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Peculiarities of the course of coronavirus disease COVID-19 in children of various ages in certain regions of Ukraine

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ABSTRACT

The research aimed to conduct a generalized analysis of clinical information of diagnosis and treatment of coronavirus disease COVID-19 in children of different ages. The study involved 699 pediatric patients with coronavirus disease COVID-19 divided into four clinical groups – 67 infants under 2 months of age (group I), 320 children at the age from 60 days to 6 years (group II), 127 children of junior and middle school age (group III) and 155 patients at the age over 12 (group IV). A complex examination of patients included the study of the clinical, laboratory and instrumental markers, as well as analysis of the extent and duration of therapy. It was found, that coronavirus infection COVID-19 was characterized in children of different ages by lesions of the upper respiratory tract (70.1%), lower respiratory tract (54.7%), gastrointestinal symptoms (9.2%), neurological changes (17.8%). Affliction of the lung parenchyma with an appropriate clinical-radiological manifestation as a sign of COVID-19 was determined with occurrence from 23.9% to 25.9% of children with a reliable increase of chances to develop pneumonia (OR=7.5) at the juvenile age. The most frequent changes in additional methods were leukocytosis (18.8% of cases), thrombocytosis (14.5% of people), leukopenia (11.1% of people) and increase of C-reactive protein in 43.7% of children. Elevated content of platelets was mainly found in group I (38.3% of cases), and it increases significantly during the period of inpatient treatment, which coincides with the tendencies to increasing occurrence of C-reactive protein content in this age cohort (OR=5.0).

Keywords: children, coronavirus disease COVID-19.

1. INTRODUCTION

Epidemic of coronavirus disease COVID-19, caused by a coronavirus SARS-CoV-2, originating from Wuhan (China) in December 2019, still remains a

global pandemic producing destructive social and economic consequences. Clinical signs of coronavirus disease COVID-19 vary from asymptomatic course to severe conditions characterized by respiratory failure, multiple organ dysfunction and systemic signs (Huang et al., 2020). At the beginning of COVID-19 pandemic on the basis of the China experience a supposition was made that among children population the disease is characterized by less epidemiological risks, obscure symptoms and inconsiderable amount of complications (Bolaños-Almeida & Segura, 2021). In comparison with adult patients the number of confirmed paediatics cases in the 1st quarter of 2020 was rather small, and a part of severe cases and lethal outcomes still lower (Morand et al., 2020). Substantial meta-analysis (Cui et al., 2021), including 48 studies and involving 5829 children of various ages showed that every fifth child with COVID-19 develops asymptomatic course, mild form of the disease was found in a 33.0% of patients, and moderate form developed in a 51.0% of children. Typical clinical signs are recognized: fever in a half of patients and cough (in 41.0% of cases). In addition, vomiting occurred in 33.0% of cases, and lymphopenia (16.0% of patients) and an increased level of creatine phosphokinase-MB (CPK-MB) fraction (37.0% of cases) were taken notice of in laboratory findings.

Another study presented by Chinese colleagues this year (Ma et al., 2021), indicates that leukopenia (21.0% of cases) and lymphocytosis (22.0% of children) are the main indices of laboratory findings for pediatric patients. Moreover, certain cases of the high levels of aspartate aminotransferase (19% of cases) and alanine aminotransferase (15% of cases), lymphopenia (16.0% of patients), leukocytosis (13% of patients), an increased concentration of C-reactive protein in the blood serum (17% of cases), D-dimer (12% of patients), creatine kinase B-fraction (5,0% of children) were registered. In general, at the first pandemic stages affliction by a coronavirus SARS-CoV-2 was considered to be less specific for the children population than that for adults (Alsohime et al., 2020). In the majority of cases infected children develop mild form of COVID-19 and 15-35% of cases are asymptomatic (Chen et al., 2020; Stokes et al., 2020).

According to official statistical data in Ukraine at the beginning of March 2021 a part of children with a verified diagnosis of COVID-19 infection compared to the adult patients was 4.7%. For the whole pandemic period in Ukraine 15 lethal outcomes among children were registered which is 0.1% in the overall age structure of mortality (PHC in Ukraine, 2021). At the same time, it should be noted that current course of COVID-19 in children has changed. The recent observations are indicative of the development of critical, dangerous for life conditions for children varying within 6-10%, and severe disease is more common in infants and children with concomitant chronic pathology (Mundeep Kainth et al., 2020; Dong et al., 2020). Meanwhile, the information concerning specificities of the course of COVID-19 infection among childrens, age peculiarities and predictors of severe development in various age groups of children population appeared to be insufficient. In addition, to combine epidemiological and clinical data from different regions of Ukraine with the purpose to report about the experience in diagnostic and therapeutic approaches used in different hospitals of Ukraine might be reasonable.

Objective

To make a generalizing analysis of clinical information from hospital bases of Ukraine in order to improve the results of diagnostics and treatment of coronavirus disease COVID-19 in children of various ages.

2. MATERIALS AND METHODS

Keeping to the principles of bioethics a polycentric retrospective open cohort study of children under the age of 18 has been conducted by means of analysis of 669 clinical case records. Analysis of infection cases caused by coronavirus SARS-CoV-2 was made at the hospital departments of Kyiv (Municipal Nonprofit Institution (MNI) «Kyiv Municipal Children's Clinical Infectious Hospital», 340 children), Vinnytsia (MNI «Vinnytsia Regional Clinical Children's Infectious Hospital of the Vinnytsia Regional Council», 83 patients), Chernivtsi (Regional MNI «Chernivtsi Regional Children's Clinical Hospital», 188 patients) and Odessa (MNI «Odessa Municipal Clinical Infectious Hospital», 58 patients), that were opened with the goal of giving aid to children with coronavirus infection in the relevant regions of Ukraine.

Examination, verification of clinical diagnosis and assessment of severity of coronavirus disease COVID-19 were conducted according to the Protocol «Giving Medical Aid for treatment of coronavirus disease COVID-19» № 762 dated 02.02.2020 with changes. SARS-CoV-2 was verified by means of reverse transcription polymerase chain reaction (RT-PCR) of the smear taken from the nasal pharynx based on its positive results. Molecular-genetic PCR examination with detection of SARS-CoV-2 antigens in the hospitalized individuals with suspected COVID-19 conducted during March-November, 2020, enabled to differentiate the cohort of children involved into our study. Coronavirus was verified in the certified virological laboratories of the relevant regional laboratory centers of the Ministry of Health of Ukraine, and the rest of laboratory and instrumental examinations were made at the

hospital bases. Testing was administered by clinical and epidemiological indications. To determine SARS-CoV-2 antigens the material of isolated nasopharyngeal or naso- and oropharyngeal smears was used.

A complex of clinical, laboratory and instrumental markers of the infection caused by coronavirus COVID-19 was determined in hospitalized children. Children were monitored during the whole period of their staying in the hospital, but it was not longer than 14 days with an average period for the general cohort of patients 7.9±0.17 days. The main age of children from the cohort examined was 5.9±0.22 years, rural residents was 51.6%. 4 groups of comparison were formed in the basis of age differentiation considering the studies of other researchers (Mundeep Kainth et al., 2020). The first (I) group included infants under 2 months of age (67 babies, 10% from the total cohort, 74.6% of the known epidemiological contact), the second (II) group included 320 children (47.8% from the total cohort, 72.5% of the known epidemiological contact) at the age from 60 days to 6 years, a subgroup including 127 children of junior and middle school age (19% from the total cohort, 66.9% of the known epidemiological contact) formed the third (III) group, and the fourth (IV) group included 155 teenagers (23.2% from the total cohort, 73.9% of the known epidemiological contact) at the age over 12. The main demographic characteristics of the clinical groups are presented in Figure 1 and indicate of similar gender and address ratio with a little prevailing of boys – rural residents in the total cohort. Inconsiderable prevalence of girls – urban residents was found among teenagers only.

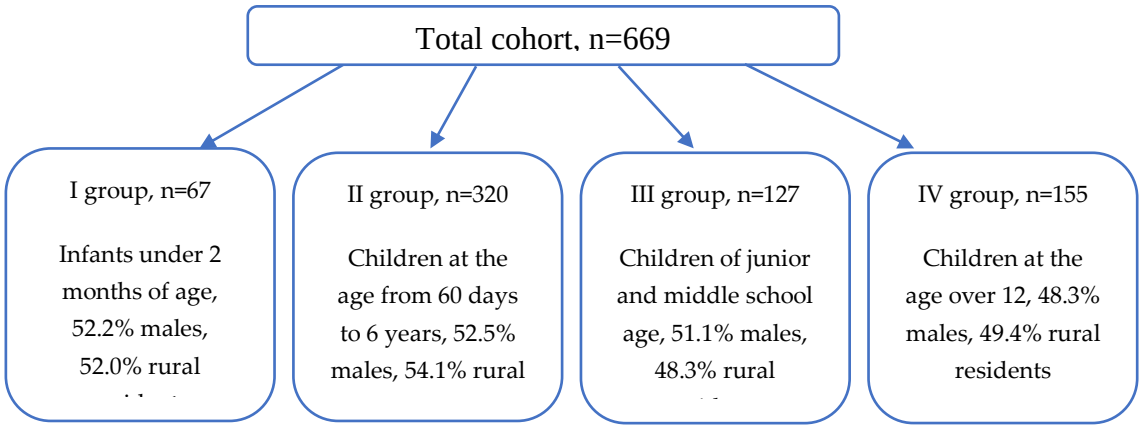


Figure 1 Demographic characteristics of children from the clinical groups

Distribution of patients by their age allowed coming to the conclusion that in Kyiv and Chernivtsi regions a part of hospitalized infants under 2 months of age was the highest – it constituted 12.4% and 12.8% respectively. In Vinnytsia region a part of sick children under two months of age was only 1.2%, and in Odessa region such infants were not included into the analysis. Every fifth patient involved into the study in Kyiv and Chernivtsi regions (20.0% and 22.8% respectively) related to the fourth age group. In Odessa region the part of teenagers was 34.5% and in Vinnytsia – 30.1%. Gender distribution of patients involved into the analysis in different regional centers was practically similar, since a part of boys was 53.8% in Kyiv region, 50.0% in Chernivtsi region, 49.4% in Vinnytsia region and 41.4% in Odessa region ($p>0.05$).

The results were analyzed by means of descriptive statistics methods. The arithmetic mean (M) and the value of standard error (m) were determined for absolute values. Student's coefficient (t) was calculated while evaluating probable error of the parameters. Probable error was the difference with $p<0.05$. In population analysis the attributive risk (AR), relative risk (RR), odds ratio (OR) were evaluated with calculation of confidence intervals (CI) for the relative risk and odds ratio (95 % CI). Wilcoxon test for dependent samples (V), the value of normal Z-approximation (Z), probability of differences by Wilcoxon criterion (p-value) were applied for the parameters in the dynamics of treatment.

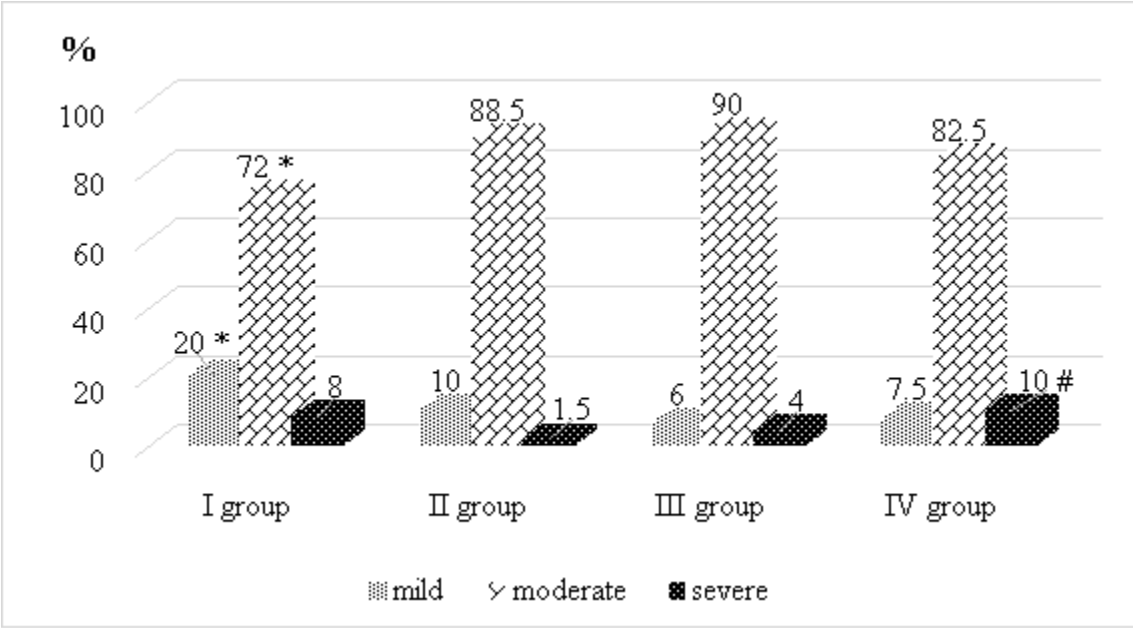
3. RESULTS

Past history peculiarities of the patients hospitalized were certain diseases available such as chronic tonsillitis (5.2%), bronchitis (2.4%) and community-acquired pneumonia (6.1%) among all the children examined. A positive epidemiological contact was found in more than two thirds of cases from the total cohort of sick children, and epidemiologically significant familial contacts predominated. Thus, a familial contact with an individual infected by coronavirus was confirmed in 70.7% of cases in Odessa region, 66.3% in Vinnytsia region, 64.1% in Kyiv region and 63.3% in Chernivtsi region (in all the cases $p>0.05$). Though the more active social activity of schoolchildren and teenagers was (III-IV groups), the lower epidemiological role of familial contact became (from 74.6% among children from I group to 47.7% among teenagers). The value of contacts increased in organized groups: 3.9% - in

III group and 16.2% cases among representatives of IV group. The part of unidentified sources of infection among hospitalized children was on an average 34.6% in Chernivtsi region, 30.6% in Kyiv region, 28.9% in Vinnytsia region, and 13.8% in Odessa region, which was the lowest compared to other regions ($p<0.05$).

Classification of coronavirus disease COVID-19 according to its severity was mainly characterized by subjective approach and reflects multifocal lesions. Figure 2 illustrates distribution of children from various age groups by severity of COVID-19. A prevailing majority of children from the total cohort (85.7%) were hospitalized in a moderate condition of the disease course. The largest part of children with mild disorders of general state of health due to coronavirus disease was registered among infants from I group. It was explained by extended indications for admission of patients under the age of 2 months, which takes place not only due to clinical-epidemiological characteristics but also age characteristics.

Thus, the patients from I age group had three times as many chances of a mild form of coronavirus disease COVID-19 than sick teenagers: OR=3.1 (95% CI: 1.26-7.52), RR=1.6 (95% CI: 0.71-3.46), AR=0.26. However, teenagers infected by COVID-19 had a significantly higher risk of a severe disease in comparison with the representatives from II clinical group: OR=7.3 (95% CI: 1.28-41.56), RR=1.8 (95% CI: 0.33-9.91), AR=0.39 and junior school children OR=2.7 (95% CI: 0.81-8.81), RR=1.5 (95% CI: 0.49-4.55), AR=0.23.



Note: $p<0.05$ * on the assumption of I: II, III; # on the assumption of II, III: IV

Figure 2 Distribution of children from the age groups according to severity of coronavirus disease COVID-19

Unfavorable clinical background in the form of chronic comorbidities was observed in 37 children (5.5%), including anemia, congenital art defects and abnormalities, excessive body weight, bronchial asthma and neurological organic pathology. In the disease debut at the out-patient stage of giving medical aid the main complaints of parents and/or children of the general cohort were often the following: fever (78% of cases), fatigue (75.2% of cases), pain/tickle (discomfort) in the throat (70.1% of patients), cough (54.7%), poor appetite (52.8% of patients). Peculiarities of COVID-19 clinical signs in children from different age groups summarized in the four regions of Ukraine, and recorded on admission of children to the hospital (on an average 4.3±0.14 day of the disease) are presented in Table 1.

Table 1 Peculiarities of COVID-19 clinical symptoms in children from various age groups

№	Characteristics	Total cohort, n=669	I group, n=67	II group, n=320	III group, n=127	IV group, n=155	P
	Fever, %	51.1	52.2	52.5	51.1	48.3	in all the cases >0.05
2.	Fatigue, %	51.6	52	54.1	48.3	49.4	in all the cases >0.05
3.	Myalgia/arthralgia, %	4.8	-	-	10.3	12.8	<0.05 III,IV:tc

4.	Rashes, %	1.3	1.5	0.9	1.6	1.3	in all the cases >0.05
5.	URT symptoms: -rhinorrhea, % -blocked nose, % -pharyngitis, %	 31.7 27.8 70.1	 35.8 35.8 68.6	 35.3 28.7 66.5	 32.2 22 73.2	 21.9 27.9 75.4	 <0.05 IV:tc, I,II,III:IV <0.05 I:III <0.05 II:III
6.	LRT symptoms: -cough, % -dyspnea, % -crackles, % -chest pain, % -hypoxemia, SaO_2 <95%	 54.7 8.1 8.9 3.1 3.1	 47.8 4.5 3.0 - -	 47.8 7.4 7.8 0.6 2.7	 59.0 4.2 16.5 5.5 1.6	 68.3 15.5 7.7 7.7 6.5	 <0.05 II, IV:tc; I,II:IV; III:IV <0.05 III, IV:tc; I,II,III:IV <0.05 I,III:tc I,II:III; III:IV <0.05 I,II,IV:tc; II:III,IV <0.05 III:IV
7.	Gastrointestinal symptoms: -poor appetite -nausea -vomiting -diarrhea -abdominal pain	 52.8 1.3 1.8 4.3 1.8	 62.7 - 1.5 - -	 57.8 0.9 1.6 5.3 0.9	 40.9 0.8 2.4 2.4 3.1	 47.4 3.2 1.9 5.8 3.9	 <0.05 III:tc; I,II:III:IV in all the cases >0.05 in all the cases >0.05 in all the cases >0.05 in all the cases >0.05
8.	Neurological symptoms: -headache -impairment of consciousness -hyposmia -taste impairment	 6.7 0.7 5.5 4.9	 - 1.5 - -	 0.9 0.6 0.3 0.3	 13.4 1.6 3.1 2.4	 15.5 1.3 20.6 18.7	 <0.05 II,III,IV:tc; I:II,IV; II:III,IV in all the cases >0.05 <0.05 II,IV:tc; II:III,IV <0.05 II,IV:tc; II:III,IV

Notes: URT – upper respiratory tract; LRT – lower respiratory tract, tc – total cohort.

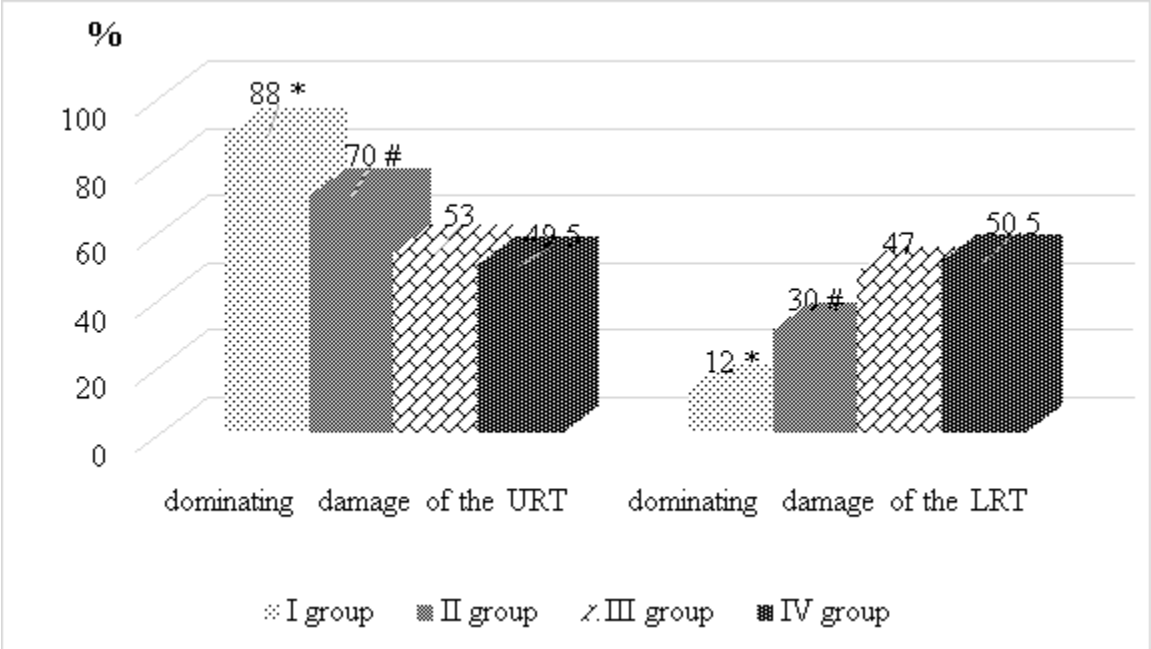
Analysis of clinical course in children enabled to differentiate certain age peculiarities dealing with the frequency of certain symptoms in children from the age clinical groups. Thus, every third patient from I, II and III groups presented rhinorrhea, while the rate of this symptom in teenagers was 21.9%, but cough and dyspnea occurred reliably more often in teenagers. It was patients in the fourth group who were more likely to complain of chest pain, cephalgia, as well as neurological symptoms such as hyposmia and taste disturbances.

Clinical signs of the upper respiratory tract damage with age were found to become less prominent, but a part of children with subjective and objective signs of acute pharyngitis increased. The number of children with clinical signs of the lower respiratory tract damage including cough, dyspnea, crackles, and chest pain was found to increase with age. A half of the children from the total cohort presented gastrointestinal signs mostly in the form of low/lost appetite, but dyspeptic disorders occurred only in 5-6% of children from various age groups. Neurological symptoms in the form of cephalgia were quite rare, reduction / loss / distortion of smell and taste are found in the group of teenagers, tonoclonic spams occurred only in one child of a junior age.

The major part of children with severe degree of general condition impairment due to coronavirus disease COVID-19 was registered in the group of teenagers (IV group), which can be explained by dominating damage of the lower respiratory tract and development of pneumonia in 37.4% of patients from this age group in comparison with the patients from the first group, where pneumonia rate did not exceed 9.0% of cases ($p<0.05$), the second group – 17.8% cases ($p<0.05$), though it was practically similar to

that of the schoolchildren (37.8%, p>0.05) (Fig. 3). The frequency of verification of alveolar tissue inflammation as a manifestation of coronavirus disease COVID-19 was 25.9% in children from Kyiv and Odessa regions, in Vinnytsia region pneumonia rate was 25.3% among the hospitalized cases, and in Chernivtsi region – 23.9% (p>0.05 in all the cases).

The study is indicative of the fact that patients of a juvenile age in comparison with infants presented statistically significant higher risk of the lower respiratory tract damage resulting from coronavirus disease COVID-19: OR =7.5 (95% CI: 3.64-15.36), RR=3.3 (95% CI: 2.70-4.12), AR=0.45. The younger the patients were the lower was the risk, and for the patients of junior and middle school age it was: OR=6.5 (95% CI: 3.17-13.36), RR=3.1 (95% CI: 2.52-3.74), AR=0.42, and for children from the second group – OR=3.1 (95% CI: 1.50-6.58), RR=2.0 (95% CI: 1.68-2.26), AR=0.27.



Note: p<0.05 * on the assumption of I: II, III, IV; # on the assumption of II: III, IV; URT – upper respiratory tract; LRT – lower respiratory tract.

Figure 3 Distribution of children from the age groups by a dominating type of damage with COVID-19

Relatively more severe course of coronavirus disease COVID-19 in children of school and juvenile ages with a prevailing tendency to involvement of the lower respiratory tract and inflammatory process was reflected in an average hospital stay of children of various ages in hospital bases of Ukraine. Thus, an average period of hospital stay for the children from the I group was 6.1±0.61 days, for the II group – 7.2±0.22 days, for the patients of junior and middle school ages – 8.5±0.31 days, and for teenagers – 9.8±0.42 days ($p_{I,II:III,IV}<0.05$). On admission, PCR-test positive results for coronavirus COVID-19 were obtained in 89.2% of children from the total cohort on an average on the 4.3±0.14 day of the disease. Thus, a positive test was confirmed in I group in 85.1% of infants on the 2.8±0.43 day since the onset of the disease, in II group – in 87.8% of children on an average one day later (3.8±0.17 day since the I clinical signs), in III group – in 88.7% of patients on the 5.3±0.41 day, in the group of teenagers a positive test was found on an average in 90.3% of patients on the 5.1±0.31 day of coronavirus disease.

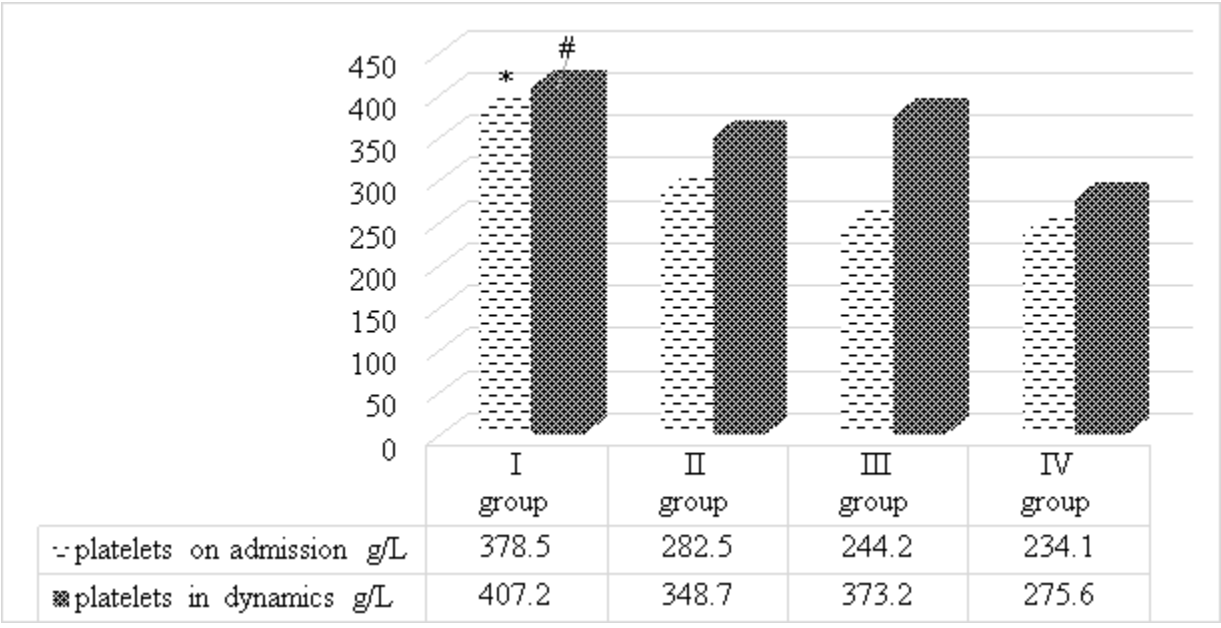
The frequency of PCR positive results on SARS-CoV-2 on admission of children to the hospital was the highest at children's infectious in-patient departments of Kyiv and Chernivtsi, while in Vinnytsia region positive results were registered in 90.9% of children, and in Odessa – 76.1%. A part of pseudonegative results of the molecular-genetic examination by means of PCR appeared to be the biggest among infants, which can be objectively explained by certain difficulties to take nasopharyngeal smears. At the same time, early testing of children of the first two clinical groups is stipulated by early visits of infants' parents to the doctors. Further PCR retesting confirmed the diagnosis of coronavirus disease COVID-19. The amount of laboratory examinations at the in-patient departments included a wide range of examinations and tests. At the same time, analysis of the values of the body inflammatory response and the blood clotting system state were considered to be pathologically substantiated (Table 2).

Table 2 Results of laboratory methods of examination of children from clinical groups

№	Laboratory and instrumental characteristics	Total cohort, n=669	I group, n=67	II group, n=320	III group, n=127	IV group, n=155	P
1.	Blood count leukocytes, g/L, M±m	8.2±0.16	9.8±0.53	9.8±1.27	7.7±0.34	7.0±0.27	<0.05 I,II:III,IV
2.	Leukocytosis, %	18.8	9.2	25.4	23.6	17.1	<0.05 I,II:tc; I:II,III; II:IV
3.	Leukopenia, %	11.1	16.9	7.0	10.9	9.7	<0.05 II:tc; I:II
4.	Platelets, g/L, M±m	275.6±4.54	378.5±17.5	282.5±6.31	244.2±6.61	234.1±8.12	<0.05 I:II,III,IV
5.	Thrombocytosis, %	14.5	38.3	10.7	5.2	3.5	<0.05 I,III,IV:tc; I:II,III,IV; II:III,IV
6.	Thrombocytopenia, %	5.9	1.5	4.7	1.1	16.5	<0.05 I,II,IV:tc; I,II:III,IV
7.	PTI, %, M±m	89.3±0.35	89.9±0.71	89.2±0.52	89.8±0.79	89.2±0.72	in all the cases >0.05
8.	CRP, more than 6,0 mg/L, %	43.7	73.9	45.5	46	36.3	<0.05 I:tc; I:II,III,IV; II:IV

Note: PTI – prothrombin index; CRP – C-reactive protein; changes in the absolute content were compared with reference values of age norms, tc – total cohort.

In addition to physiological age-related decrease of the absolute amount of leukocytes, leukopenia with underlying COVID-19 was more often registered in children of the first two months of life (I group), while leukocytosis was found in every fourth-fifth child older than 2 months. The older the patients in the total cohort were, the smaller was a part of patients with peripheral blood thrombocytosis and the rate of thrombocytopenia registration increased. However, special attention was drawn to the number of cases of coronavirus disease with an increased content of platelets in the peripheral blood practically by 40.0% in children of the first two months of life and every tenth child of the early and preschool ages found on admission to hospital. On average, the analysis of the hemogram was performed on 4.1 days of the disease (from 2.3 to 4.9 days of the disease) with a repetition of the hemogram on average for 10.3 days (from 7.3 to 11.4 days). In the dynamics of treatment in the total cohort of children irrespective of their age the absolute platelet content in the peripheral blood increased (V=25.6; Z=2.88, p=0.004). In our opinion, it should be considered while making up a plan of a comprehensive treatment of patients (Fig. 4).



Note: p<0.05 * on the assumption of I: II, III, IV; # on the assumption of I,II:IV

Figure 4 Mean values of the platelet absolute content in the blood in the dynamics of treatment of children from the groups of comparison

Examination of such marker of the acute phase of the inflammatory process as the serum concentration of C-reactive protein enabled to adduce a conclusion that in children of the first two months of life the cases of an excessive amount of this pro-inflammatory marker higher than 6.0mg/L occurred reliably more frequently. Thus, the clinical and epidemiological risk of serum C-reactive protein content more than 6.0 mg/L in children of the first clinical group compared to the teenagers was the following: OR=5.0 (95% CI: 2.71-9.09), RR=2.3 (95% CI: 1.74-3.07), AR=0.38. And all those cases were associated with pneumonia in infants. At the same time, among the patients of a juvenile age this marker was characterized by insufficient diagnostic value in verification of pneumonia (sensitivity 48.1%, specificity 71.8%). Though, with the mentioned level of the marker in the blood the risk of acute pneumonia with underlying coronavirus infection in teenagers reliably increased statistically: OR=2.4 (95% CI: 1.31-4.24), RR=1.5 (95% CI: 1.03-2.18), AR=0.21.

X-ray examination in the in-patient departments was conducted in less than a half of cases. X-ray results showed that bronchial-pulmonary lesions associated with COVID-19 differed in children of various age groups which is indicative of different level and character of such lesions. The rate of registration of interstitial changes was found to decrease with the age of children, and on the contrary, ground-glass opacity has a tendency to increase. The right-side localization of the lung parenchyma lesions made up the greater part in children o of the first two months of life, and the rate of bilateral lesions increased with age (Table 3).

Table 3 Results of instrumental visualization of chest organs in children from clinical groups

Laboratory and instrumental characteristics	Total cohort, n=669	I group, n=67	II group, n=320	III group, n=127	IV group, n=155	P
X-ray examination of the chest organs						
Made, %	44.1	38.8	40.3	52	47.8	<0.05 II:III
Aberration, %	59.4	85.7	55.4	40.0	67.4	<0.05 I,III:tc; I:II,III,IV; II:III,IV; III:IV
Interstitial changes, %	85.1	100.0	90.3	84.4	73.8	<0.05 I,II:tc; I:II,III; II:IV
Changes of the lung roots, %	80.0	87.5	82.0	87.1	69.4	<0.05 I,II,IV:tc; I:II,III,IV; II,III:IV
Ground-glass opacity, %	6.9	0	5.3	7.7	8.0	in all the cases >0.05
Foci of infiltration, %	41.4	0	35.0	46.2	41.7	<0.05 II:III
Right-side lung lesion, %	43.8	83.3	41.4	41.5	41.7	<0.05 I:tc; I:II,III,IV
Left-side lung lesion, %	19.6	0	24.1	22.0	16.6	<0.05 II:IV
Bilateral lung lesion, %	36.6	16.7	34.5	36.5	41.7	<0.05 I:tc; I:II,III,IV
Computed tomography of the lungs						
Aberration, %	47.6	-	45.0	53.8	50.0	in all the cases >0.05
Ground-glass opacity, %	73.7	-	75.0	75.0	72.7	in all the cases >0.05
Foci of infiltration, %	27.8	-	25.0	50.0	20.0	<0.05 III,IV:tc; II,III: IV
Peribronchial changes, %	25.0	-	-	0	33.3	<0.05 IV:tc
Signs of fibrosis, %	11.1	-	0	0	18.2	<0.05 IV:tc
Right-side lung lesion, %	54.3	-	75.0	50.0	47.8	<0.05 II:tc; II:III,IV
Left-side lung lesion, %	48.6	-	50.0	66.7	47.6	<0.05 III:tc; II:III,IV

Note: tc – total cohort.

Table 4 presents special features of therapeutic tactics used for children of various ages suffering from COVID-19, who were treated at in-patients departments of different regional hospital bases. Thus, only 17 children (2.54% of the total cohort) required respiratory support, and only one patient (0.15%) required artificial pulmonary ventilation. According to clinical specificities and degree of lesions of the respiratory tract the period of oxygen support of patients was found to naturally increase with age and a tendency to a higher rate of cases when oxygen support of patients was required increased respectively.

Table 4 Certain aspects of therapeutic tactics in children of clinical groups

№	Characteristics	Total cohort, n=669	I group, n=67	II group, n=320	III group, n=127	IV group, n=155	P
1.	Rate of respiratory support (oxygen therapy), %	2.5	3	2.2	1.5	3.9	in all the cases >0.05
2.	Duration of oxygen therapy, days, M±m	3.6±1.04	1.5±0.50	1.1±0.14	4.5±1.5	6.8±2.39	<0.05 I,II:III,IV
3.	Infusion therapy, %	6.4	10.4	4.7	3.9	10.3	<0.05 II,III:IV
4.	Duration of infusion therapy, days, M±m	2.6±0.55	4.3±2.47	1.7±0.25	1.6±0.6	2.9±0.98	in all the cases >0.05
5.	Systemic glucocorticosteroids (GCS), %	6.7	4.5	7.5	5.5	7.1	in all the cases >0.05
6.	Duration of systemic GCS therapy, days, M±m	3.2±0.40	2.0±0.23	2.4±0.31	3.6±0.71	5.0±1.31	<0.05 I,II:IV
7.	Antiviral drugs, %	12.1	22.4	17.2	5.5	2.6	<0.05 I,II,III,IV:tc; I,II:III,IV
8.	Antibacterial therapy, % -monotherapy, % -combined , %	69.9 52.3 17.6	34.3 31.3 3.0	73.1 59.3 13.8	69.3 46.5 22.8	79.4 51.6 27.8	<0.05 I,IV:tc; I:II,III,IV; III:IV <0.05 I,II:tc; I:II,III,IV; II:III <0.05 I,IV:tc; I:II,III,IV; II:III, IV
9.	Antibacterial therapy, % -aminopenicillins -macrolides -cephalosporins II -cephalosporins III -aminoglycosides - fluoroquinolones -glycopeptides	0.3 29.6 2.1 49.3 2.7 2.1 0.7	1.5 13.4 - 20.9 1.5 - 1.5	- 29.7 2.2 49.3 2.2 - 0.3	- 33.9 2.3 52 2.3 1.5 1.5	0.7 32.9 2.6 59.3 4.5 7.7 0.6	in all the cases >0.05 <0.05 I:tc; I:II,III,IV in all the cases >0.05 <0.05 I,IV:tc; I:II,III,IV; II: IV in all the cases >0.05 <0.05 III,IV:tc; in all the cases >0.05

Note: tc – total cohort.

Restoration and support an adequate water balance by means of infusion therapy with glucose-salt solutions was performed in 43 patients, which was only 6.4% of the total cohort of afflicted children. Pre-venous immunoglobulin was used for 3 children (0.45% of the total cohort), direct action anticoagulants were injected to 8 patients (1.2% of the total cohort) of a school and juvenile age. Infusion support of water balance was most often used for children from I and IV clinical groups. In the first case it could be explained by the intensity of water-salt metabolism, and in the second one – marked intoxication available. At the same time, duration of infusion therapy was not considerably longer in the group of infants, and it was not longer than 4 days for sick schoolchildren. Systemic glucocorticosteroids were more often indicated for the patients from II and IV groups, and duration of their administration was reliably longer for the latter. The drugs with antiviral activity most often administered were the following: interferon alpha 2b (7.9%), inosine pranobex (4.5%), natural flavonoids (3.1%), acyclovir (0.3%) and oseltamivir (0.3%). It should be

noted that antiviral drugs were indicated for every fifth child from I group and 8.6 times less for the patients of a juvenile age. Meanwhile, administration of antibacterial therapy had a reverse tendency. Thus, except infants, most patients in groups II, III and IV received antibiotics, and the frequency of their appointment, especially in the form of combination of drugs, increased with the patients' age. At the same time, in group I antibacterial therapy was used in a third of cases and mainly in the form of monotherapy.

Discrete analysis of the groups of antibacterial drugs used found that under conditions of in-patient department's patients suffering from COVID-19 most often received third generation cephalosporins (49.3%) and macrolides (29.6%). All the patients were discharged from the hospitals in a relatively satisfactory condition, and lethal outcomes were not registered in the examined cohort.

4. DISCUSSION

Our study involved 669 patients at the age from birth to 18 years who were hospitalized in specialized in-patient departments in the four regional centers of Ukraine where medical aid is given to children with infectious disease caused by SARS-CoV-2. All the children received inpatient treatment in the same period from March to November 2020. They were residents of the 4 regions of Ukraine located in the center, south and west of the country (Kyiv, Odessa, Vinnytsia, Chernivtsi). Therefore, the results obtained could reflect demographic, epidemiological and clinical specificities of COVID-19 course among the children population of Ukraine and they are comparable between themselves. The mean age of the examined cohort was 5.9±0.22 years, which is a little lower than that of the patients in the Wuhan Children's Hospital (China) (Dong et al., 2020). The mean age of Chinese hospitalized patients was 6.7 years (min 1 day – max 15 years). This difference is connected with the fact that our study involved patients from birth to 18 years. Nevertheless, acute respiratory viral disease caused by SARS-CoV-2 are well known not to be limited by age, and thus children of any age can be infected including infants and children of an early age (Wei et al., 2020).

An average hospital stay was 7.9±0.22 days, and 85.7% of our patients had a moderate course of the disease. Our findings match numerous publications which indicate that the majority of children with COVID-19 have mild and moderate course of disease. Occurrence of severe and critical forms of the disease among the hospitalized children ranges from 3.0% to 10.6% of cases and depends on their age (Dong et al., 2020; Cui et al., 2020; Tagarro et al., 2020). In our study the biggest part of children with severe infection COVID-19 is registered in the group of teenagers which is caused by the development of pneumonia in 37.4% of cases. At the same time, Wardell et al., (2020) reports the risk of a severe development of the pathology during the neonatal period. Other authors agree with this opinion and in pediatric COVID-19, and they differentiate infants as a high risk group concerning unfavorable consequences (Parri et al., 2020). Examination of the main demographic characteristics found inconsiderable prevalence of boys, rural residents (51.1% and 51.6%), in all the regions of Ukraine presented in this polycentric study which coordinates with the previous studies conducted by other composite authors (Lu et al., 2020).

Results of the meta-analysis (Wang et al., 2020) dealing with the clinical characteristics of COVID-19 course in the pediatric population indicate that about 83% (95% CI: 78-88%) of patients seem to be infected with coronavirus SARS-CoV-2 from their family members. Other studies report the occurrence of infected children within their families ranging from 45 to 91% cases (Lu et al., 2020). In our study the identified epidemiological contact was found in the total cohort in 71.9% of cases with prevailed epidemiologically significant familial contacts, and their role decreased as far as social activity of children increased. Our patients suffering from COVID-19 were distributed into four groups on he basis of age differentiation similar to that in the researches of other (Mundeep Kainth et al., 2020), since we considered that such an approach to distribution of children with coronavirus infection could be useful to study specificities of the course of the disease in various age groups, and it could be helpful in the development of differential approaches in the management of patients.

Children at the age from 2 months to 6 years prevailed among those involved into the analysis (47.8%), the group of juvenile age patients was the second by the number of cases (older than 12 years) – 23.3%. Though, the group of patients under 60 days of life was the smallest in our cohort (10%), it deserves special consideration. In spite of the fact that the biggest part of children with a mild course of the disease is found among infants, it should be remembered that it is this age group that is hospitalized not only for their clinical-epidemiological indications but age ones as well considering the risk of a possible development of a serious bacterial infection (Mundeep Kainth et al., 2020; Parri et al., 2020). At the same time, patients of the first 60 days of life involved in our analysis had three times higher chances of a mild infection COVID-19 compared to the teenagers (OR=3.1; 95% CI: 1.26-7.52).

According to the results of our study the most frequent clinical symptoms found in the total cohort of patients were fever (51.1%), general fatigue (51.6%), sore throat (70.1%), cough (54.7%) and poor appetite (52.8%). In general our findings correlate with other studies (Dong et al., 2020) reporting that the symptoms were similar to those of acute respiratory infection including fever, cough, sore throat, sneezing, muscle pain and fatigue, and only a part of children had crackles. Our patients presented muscle pain

in 4.8% of cases in the total cohort with the prevalence of teenagers (12.8%), which does not seem to be verified in infants since their parents think it is general weakness or fatigue. Cough, nasopharyngeal erythema and fever of 37,5°C were registered among our patients more often than in another study (Dong et al., 2020). Other authors (Lu et al., 2020) reported that in their studies 32.1% of children suffered from fever higher 38° C and the majority of them developed febrile fever within the range of 38.1-39.0°C. Still other investigations showed that, as a rule, temperature rise of children with underlying infection COVID-19 does not elevate 39°C (Cai et al., 2020; CDC COVID-19 Response Team, 2020). Other authors (Yang et al., 2020) indicate that 76.1% of children with ARVI-SARS-CoV-2 suffer from fever.

The patients suffering from infection caused by SARS-CoV-2 virus who develop gastrointestinal symptoms at the very onset of the disease deserve special attention. In spite of the fact that gastrointestinal symptoms such as nausea, vomiting and diarrhea are infrequent with coronavirus infection, certain studies involving children evidence occurrence of SARS-CoV-2 virus in feces of such patients (Young et al., 2020; Ong et al., 2020). Moreover, a positive test result of rectal smear is found to remain even when nasopharyngeal test results are negative, which confirms the possibility of fecal-oral transmission of the virus (Xu et al., 2020) that is crucial for little children. Furthermore, at the early stage of the disease COVID-19 may develop in the form of gastrointestinal disorders without involvement of the respiratory tract (Chen et al., 2020). The most frequent gastrointestinal disorders registered in the total cohort of hospitalized patients in our study were poor appetite – in 52.8% of patients, diarrhea - in 4.3% of cases, vomiting – in 1.8% of cases, though occurrence of the clinical symptoms in other studies (Young et al., 2020) was higher. On the contrary, in the group of teenagers diarrhea and abdominal pain were registered more often (5.8% and 3.9% of cases respectively) in comparison with the children from other age groups.

As to the severity of the disease, the study carried out by Huang et al., (2020) admitted that in 90% out of 2143 children with the diagnosed coronavirus infection the disease was asymptomatic, mild or moderate, 5.2% of patients developed severe form, and in 0.6 % the disease was critical. In general, these results coincide with our findings, but we registered a bigger part of patients with severe disease among teenagers which can be explained by dominating signs of lower respiratory tract lesions in such patients followed by the development of pneumonia in 37.4% of cases. The patients of a juvenile age had considerably higher chances of COVID-19 severe course, and these chances seven times increased in comparison with patients of early and preschool ages (OR=7.3; 95% CI: 1.28-41.56). In comparison with infants schoolchildren had considerably higher risk of lower respiratory tract lesions resulting from COVID-19 (OR=6.5; 95% CI: 3.17-13.36), and this tendency increased with age, for example, in adolescence (OR=7.5; 95% CI: 3.64-15.36). Nevertheless, only 17 children from the total cohort required respiratory support, and 1 child was on artificial lung ventilation.

Analysis of the current scientific observations demonstrated that laboratory examinations carried out in the adult population of patients suffering from COVID-19 allowed identification of an increase level of liver diseases, anemia, high markers of inflammatory process, such as erythrocyte sedimentation rate (ESR), C-reactive protein, procalcitonin, and sometimes hyperglycemia (Chen et al., 2020). Results of investigations of children population according to certain data obtained (Henry et al., 2020) are indicative of the fact that 69.2% of afflicted children retained a normal content of leukocytes in the peripheral blood, though, there were some cases of lymphopenia (3% of cases), neutrophilia (4.6% of observations) and neutropenia (6.0% of the patients) found. According to certain reported information (Zhao et al., 2020), an increase content of CRP and procalcitonin in the blood serum was registered in 13.6% and 10.6% of cases respectively.

Our study determined that children of the first two months of life differed from other patients by reliably lower content of leukocytes in the peripheral blood. At the same time, leukocytosis was registered in 17.1 – 25.4% of cases in the groups of children suffering from infection COVID-19 older than 2 month of age. A part of patients with thrombocytosis was found to decrease, and those with thrombocytopenia in the peripheral blood were found to increase. Though our attention was drawn to the fact, that on admission to the hospital by results of blood counts practically 40% of children in their first two months of life and with relatively mild course of COVID-19, had an elevated level of platelets. Moreover, the conducted dynamic analysis of an absolute amount of platelets was indicative of statistically significant increase of this parameter (p=0.004) in the total cohort of patients irrespective of the age factor. It should be noted that other authors in their publications on the examples of COVID-19 clinical cases among neonates (Wardell et al., 2020) also emphasized thrombotic complications and hypercoagulation signs caused by SARS-CoV-2.

A diagnostic value of CRP as a marker of inflammatory response in children appeared to be insufficient due to false positive results obtained in infants and false negative results of older ones. Though, in comparison with teenagers infants from I group presented a considerable risk (OR=5.0; 95% CI:2.71-9.09) of increasing CRP concentration in the blood serum higher than 6.0 mg/L, and it was associated with pneumonic process available. At the same time, similar level of CRP in the blood serum of afflicted teenagers was indicative of the risk of pneumonia: OR=2.4 (95% CI: 1.31-4.24). Instrumental examinations on visualization of lung lesions caused by SARS-CoV-2 performed in less than in a half of patients enabled to suggest that computed tomography method

allows better identification of left side lesions compared to chest X-ray in children (specificity – 80.4%, positive predictive value – 71.3%).

In general, analysis of epidemiological, clinical and laboratory features of infection COVID-19 among children from various age groups from different hospital bases of Ukraine coordinated with a conception developed on the cohorts of adult patients with coronavirus disease caused by SARS-CoV-2 considering pathogenesis of the disease from the positions of the pulmonary immune-vascular coagulopathy (McGonagle et al., 2020) in more favorable clinical form. The major results of analysis of the therapeutic tactics applied are indicative of the fact that oxygen support was required by 2.54% of patients only, 1 child was on artificial ventilation, and duration of oxygen therapy increased with age of children. Teenagers suffering from COVID-19 took systemic glucocorticosteroids for a longer period of time, they used antiviral drugs less. They received antibiotic therapy and required infusion therapy with glucose-salt solutions more frequently. All the patients involved into the study were discharged from hospitals. Lethal outcomes were not registered.

5. CONCLUSIONS

The study demonstrates that children of various age groups who were examined and treated for infection COVID-19 in the four regions of Ukraine during the period from March 2020 to November 2020 in general presented the clinical manifestation of the disease similar to that reported from other continents of the Earth (China, USA etc.) considering occurrence of the signs of certain symptoms and results of treatment. Severity of symptoms caused in children by SARS-CoV-2 virus did not depend on the territory of residence of patients, but it reflected common features of sorting out patients on their admission to hospitals. Infection by SARS-CoV-2 virus of children from various age groups depends on familial contacts with afflicted family members (from 63.3% to 70.7% in the different regions of Ukraine) and social activity of children of a senior age (about 16.2% of cases in the group of teenagers). At the same time, 13.8-34.6% of observations concerning epidemiological surroundings of children in different regions of Ukraine remain unknown.

The leading symptoms of children suffered from COVID-19 in Ukraine remain respiratory tract lesions with prevailing involvement of the upper respiratory passages and higher chances of milder forms of the disease (OR=3.1) among junior children, and involvement of the lower respiratory tract and higher chances of severe course among senior children (OR=7.3). Affliction of the systems of internal organs by SARS-CoV-2 virus in children from different regions of Ukraine was characterized by multi-systemic type and manifested by changes in the upper respiratory tract in 70.1% of cases, lower respiratory tract lesions in 54.7% of observations, infectious-inflammatory changes in 57.2% of cases, gastrointestinal symptoms in 9.2%, and neurological signs in 17.8%. Affliction of the lung parenchyma with an appropriate clinical-radiological manifestation as a sign of infection COVID-19 was determined with occurrence from 23.9% to 25.9% of children examined in different regions of Ukraine with a reliable increase of chances to develop pneumonia (OR=7.5) at the juvenile age.

The most frequent changes in additional methods of examination were leukocytosis (18.8% of cases), thrombocytosis (14.5% of patients), leukopenia (11.1% of children), and increase of CRP in 43.7% of children. Elevated content of platelets was mainly found in children of the first two months of life (38.3% of cases), and it reliably increase during the period of in-patient treatment (V=25.6; Z=2.88, p=0.004), which coincided with the tendencies to increasing occurrence of CRP content in this age cohort (OR=5.0). The treatment of children was carried out according to the current recommendations and protocols, and lethal outcomes among the cohort examined were not registered.

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Author Contributions

All authors contributed to the research and/or preparation of the manuscript.

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Conflict of Interest

The authors declare no conflict of interests.

Informed consent

Written & Oral informed consent was obtained from all individual participants included in the study.

Ethical approval

The research protocol and informed consent form were approved by the Commission on Biomedical ethics in biomedical scientific research of the O.O. Bogomolets National Medical University, National Pirogov Memorial Medical University, Vinnytsya, Odessa National Medical University, Bukovinian State Medical University (Protocol No. 5, 18.02.2021).

Data and materials availability

All data associated with this study are present in the paper.

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