%)

of children, up to 7 days — in 12 (20.0±5.16%) and longer than a week — in 6 (10.0±3.87%).

From the first days of the disease, catarrhal manifestations were observed in children. Thus, pharyngitis occurred among children of all ages, but more often among children, 4–6 years 6 (85.71±13.23%) compared with children 7–12 years old and 13–17 years old 10 (55.56±11.71%) and 10 (66.67±12.17%), respectively, and only in every third child under 3 years old 6 (30.0±10.25%).

Dry obsessive cough in children infected with COVID-19 was more common in the age groups from 7 to 12 years old and 13–17 years old (14 (77.78±9.79%) and 11 (73.33±11.42%), respectively), and only in 3 (42.86±18.7%) of patients aged from 4 to 6 years old ($p<0.05$).

Difficulty in nasal breathing occurred only in 5 (25.0±9.68%) of children under 3 years old, in 1 (14.28±13.23%) from 4 to 6 years old, in 3 (16.67±8.78%) from 7 to 12 years old, and 1 (6,67±6.44%) from 13 to 17 years old. At the same time, rhinorrhea occurred only in 4 (20.0±8.94%) of patients younger than 3 years old, in 1 (14.28±13.23%) from 4 to 6 years old, in 1 (5.56±5%) from 7 to 12 years old, and 2 (13.33±8.78%) from 13 to 17 years old. Loss of sense of smell was observed rarely, only in children 13–17 years old 3 (20.0±10.3%). Digestive disorders, for instance, in the form of diarrhea, were observed only in 3 (5.0 ± 2.81%) of children aged 7–12 years old.

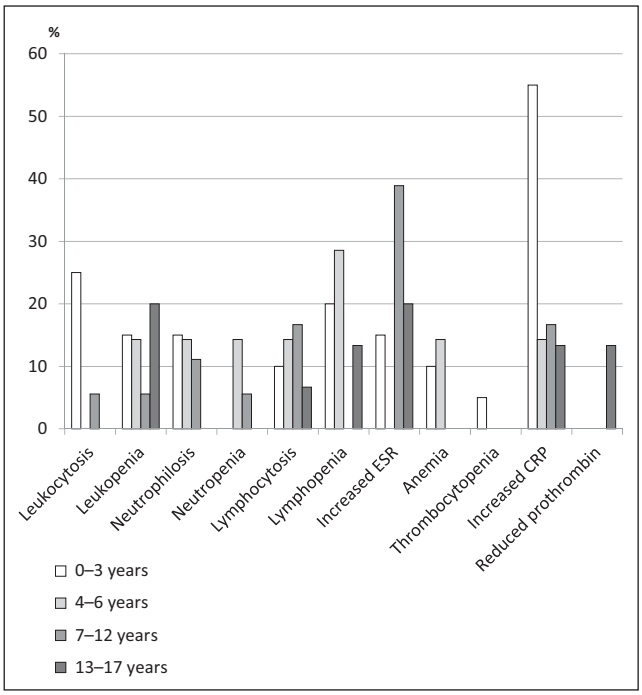

Fig. 1. Comparative characteristics of laboratory parameters in COVID-19 depending on the age of children

The rash (rarely pale pink maculopapular) occurred in only one (1.67±1.65%) child aged 5 years old.

The evaluation of the blood test data of patients with COVID-19 showed all indicators remained within normal limits in 22 (36.67±6.22%) of children (Fig. 1). However, among the changes were observed both neutrophilic leukocytoses 6 (10.0±3.87%) with increased erythrocyte sedimentation rate (ESR) 13 (21.67±5.32%) and lymphocytosis 7 (11.67±4.14%). Leukopenia and lymphopenia were detected in 8 (13.33±4.39%) children. Of these, 5 (25.0±9.68%) of children younger than 3 years old and 1 (5.56±5.4%) from 7 to 12 years old of age had leukocytosis.

The results demonstrate that leukopenia was observed in children of all ages: in children under 3 years old — in 3 (15.0±7.98%), 4–6 years old — in 1 (14.28±13.23%), 7–12 years old — 1 (5.56±5.4%) and 13–17 years old — 3 (20.0±10.3%), ($p<0.05$).

In addition, increasing neutrophils were observed only in 6 (10.0±3.87%) of all children with COVID-19, and in 3 (15.0±7.98%) under 3 years old, in 2 (11.11±7.41%) from 7 to 12 years old and one (14.28±13.23%) from 4 to 6 years old child.

As for lymphocytosis it was detected only in 2 (10.0±6.71%) of patients under 3 years old, in 1 (14.28±13.23%) — 4–6 years old, in 3 (16.67±8.78%) — 7–12 years old and in 1 (6.67±6.44%) — 13–17 years old.

To compare, lymphopenia was determined only in children younger than 3 years old 4 (20.0±8.94%), ($p<0.05$), 4–6 years old — 2 (28.56±17.07%) and 13–17 years old — 2 (13.33±8.78%). Lymphopenia was not detected in children aged 7–12 years.

The data also showed hypochromic anemia in 2 (10.0±6.71%) children under 3 years old and 1 (14.28±13.23%) from 4 to 6 years old.

Evaluation of thrombocytes was detected decreasing in only 1 (5.0±4.87%) 3-year-old child with COVID-19 and normal in others.

The results of ESR evaluation found acceleration most often in children from 7 to 12 years old in 7 (38.89±11.4%), in children younger than 3 years old 3 (15.0±7.98%) and 3 (20.0±10.3%) from 13 to 17 years old. ESR remained within normal limits in children from 4 to 6 years old ($p<0.05$).

The biochemical blood test data revealed an increasing C-reactive protein (CRP) in 17 (28.33±5.82%) of all patients with COVID-19. Moreover, CRP was more frequently increased in under 3 years old children — 11 (55.0±11.12%) compared with patients

in 4–6 years old — 1 (14.28±13.23%), 7–12 years old — 3 (16.67±8.78%), and 13–17 years old — 2 (13.33±8.78%).

At the same time, a decrease in prothrombin levels was found only in 2 (13.33±8.78%) children of 16 and 17 years old ($p<0.05$).

As for the data obtained during x-ray examination and/or computed tomography of the lungs, it was found that 34 (56.67±6.39%) of all children with COVID-19 had no pathological changes. However, in 13 (21.67±5.32%) of children, the strengthening of the pulmonary pattern and the expansion of the roots of the lungs were determined (Fig. 2). The areas of lung parenchyma compaction by the type of «frosted glass» reveals in 15 (25.0±5.59%) of children. The X-ray/CT signs of pneumonia were more common in children from 7 to 12 years old 7 (38.89±11.49%), but only 4 (20.0±8.94%) in younger 3 years old, 1 (14.28±13.23%) from 4–6 years old, and 3 (20.0±10.3%) from 13 to 17 years old children.

Signs of bronchitis were found in every third child under 3 years old 7 (35.0±10.67%), in 4 (22.22±9.79%) of children from 7 to 12 years ols, and in 2 (13.33±8.78%) from 13 to 17 years old.

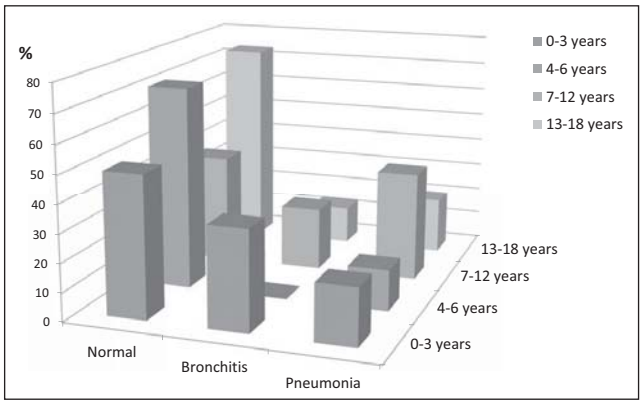

Fig. 2. Comparative characteristics of lung lesions in COVID-19 depending on the age of children according to chest x-ray/CT

Conclusions

In summary, the highest probability of infection in children with SARS-CoV-2 belongs to the family (56.67%). The children in all age groups, and both genders were equally susceptible to COVID-19, the ratio of girls to boys was 53.33% and 46.67%, respectively.

The data shows that the severity and duration of clinical and laboratory signs of COVID-19 depend on the child's age. Thus, the most varied course of the diseases with intoxication (75.0±9.68%), increased body temperature to febrile (30.0±10.25%) or subfebrile (30.0±10, 25%), nasal congestion (25.0±9.68%), runny nose (20.0±8.94%), dry cough (60.0±10.95%), leukocytosis, lymphopenia, hypochromic anemia, increased ESR and C-reactive protein (55.0±11.12%) and X-ray signs of bronchitis (35.0±10.67%) were observed in children under 3 years old.

The course of COVID-19 in children 4–6 years old is an acute onset (85.71±13.23%), fever lasting less than a week (85.71±13.23%), pharyngitis (85.71±13.23%), lymphopenia (28.56±17.07%) and no bronchial and pulmonary lesions (71.43±17.07%).

Intoxication (88.89±7.41%), headache (16.67±8.78%), fever (83.33±8.78%) to high numbers, pharyngitis (55.56±11.71%), dry cough (77.78±9.79%), ESR acceleration (38.89±11.4%) and pneumonia (38.89±11.49%) is manifested by COVID-19 in children from 7 to 12 years old.

Children older than 13 years old with COVID-19 are typically seeing the lightest long course with subfebrile fever (46.67±12.88%), pharyngitis (66.67±12.17%), dry cough (73.33±11.42%), smell loss (20.0±10.3%) without of bronchial and pulmonary lesions (73.33±11.4%).

The course of COVID-19 in children of all age groups is mostly of moderate severity with a favorable prognosis (34 (56.67±6.39%) hospitalized children did not have any complications). Only children from 7 to 12 years old need additional attention because of severe manifestations of intoxication 16 (88.89±7.41%) and the risk of complications with pneumonia 7 (38.89±11.49%).

No conflict of interests was declared by the authors.

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Стаття надійшла до редакції 05.09.2022 р., прийнята до друку 15.11.2022 р.