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Research Article

Hepatobiliary System Lesions in Children with COVID-19. Literature Review and Own Observations

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Abstract

Background: The relevance of this topic is due to the increasing incidence of hepatobiliary system in patients infected with SARS-CoV-2. COVID-19-associated hepatitis occurs in 15 - 65% of adult patients and 6 - 27% of children.

Aim: To determine the association of hepatobiliary disorders with different variants of SARS-CoV-2 in children with coronavirus infection (COVID-19) who underwent inpatient treatment during a pandemic.

Materials and Methods: 945 case histories of children from birth to 17 years of age, who were hospitalized in KCC-CIDH in Kyiv, Ukraine with a diagnosis of coronavirus disease in the period from June 2020 to February 2022, were retrospectively studied. Among them were selected cases with elevated bilirubin, ALT and AST. The peculiarities of the results of instrumental and laboratory researches were determined. A distinction was made by age and periods of the pandemic. Statistical software EZR v. 1,54 was used to conduct a statistical study of the obtained results, using the methods of descriptive statistics.

Results: An increase in ALT was observed in 8.4% (72/854) cases, an increase in AST in 19% (162/854) patients and an increase in total bilirubin in 3,6% (31/854) patients. In the age structure there was a predominance of all indicators in groups of children from birth to 1 year and age category 1 - 5 years. According to ultrasound, hepatomegaly was registered in 165 (17,5%) with a predominance in children 1 - 5 years, which accounted for 57 (6%) cases. There was a statistically significant increase in ALT and AST during the fourth wave compared to previous outbreaks, $p < 0,001$.

Conclusion: The dependence of transaminase changes on the COVID-19 period in children was revealed. Liver damage may be related to SARS-CoV-2 virus. However, there is still a need for further research to study this relationship in detail and to understand the pathogenetic mechanisms of hepatitis in coronavirus infection in children.

Keywords: *Coronavirus Infection; Children; Hepatitis; Bilirubin; ALT; AST; Hepatobiliary System*

Introduction

The world has been resisting the COVID-19 pandemic for more than two years. As of June 2022, 537 million confirmed cases have been reported worldwide, of which 6,31 million are fatal. There are more than 5 million confirmed cases in Ukraine, of which more than 108 thousand are fatal [1].

Among the wide range of manifestations of COVID-19, liver damage is attracting more and more attention, which can be observed in 15 - 65% of adult patients and 6 - 27% of children [22,23]. In one of the first published analyzes of hepatobiliary disorders in children with positive SARS-CoV-2, researchers proposed the term of COVID-19 induced hepatitis «CIH». According to the authors, up to 60% of patients with respiratory viral infections may have liver dysfunction. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) had significant abnormalities in 14-53% of patients with COVID-19 (7/114, 6,14%), $p > 0,05$. Disorders of liver enzymes in severe pneumonia were significantly higher than in patients with mild disease (37,87 ± 32,17 vs. 21,22 ± 12,67; 38,87 ± 22,55 vs. 24,39, ± 1,0,0). Patients with community-acquired pneumonia had significantly fewer synthetic liver dysfunction (32/114, 28,07%) compared with pneumonia with COVID-19 (60/115, 52,17%), $p < 0,01$ [2].

Later, during the COVID-19 outbreak, which was accompanied by the spread of the delta variant, Indian scientists classified similar changes in children with laboratory-confirmed cases of COVID-19 as COVID-19 Associated Hepatitis in Children «CAH- C". The researchers conducted an observational cohort study of cases of acute hepatitis in children who were hospitalized between April and July 2021 with a positive SARS-CoV-2. Hepatitis was divided into two categories based on the likely association with COVID-19, disease severity, inflammatory marker levels, and the presence/absence of multisystem lesions (based on clinical, laboratory, and radiological data). The first category of CAH-C, which included children under 14 years of age, with laboratory indicators of COVID-19 and sudden onset of hepatitis, characterized by elevated transaminases, jaundice, no pronounced inflammatory reactions and no other causes of hepatitis or previous liver disease. The second category was interpreted as hepatitis associated with multisystem inflammatory syndrome (MIS-C). This group was represented by patients with MIS-C manifestations according to the Centers for Disease Control and Prevention (CDC) [3] and elevated transaminases [19]. Among the 475 children examined, 47 (9,9%) had hepatitis, of which 37 had CAH-C with symptoms of hepatitis, with unmarked inflammatory markers, and a relatively mild, uncomplicated course. While the other 10 hepatitis associated with MIS-C had a prolonged and severe course, multiple lesions of various organs and systems and required treatment in the intensive care unit. The mortality rate in this group was 30%. In both groups the age category of patients 2 - 6 years prevailed. Patients with hepatitis associated with COVID-19 in most of cases (29/37) had significantly elevated transaminases with a median of 1326,2 (IQR 70-5685) IU/l, total bilirubin with a median of 4,05 (IQR 1,4-17,1) mg/dl and was accompanied by general intoxication symptoms with a favorable course [19].

We also considered a retrospective cohort study of 44 patients hospitalized in New York Children's Hospital with liver disease in MIS-C. Hepatitis was recorded in 19 (43%) patients and was a predictor of severity. Children with hepatitis had significantly higher rates of shock (21,1% vs. 0%, $p = 0,008$), needed more for respiratory support (42,1% vs. 12%, $p = 0,005$) and had longer hospital stays (median 7 days [IQR 5,10] against 4-day [IQR 3,5, 6,5], $p < 0,05$). Patients with hepatitis also had significantly higher levels of ferritin (706,9 vs. 334,2 mg /ml, $p < 0,01$), interleukin-6 (233,9 vs. 174,7 pg /ml, $p < 0,05$), troponin (83 vs. 28,5 ng /l, $p < 0,05$) and natriuretic peptide (7424,5 vs. 3209,5 pg/ml, $p < 0,05$). According to instrumental methods, liver damage was confirmed in 8 (42,1%) patients. Four of the six patients on ultrasound showed lesions of the hepatobiliary system: in 2 cases - ascites (one patient also had a thickening of the gallbladder wall), each - hepatomegaly or thick-walled gallbladder. All known etiologies of hepatitis were excluded in all patients. Improvement was observed in 17 (89,5%) patients with complete normalization in 9 (47,4%) patients within a month [20].

In the adult population, according to Zhenyu Fan., *et al*. liver dysfunction was found in half of the cohort surveyed (50,7%) of patients with coronavirus infection. The average age of patients was 50,5 years (IQR, 36-64). In patients, there was an increase in ALT (n = 27, 41-

115 IU/l), AST (n = 32; 37-107 IU/l), and total bilirubin (n = 9,21-46,6 μmol /l). Patients with hepatic impairment also had significantly lower CD4 + and CD8 + T cell counts compared with patients with normal liver function [7].

Similar to this publication, numerous Chinese scientists also pointed to a analogous incidence of liver involvement in adults with COVID-19, ranging from 15% to 55%. The authors, in particular, focused on abnormal ALT and AST levels, which were accompanied by a slight increase in bilirubin [4-10]. In fatal cases, the incidence of liver damage reached 78% [11,12].

Taking into account the available literature, it is clear that liver damage on the background of COVID-19 is quite common, but the final pathogenetic mechanisms of this complication are not defined. One of the assumptions of pathogenesis is the cytopathic effect caused by the virus. In addition, liver damage can be caused by the use of hepatotoxic drugs, including antiviral and antimicrobial drugs [16]. According to Hoffmann M., the influx of SARS-CoV-2 on hepatocytes is due to the presence of receptors for angiotensin-converting enzyme type 2 (ACE2), which serve as a gateway for virus penetration [13]. The results of a study by Chai., *et al*. discovered that both liver cells and bile duct cells express ACE2 inhibitors [14]. In addition, the authors determined that the expression of ACE inhibitors in bile duct cells is much higher than in hepatocytes and compared with the level of ACE inhibitors in alveocytes. Epithelial cells of the bile ducts play an important role in the immune response and liver regeneration. The results of studies may indicate liver damage in patients with COVID-19 due to cholangiocyte damage [15,21].

Due to the increased incidence of liver damage during SARS-CoV-2 circulation, it can be assumed that the virus has hepatotropic properties that may be exacerbated with the spread of new strains. Given this, we decided to analyze cases of coronavirus disease in children who were hospitalized in an infectious disease hospital in Kyiv to assess biochemical parameters in order to identify the nature of liver damage in patients at different times of the pandemic.

Aim of the Study

To determine the association of hepatobiliary system lesions with different variants of SARS-CoV-2 in children with COVID-19 who received inpatient treatment during a pandemic.

Materials and Methods

The study was one-center, retrospective, cohort. A total of 1,668 children with a confirmed diagnosis of COVID-19 were under the supervision of an infectious hospital. Of these, 945 cases of children under the age of 17 who were hospitalized at the Kyiv City Children's Clinical Infectious Diseases Hospital (KCCCIDH) in Kyiv, Ukraine with a diagnosis of coronavirus disease in the period from June 2020 to February 2022 were retrospectively studied. The study did not include cases where the diagnosis of COVID-19 was not laboratory confirmed, as well as cases of comorbid conditions and co-infections that could affect the results of laboratory and instrumental studies of the hepatobiliary system.

The peculiarities of the results of instrumental and laboratory researches were determined. A distinction was made by age and periods of the pandemic. There were four main categories according to age: from birth to 12 months, from 1 to 5 years, from 6 to 9 years and over 10 years. Depending on the period of hospitalization, patients were differentiated into four periods according to outbreaks: 1 wave - from June to November 2020 (340 cases); 2nd wave - from February to May 2021 (191 cases); 3rd wave - August-December 2021 (334 cases); 4th wave - January-February 2022 (80 cases).

The study was conducted in accordance with the standards of bioethics, was agreed with the bioethics commission of the hospital. There was no need to obtain informed consent from patients, as only retrospective analysis of routine medical records was performed.

To conduct a statistical study of the results, we used the package Statistical software EZR v. 1.54 (graphical user interface for R statistical software version 4.0.3, R Foundation for Statistical Computing, Vienna, Austria), using descriptive statistics methods. The median (M), quartile interval (IQR, 1st - 3rd quartile) were determined and multiple comparisons were made using the Dunn test and Kruskal-Wallis rank one-factor analysis. The reliability of the difference between nonparametric parameters was determined using the Chi-square test or Fisher's exact test, for parametric data used the Mann-Whitney test. The difference at the error value $p < 0,05$ was considered significant.

Results

Among 945 cases, 854 children (90,3%) were covered by biochemical studies. Elevated ALT levels (above 41 U/l) were observed in 72 (8,4%) cases out of 854 surveyed children. An increase in ACT (above 41 U/l) was recorded in 162 (19%) patients and an increase in total bilirubin (more than 21 μmol /l) was observed in 31 (3,6%) patients from the examined cohort of patients. Figure 1 shows the frequency of the above indicators in children depending on age.

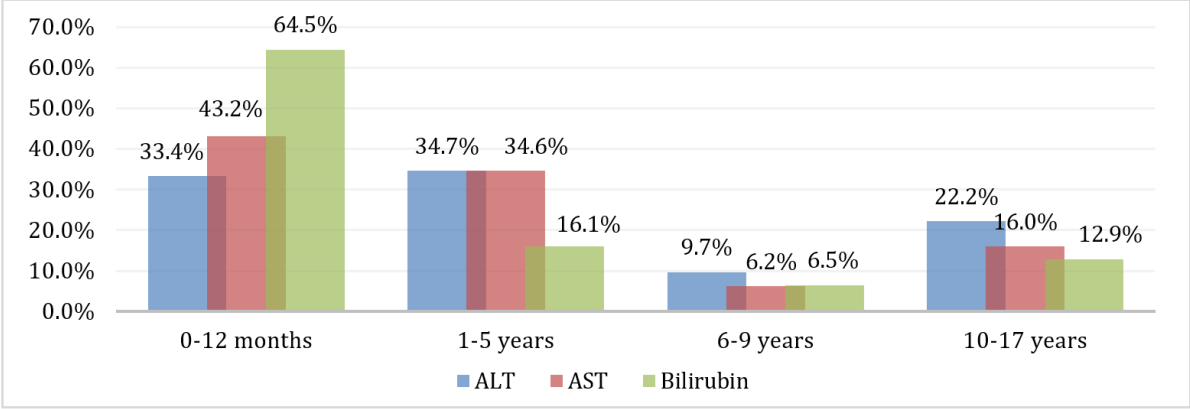

Figure 1: *Distribution of biochemical parameters in patients by age.*

In the age structure (Figure 1) there was a predominance of all indicators in groups of children from birth to 1 year and age category 1 - 5 years. Elevation of ALT was observed in 24 (33,4%) children under the first year of life against 25 (34.7%) children 1 - 5 years ($p = 0.8$), 7 (9.7%) cases 6 - 9 years $p < 0,001$) and 16 (22,2%) patients older than 10 years ($p = 0,14$). The increase in AST was recorded in 70 (43,2%) children from birth to 1 year, compared with 56 (34,6%) cases of children aged 1 - 5 years ($p = 0,11$), 10 (6,2%) patients 6 - 9 years ($p < 0,001$) and 26 (16,%) cases older than 10 years ($p < 0,001$). Total bilirubin - in 20 (64,5%) children under 1 year against 5 (16%) cases 1 - 5 years ($p < 0,001$), 2 (6,5%) patients 6 - 9 years ($p < 0,001$) and 4 (12,9%) patients aged 10 - 17 years ($p < 0,001$). These indicators were registered in children from the beginning of the disease, for the first three waves the median of the disease was 3 days (IQR 1-5), and for the fourth - the median was 1 day (IQR 1 - 3 days), $p < 0,001$.

The frequency of increased transaminases and bilirubin in children during various outbreaks of coronavirus infection is shown in figure 2.

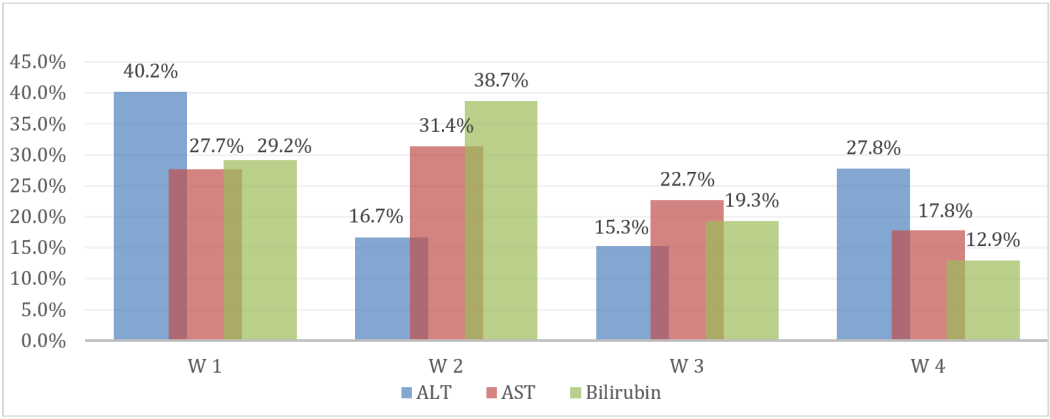

Figure 2: *Frequency of elevated transaminases and bilirubin in children during the four waves of COVID-19.*

During the first wave of the disease there was a predominance of ALT in children compared to subsequent waves (Figure 2), 40,2% vs. 16,7%, 15,3% and 27,8% of the period of subsequent outbreaks (p = 0,002). The highest frequency of AST was recorded during the second period of COVID-19, was 31,4%, against 27,7% of the first wave (p = 0,47), 22,7% of the third (p = 0,08) and 17,8% of the fourth, respectively (p = 0,005). The highest value of total bilirubin was observed during the second wave period, was 38,7% against 29,2% of the first outbreak (p = 0,4), 19,3% of the third (p = 0,09) and 12,9% of the fourth (p = 0,02). Table 1 presents a detailed description of the indicators depending on the age during each wave.

Wave	Age	ALT		AST		Total bilirubin		Direct bilirubin	
		n, (%)	Average (U/l)	n, (%)	Average (U/l)	n, (%)	Average (µmol/l)	n, (%)	Average (µmol/l)
1 wave	0 - 12 months	8 (11%)	66,9	15 (9,2%)	83,9	3 (9,7%)	27,6	0	-
	1 - 5 years	10 (13,9%)	63,4	10 (6,2%)	85	2 (6,5%)	55,2	0	-
	6 - 9 years	4 (5,6%)	111,8	5 (3,1%)	166,4	2 (6,5%)	76,5	0	-
	10 - 17 years	7 (9,7%)	56,6	15 (9,2%)	46,2	2 (6,5%)	23,2	0	-
2 wave	0 - 12 months	4 (5,6%)	49,3	26 (16%)	51,2	8 (25,8%)	120,3	5 (83%)	35,3
	1 - 5 years	3 (4,2%)	50	19 (11,7%)	50,8	3 (9,7%)	41	0	-
	6 - 9 years	0	-	1 (0,6%)	58	0	14,6	0	-
	10 - 17 years	5 (6,9%)	88,6	5 (3,1%)	110,6	1 (3,2%)	29	0	-
3 wave	0 - 12 months	2 (2,8%)	42	11 (6,8%)	48,9	5 (16,1%)	191,2	1 (17%)	20
	1 - 5 years	5 (6,9%)	47,8	20 (12,3%)	47,4	0	12,6	0	-
	6 - 9 years	1 (1,4%)	48	2 (1,2%)	47,5	0	14,8	0	-
	10 - 17 years	3 (4,2%)	59,3	4 (2,4%)	61,9	1 (3,2%)	23,3	0	-
4 wave	0 - 12 months	10 (13,9%)	53,3	18 (11,1%)	56,3	4 (12,9%)	147,5	0	-
	1 - 5 years	7 (9,7%)	48,2	7 (4,3%)	63	0	13,3	0	-
	6 - 9 years	2 (2,8%)	41	2 (1,2%)	48	0	15,9	0	-
	10 - 17 years	1 (1,4%)	50	2 (1,2%)	71,2	0	16,4	0	-

Table 1: *Structure of increased biochemical parameters depending on disease outbreaks and age.*

During the first outbreak of COVID-19, an increase in ALT was observed in 29 (40,2%) patients, with the highest frequency of children 1 - 5 years -10 (13,9%) cases (Table 1). The increase in AST during this wave was recorded in 45 (27,7%) patients with a predominance of children under 1 year and adolescents, in 15 (9,2%) cases. Hyperbilirubinemia was observed in 9 (29,2%) children, with a prevalence in patients under 1 year, 3 (9,7%) cases. The highest concentrations of transaminases and bilirubin were observed in children 6 - 9 years (ALT average value - 111,8 U/l, AST-166,4 U/l, bilirubin - 76,5 μmol/l).

The period of the second wave was characterized by a predominance of elevated rates in the age group of children under 1 year and adolescents. High ALT levels were observed in 12 (16,7%) patients, with the highest concentration in adolescents (average value 88,6 U/l). The increase in AST was recorded in 51 (31,4%) with a predominance of children older than 10 years (average value 110,6 U/l). Elevated total bilirubin levels were found in 12 (38,7%) patients, with a predominance in young children (120,3 μmol/l). In 5 cases there was also an increase in bilirubin due to the direct fraction (average value of 35,3 μmol/l).

The next was an outbreak corresponding to the third wave of COVID-19. The predominant age group during this outbreak was children aged 1 - 5. Elevated levels of aminotransferases were observed in 11 (15,3%) -ALT and 37 (22,7%) cases of AST. The highest enzyme values were observed in children older than 10 years, 59,3 U/l for ALT and 61,9 U/l for AST. Bilirubinemia was recorded in 6 (19,3%) patients, most of whom were children under 1 year of age with an average concentration of 191,2 μmol/l. In one patient, the increase in total bilirubin prevailed due to the direct fraction, which was 20 μmol/l.

The predominant age group of patients with increased aminotransferases and bilirubin during the fourth wave was children from birth to 1 year. An increase in ALT was registered in 20 (27,8%) patients (average value 53,3 U/l), AST in 29 (17,8%) patients (average value 56,3 U/l) and bilirubin in 4 (12,9%) children (average value 147,5 μmol/l).

The vast majority of hospitalized children also underwent instrumental research methods, depending on the data of objective examination and clinical symptoms, including abdominal ultrasound. The age structure of the detection of hepatomegaly on ultrasound is presented in figure 3.

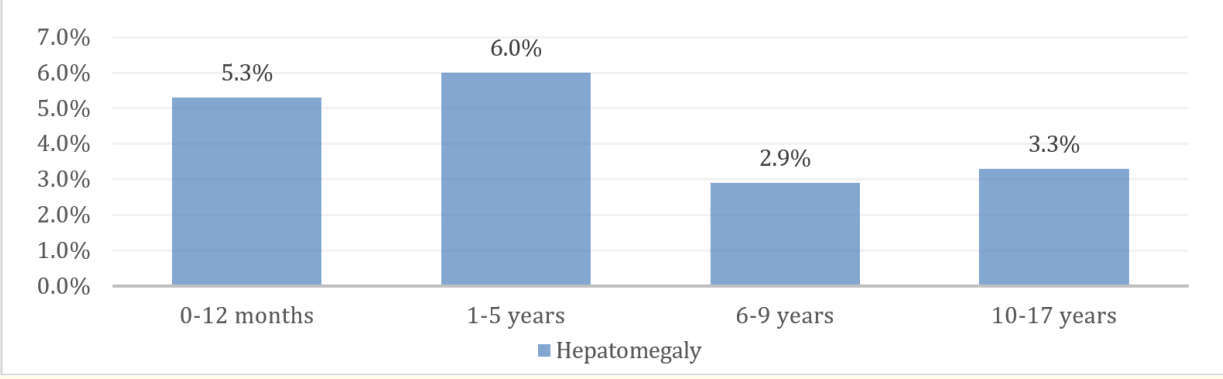

Figure 3: *Frequency of hepatomegaly detection on ultrasound depending on age.*

According to instrumental methods of examination (Figure 2), ultrasound of the abdominal cavity revealed an increase in the liver in 165 (17,5%) patients with 945 cases. According to the age distribution, the predominant age group of children with hepatomegaly was the category of patients 1 - 5 years, was 57 (6%) cases against 50 (5,3%) cases in children of the first year of life (p = 0,4), 27 (2,9%) in patients aged 6-9 years (p < 0,001) and 31 (3,3%) in children older than 10 years (p = 0,002).

It should be added that among the possible causes of damage to the hepatobiliary system may be the impact of antibiotic therapy used in the treatment of the underlying condition. Therefore, it should be noted that the frequency of antibiotics in children was the same during all four waves of the disease, thus eliminating the possible link between the effects of the antibacterial agent and elevated transaminases.

Statistical software EZR v.1,54 was used for statistical assessment of biochemical parameters in children with COVID-19. The median, quartile interval (IQR, 1st - 3rd quartiles) were determined, multiple comparisons were made using the Dunn test and Kruskal-Wallis rank one-factor analysis. The resulting variables were W1 for the first wave of the disease, W2 for the second, W3 for the third, and W4 for the fourth outbreak.

Table 2 and figure 4 show the average ALT values in children with coronavirus infection over the period of four outbreaks.

Variable	Quantity	Median	I quartile	III quartile	Minimum	Maximum	Derivative of the median	Left (95% RI)	Right (95% RI)
W1	301	20	17	27	12	180	1,41	19	22
W2	182	20	17	25	10	129	1,34	19	22
W3	297	20	17	24	7	70	0,59	19	21
W4	74	33	26	44	14	53	1,68	30	37

Table 2: *Interval estimation of ALT average values in children during four COVID-19 outbreaks.*

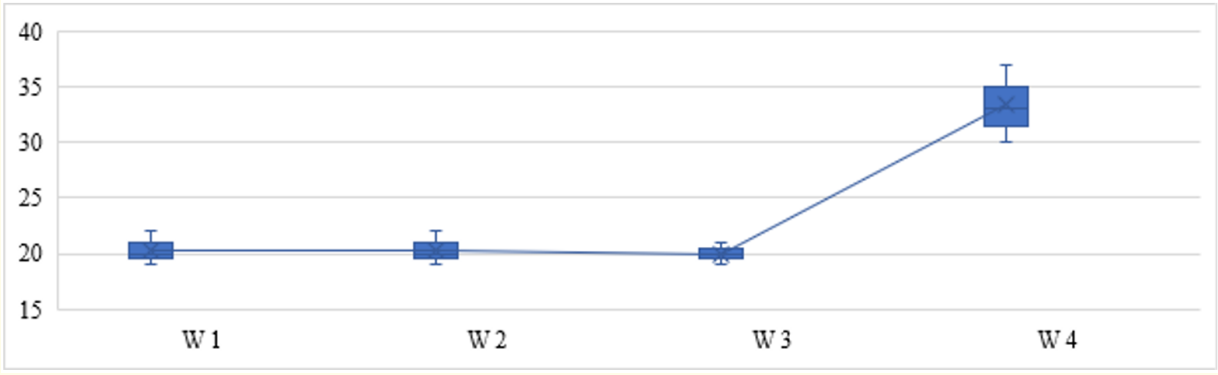

Figure 4: *Interval estimation of ALT average values in children during four COVID-19 outbreaks (the average value, the error of the average and 95% RI are indicated).*

According to the obtained data (Table 2 and figure 4), when conducting a multiple comparison of the average values of ALT for 4 samples, the rank one-factor analysis of Kruskal-Wallis revealed a difference in the level of significance p < 0,001. Multiple comparisons by the Dunn test revealed a statistically significant difference in ALT during the fourth wave compared to the first, second and third, p < 0,01.

The interval characteristics of AST average values in children during the four outbreaks are presented in table 3 and figure 5.

Variable	Quantity	Median	I quartile	III quartile	Minimum	Maximum	Derivative of the median	Left (95% RI)	Right (95% RI)
W1	299	32	24,6	44	16	265	2,05	29,6	34,6
W2	176	32,6	25	43,8	16	148	1,73	30	35,8
W3	297	29	24	37	12	93,9	0,73	27	29,7
W4	74	48	36	55	16	79,1	2,29	44	50

Table 3: *Interval estimation of AST average values in children during four COVID-19 outbreaks.*

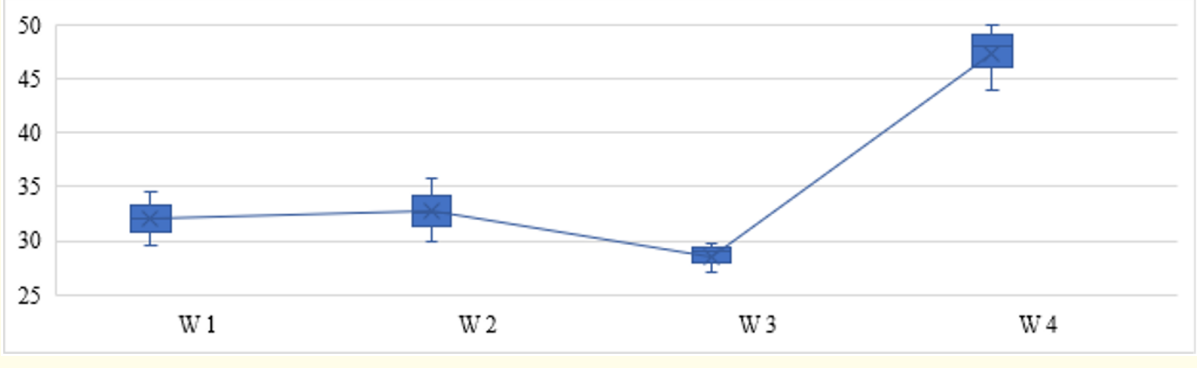

Figure 5: *Interval estimation of AST average values in children during four COVID-19 outbreaks (the average value, the error of the average and 95% RI are indicated).*

According to the rank one-factor analysis of Kruskal-Wallis, a difference in the level of significance p < 0,001 was revealed. Multiple comparisons by the Dunn test revealed a statistically significant difference in AST during the fourth wave compared to the previous three, p < 0,01.

Interval estimates of average bilirubin levels in children during the four COVID-19 outbreaks are shown in table 4 and figure 6.

Variable	Quantity	Median	I quartile	III quartile	Minimum	Maximum	Derivative of the median	Left (95% RI)	Right (95% RI)
W1	305	14,6	12,6	16,4	8,6	114,9	0,52	12,6	15
W2	180	14,6	11,6	16,4	9,8	306,45	2,73	14	15,5
W3	297	14,6	12,6	15,5	9	305	1,81	12,6	15
W4	74	15,5	12,6	16,4	8,6	269	6,07	14,6	16,4

Table 4: *Interval estimation of bilirubin average values in children during four COVID-19 outbreaks.*

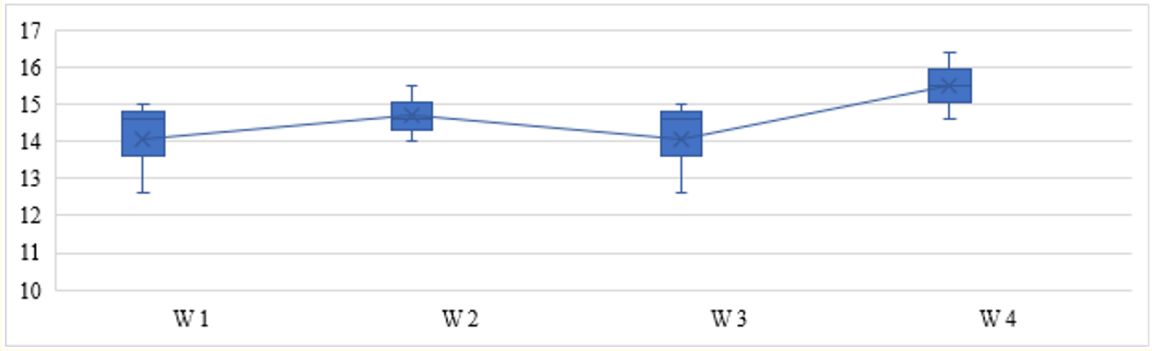

Figure 6: *Interval estimation of bilirubin average values in children during four COVID-19 outbreaks (the average value, the error of the average and 95% RI are indicated).*

According to the obtained data of the interval assessment of bilirubinemia in children during the four outbreaks of COVID-19 (Table 4 and figure 6) no statistically significant difference was found, p = 0,123.

The following are clinical cases of hepatitis in children with coronavirus infection who were hospitalized in an infectious disease hospital in Kyiv.

Clinical case 1

U 07.1 - COVID-19, J12.8 - Another viral pneumonia.

The child, 5 years old, was admitted to KCCCIDH with complaints of fever up to 38°C, nasal breathing difficulties, runny nose and cough.

From the anamnesis of the disease: The child fell ill 5 days before hospitalization with fever, shortness of breath, loss of appetite and weakness. The family doctor diagnosed acute respiratory viral infection and prescribed symptomatic treatment. On the 5th day of the disease, due to the lack of positive dynamics and the appearance of complaints of chest pain, he was hospitalized in an infectious hospital.

Objectively: A state of moderate severity due to intoxication and hyperthermic syndromes, the child is conscious, the position is active. The physique is normosthenic. The skin and mucous membranes are pale, there is no rash, the mucous membrane of the oropharynx is moderately hyperemic, the tonsils are not enlarged, there are no layers. The tongue is dry, covered with white plaque. Lymph nodes without features. Nasal breathing is difficult, secretion from the nasal passages is mucous. Auscultatory breathing is hard, on the left side are heard various wet rales. Heart tones are sonorous, rhythmic. The abdomen is soft, painless. Liver +1 cm, spleen is not palpable. Stool and urination are normal.

The results of laboratory tests (at the time of the 6th day from the onset of the disease):

- Nasopharyngeal RNA swab of COVID-19 virus: - detected.
- HbS-ag was not detected, markers of viral hepatitis A, B, C, D were not detected.

- General blood test: Erythrocytes - 5,06 T/l; Platelets - 230,0 G/l; Leukocytes - 8,6 G/l; Erythrocyte sedimentation rate (ESR) - 6 mm/h, eosinophils-1%, rod-shaped granulocytes-8%, segmental neutrophils-40%, lymphocytes-42%, monocytes-9%.

- Biochemical analysis of blood: Total bilirubin - 55,2 μmol/l; direct - 0 μmol/l; ALT -53 U/l; AST- 135 U/l; creatinine - 48 μmol/l; urea-4,3 μmol/l; procalcitonin - 0,046 ng/ml; fibrinogen - 3,1G/l; APTT - 30'; PT- 92'.

Instrumental research methods: On the radiograph enhancement of the pulmonary pattern, edema of the lung roots, pronounced interstitial changes more on the left side.

Ultrasound of the abdominal cavity: Increase in the size of the liver by 2 cm, spleen by 1 cm.

The treatment was carried out in accordance with the current order of the Ministry of Health of Ukraine and the local protocol of KCC-CIDH and included antibiotic therapy, infusion therapy and the use of symptomatic drugs. During the hospitalization with the treatment the child's condition significantly improved, she was discharged in satisfactory condition.

Clinical case 2

U 07.1 - COVID-19, J12.8 - Another viral pneumonia. Viral enteritis.

The child, 6 years old, came with complaints of fever up to 39.3°C, difficulty breathing, runny nose, cough and diarrhea.

From the anamnesis of the disease: Sick for 3 days, the disease began with fever, vomiting, loss of appetite and weakness. On the 3rd day of the disease, multiple bowel movements were rare, the temperature was maintained and a cough appeared, so he was hospitalized.

Objectively: The condition is severe due to intoxication, hyperthermic syndromes and gastroenteritis, the child is conscious, lethargic. The skin and mucous membranes are pale, dry, the mucous membrane of the oropharynx is hyperemic, the tonsils are not enlarged, there are no layers. The tongue is dry, covered with white plaque. Lymph nodes without features. Nasal breathing is difficult, there is no discharge from the nasal passages. Auscultatory breathing is hard, wet rales of various calibers are heard on both sides. Heart tones are sonorous, rhythmic. The abdomen is soft, painless, accessible to deep palpation. Liver +1,5 cm, spleen is not palpable. Urination is normal. Liquid, unfurnished stool 3 - 5 times a day.

The results of laboratory tests:

- Nasopharyngeal RNA swab of COVID-19 virus: - detected.

- HbS-ag was not detected, markers of viral hepatitis A, B, C, D were not detected.

- Blood test: At the time of hospitalization: Erythrocytes - 5,23 T/l; Platelets - 281,0 G/l; Leukocytes - 14,7 G/l; ESR - 12 mm/h, eosinophils-1%, rod-shaped granulocytes-12%, segmental neutrophils-43%, lymphocytes-32%, monocytes-12%.

- On the 4th day: Erythrocytes - 6,2 T/l; Platelets - 291,0 G/l; Leukocytes - 16 G/l; ESR - 10 mm/h, granulocytes - 37,1%; lymphocytes-17,2%.

- On the 9th day: Erythrocytes - 5,8 T/l; Platelets - 329,0 G/l; Leukocytes - 11 G/l; ESR - 8 mm/year, granulocytes - 33,3%; lymphocytes-53,6%.

- Bacteriological examination of feces: Pathogenic microflora not detected.
- Biochemical analysis: At the time of hospitalization: Total bilirubin - 113 μmol /l; Direct - 0 μmol/l; ALT -59 U/l; AST- 62 U/l; procalcitonin - 0,086 ng/ml; CRP ++++; D-dimer 3,95 ng/ml; Fibrinogen - 4,7 g/l; APTT-29'; PT-95'.
- On the 6th day: Total bilirubin - 21 μmol /l; ALT -17 U/l; AST - 36,3 U/l.

Instrumental research methods: On the radiograph enhancement of the pulmonary pattern, edema of the lung roots, expressed interstitial changes in the lungs. Ultrasound of the abdominal cavity: Echo signs of severe flatulence. Enlargement of the liver by 2.5 cm.

The treatment was carried out in accordance with the instructions of the current order of the Ministry of Health of Ukraine and the local protocol of the hospital. During the hospitalization with the treatment the child's condition significantly improved, she was discharged in satisfactory condition.

Discussion

This work was carried out in a specialized children's infectious disease hospital in Kyiv, which is a specialized hospital for children with COVID-19 in the capital since the beginning of the pandemic. Given this, the study can be considered representative in terms of the study of the child population of the largest city in Ukraine.

Statistical analysis of laboratory parameters indicates about a link between liver damage and COVID-19 in children, which showed a statistically significant increase in transaminases during the fourth wave ($p < 0,001$) compared with previous outbreaks. This correlates with data from Japanese researchers, in particular Hiroshi Nishiura, a professor at Kyoto University, who noted an increase in liver damage during the circulation of the omicron variant, which corresponds to the fourth wave period, compared to previous outbreaks [25].

Studying the possible mechanisms of hepatitis in children with coronavirus infection according to the literature, we determined that the probable is the action of the virus, or the immune-mediated mechanism of the lesion [17]. To exclude the second option, we also identified on which day of the disease elevated laboratory parameters were detected. For the first three waves, the median day of the disease was 3 days (IQR 1-5), and for the fourth, the median was 1 day (IQR 1-3 days), which may testify the viral genesis of the lesion, because in immunocompromised or autoimmune hepatitis laboratory changes fixed on 2 - 3 weeks. This is confirmed by a clinical case of liver disease in a 3-year-old child from Ohio, USA, which occurred 3 weeks after the mild form of COVID-19. Laboratory and histological examination corresponded to autoimmune hepatitis. Elevated levels of ALT 939 I/L, AST 1321 IU/L, total bilirubin 5,5 mg /DL, conjugated bilirubin 0,9 mg/DL were found. C-reactive protein, ESR, ferritin, lactate dehydrogenase, creatine kinase and troponin were within normal limits, so the diagnosis of MIS-C was excluded. Doppler abdominal ultrasound showed diffusely heterogeneous liver parenchyma, which corresponded to hepatocellular disease. Markers of viral hepatitis were negative and the child did not receive prior medication, no history of surgery and chronic diseases of the hepatobiliary system or other comorbid conditions that could provoke the development of hepatitis [24].

As for the mechanism of liver damage in MIS-C, the immune response after COVID-19, according to the literature, can begin later than the 3rd week, up to 2 - 3 months and may be accompanied by sepsis, Kawasaki disease, toxic shock syndrome, or macrophage activation syndrome [26]. Literature sources indicate an asymptomatic course in 90% of MIS-C-related cases of SARS-CoV-2, up to 5,7% require hospitalization and 0,1% are fatal [27]. Retrospective studies of pediatric patients with MIS-C have reported cases of hepatitis

with increased transaminases associated with increased inflammatory response, with a low rate of progression to liver failure (1 in 19 patients) [28], indicating that the liver may be one of the target organs in MIS-C cases. Colombian scientists have presented a case of fulminant acute liver failure in a child 10 months with MIS-C. A child without a history of hepatotoxic injury, with confirmed SARS-CoV-2 infection 45 days before the onset of liver damage, was hospitalized with symptoms of hypersomia, loss of appetite, jaundice and dark urine, and acholic stool. Paraclinical tests for hepatitis A, B, C, cytomegalovirus, Epstein-Barr virus, herpes simplex, and human immunodeficiency were negative, but IgM and IgG were positive for SARS-CoV-2. Laboratory results were consistent with encephalopathy and acute liver failure. Liver damage was associated with giant cell transformation and was fatal on day 17 of hospitalization due to the progression of multisystem damage associated with sepsis and respiratory failure and shock. Infectious, metabolic, genetic and other causes of liver failure have been ruled out. The autopsy revealed ascites, changes due to hepatic encephalopathy, subdural hematoma in the left hemisphere of the cerebellum, proximal acute renal tubular necrosis, peritubular stasis and areas of hemorrhagic infiltration of the adrenal glands [29]. A similar mechanism of damage to the hepatobiliary system in COVID-19 with the transformation of multinucleated giant cells and fulminant hepatitis has been reported in cases of adult disease [30,31].

Conclusion

Therefore, based on our results, we can indicate the dependence of changes in transaminases with the period of COVID-19 in children. Liver damage may be related to SARS-CoV-2 virus. The increase in the incidence of hepatitis associated with COVID-19 in patients of different ages is associated with the rapid spread of new variants of the virus. Timely recognition of possible manifestations of hepatobiliary lesions in children who have recently contracted a coronavirus infection is extremely important to avoid adverse effects.

Despite the fact that our study had some limitations, in particular, retrospective, patient data were studied only on the basis of one center and there was no information on children who were outpatients, however, the preliminary data are an important integral part of further scientific research, as understanding the pathogenetic mechanisms of hepatitis in coronavirus infection in children will help to optimize diagnostic algorithms and treatment approaches.

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Conflict of Interest

The authors declare no conflict of interest.

Bibliography

1. Ministry of health of Ukraine. COVID-19 pandemic in Ukraine (2020).
2. Gadour E., *et al*. "Covid-19 induced hepatitis (CIH), definition and diagnostic criteria of a poorly understood new clinical syndrome". *Gut* 69 (2020): A22.
3. HAN Archive - 00432. Health Alert Network (HAN) (2020).
4. Huang C., *et al*. "Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China". *Lancet* 395.10223 (2020): 497-506.

5. Guan W., *et al*. "Clinical characteristics of 2019 novel coronavirus infection in China". *Med Rxiv* (2020).

6. Cai Q., *et al*. "COVID-19 in a Designated Infectious Diseases Hospital Outside Hubei Province, China". *Med Rxiv* (2020).

7. Fan Z., *et al*. "Clinical features of COVID-19-related liver damage". *Med Rxiv* (2020).

8. Wang D., *et al*. "Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China". *The Journal of the American Medical Association* (2020).

9. Cao W. "Clinical features and laboratory inspection of novel coronavirus pneumonia (COVID-19) in Xiangyang, Hubei". *Med Rxiv* (2020).

10. Chen N., *et al*. "Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study". *Lancet* 395.10223 (2020): 507-513.

11. Zhang B., *et al*. "Clinical characteristics of 82 death cases with COVID-19". *Med Rxiv* (2020).

12. Huang Y., *et al*. "Clinical characteristics of 36 non-survivors with COVID-19 in Wuhan, China". *Med Rxiv* (2020).

13. Hoffmann M., *et al*. "The novel coronavirus 2019 (2019-nCoV) uses the SARS-1 coronavirus receptor2 ACE2 and the cellular protease TMPRSS2 for entry into target cells". *Bio Rxiv* (2020).

14. Chai X., *et al*. "Specific ACE2 expression in cholangiocytes may cause liver damage after 2019-nCoV infection". *Bio Rxiv* (2020).

15. Banales JM., *et al*. "Cholangiocyte pathobiology". *Nature Reviews Gastroenterology and Hepatology* 16.5 (2019): 269-281.

16. Cichoż-Lach H and Michalak A. "Liver injury in the era of COVID-19". *World Journal of Gastroenterology* 27.5 (2021): 377-390.

17. Nardo AD, *et al*. "Pathophysiological mechanisms of liver injury in COVID-19". *Liver International* 41.1 (2021): 20-32.

18. Weber S., *et al*. "Liver function test abnormalities at hospital admission are associated with severe course of SARS-CoV-2 infection: a prospective cohort study". *Gut* 70.10 (2021): 1925-1932.

19. Ratho RK., *et al*. "COVID-19 Associated Hepatitis in Children (CAH-C) during the second wave of SARS-CoV-2 infections in Central India: Is it a complication or transient phenomenon". *Med Rxiv* (2021).

20. Cantor A., *et al*. "Acute Hepatitis Is a Prominent Presentation of the Multisystem Inflammatory Syndrome in Children: A Single-Center Report". *Hepatology* 72.5 (2020): 1522-1527.

21. Zhang C., *et al*. "Liver injury in COVID-19: management and challenges". *The Lancet Gastroenterology and Hepatology* 5.5 (2020): 428-430.

22. Marjot T., *et al*. "COVID-19 and liver disease: mechanistic and clinical perspectives". *Nature Reviews Gastroenterology and Hepatology* 18 (2021): 348-364.

23. Di Giorgio A., *et al*. "COVID-19 in children with liver disease". *Frontiers in Pediatrics* 9 (2021).

24. Osborn J., *et al*. "Pediatric Acute Liver Failure Due to Type 2 Autoimmune Hepatitis Associated With SARS-CoV-2 Infection: A Case Report". *JPGN Reports* 3.2 (2022).

25. Nishiura H., *et al*. "High population burden of Omicron variant (B.1.1.529) is associated with the emergence of severe hepatitis of unknown etiology in children". *The International Journal of Infectious Diseases* 122 (2022): 30-32.

26. Kaushik S., *et al*. "Multisystem inflammatory syndrome in children (MIS-C) associated with SARS-CoV-2 infection: a multi-institutional study from New York City". *The Journal of Pediatrics* 6.45 (2020).

27. Bautista-Rodriguez C., *et al*. "Multisystem inflammatory syndrome in children: an international survey". *Pediatrics* 147.2 (2021).

28. Lingappan K., *et al*. "Understanding the age Divide in COVID-19: why are children overwhelmingly spared?" *The American Journal of Physiology-Lung Cellular and Molecular Physiology* 2 (2021): 4-9.

29. Bonilla Gonzalez C., *et al*. "Case Report: Fatal Acute Liver Failure With Giant Cell Transformation in a Pediatric Patient Associated With MIS-C". *Frontiers in Pediatrics* 9 (2021).

30. Aldossary B., *et al*. "Fulminant hepatic failure in a patient testing re-positive for SARS-CoV-2: a case report". *The International Journal of Emergency Medicine* 14 (2021): 1-5.

31. Melquist S., *et al*. "COVID-19 presenting as fulminant hepatic failure". *Medicine* 93 (2020): 2-5.

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