



Review Article

Acute Hepatitis of Unknown Origin in Children: Early Observations from the 2022 Outbreak

Li-Ya Zhang^{1#}, Li-Su Huang^{1#}, Yu-Hang Yue¹, Rima Fawaz², Joseph K. Lim^{3*} and Jian-Gao Fan^{4,5*}

¹Department of Infectious Disease, Xinhua Children's Hospital, Xinhua Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China; ²Section of Pediatric Gastroenterology and Hepatology, Yale University School of Medicine, New Haven, CT, USA; ³Section of Digestive Diseases and Yale Liver Center, Yale University School of Medicine, New Haven, CT, USA; ⁴Department of Gastroenterology, Xinhua Hospital Affiliated to Shanghai Jiao Tong University School of Medicine, Shanghai, China; ⁵Shanghai Key Lab of Pediatric Gastroenterology and Nutrition, Shanghai, China

Received: 6 June 2022 | Revised: 15 June 2022 | Accepted: 15 June 2022 | Published: 22 June 2022

Abstract

Recent reports of acute hepatitis of unknown origin in previously healthy children have been increasing worldwide. The main characteristics of the affected children were jaundice and gastrointestinal symptoms. Their serum aminotransferase levels were above 500 IU/L, with negative tests for hepatitis viruses A–E. By 31 May 2022, the outbreak had affected over 800 children under the age of 16 years in more than 40 countries, resulting in acute liver failure in approximately 10%, including at least 21 deaths and 38 patients requiring liver transplantation. There was still no confirmed cause or causes, although there were several different working hypotheses, such as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), adenovirus serotype 41, or SARS-CoV-2 superantigen-mediated immune cell activation. Here, we review early observations of the 2022 outbreak which may inform diagnosis, treatment, and prevention in the context of an overlapping COVID-19 pandemic.

Citation of this article: Zhang LY, Huang LS, Yue YH, Fawaz R, Lim JK, Fan JG. Acute Hepatitis of Unknown Origin in Children: Early Observations from the 2022 Outbreak. *J Clin Transl Hepatol* 2022;10(3):522–530. doi: 10.14218/JCTH.2022.00281.

Keywords: Hepatitis; Acute liver failure; Liver transplantation; Pediatric; Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2); Adenovirus; Causality.

Abbreviations: AAV-2, adenovirus-associated virus 2; Ab, antibody; ACE2, angiotensin converting enzyme 2; AFP, alpha-fetoprotein; Ag, antigen; AIH, autoimmune hepatitis; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CDTR, Communicable Disease Threats Report; COVID-19, 2019 coronavirus disease; ECDC, European Centre for Diseases Prevention and Control; EUR, Europe region; HAdV, human adenovirus; HHV, human herpes virus; INR, international normalized ratio; LFT, liver function test; LT, liver transplantation; NGS, next-generation sequencing; PALF, pediatric acute liver failure; PHS, Public Health Scotland; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; TB, total bilirubin; TESSy, European Surveillance System; UKHSA, the UK Health Security Agency; WHO, World Health Organization.

#Contributed equally to this work.

*Correspondence to: Joseph K. Lim, Section of Digestive Diseases and Yale Liver Center, Yale University School of Medicine, 333 Cedar Street, LMP 1080, New Haven, CT 065208019, USA. E-mail: joseph.lim@yale.edu; Jian-Gao Fan, Department of Gastroenterology, Xinhua Hospital Affiliated to Shanghai Jiao Tong University School of Medicine, Shanghai Key Lab of Pediatric Gastroenterology and Nutrition, Shanghai 200092, China. ORCID: <https://orcid.org/0000-0001-7443-5056>. Tel/Fax: +86-21-2507-7340, E-mail: fanjiangao@xinhuaed.com.cn

Introduction

Acute hepatitis is typically caused by hepatotropic viruses, such as the hepatitis viruses A, B, C, D and E. Acute hepatitis of unknown origin generally refers to liver injury caused by exclusion of known infectious or non-infectious factors. Recently, an outbreak of acute non A–E hepatitis of unknown origin in children has caused widespread concern.

Public Health Scotland (PHS) was alerted to five children aged 3–5 years who were hospitalized with severe hepatitis of unknown origin on 31 March 2022.¹ According to the information reported by the World Health Organization (WHO), European Centre for Diseases Prevention and Control (ECDC) and various countries, as of 31 May 2022, at least 813 cases of acute hepatitis of unknown origin in children have been reported in more than 40 countries in five WHO Regions across Europe, America, and Asia (Fig. 1).^{2–4} In the UK, 222 cases have been identified, with an incidence of 3.30 per million, and in the USA, 216 cases have been reported, with an incidence of 0.66 per million (Table 1). Out of the 813 cases, at least 38 (4.7%) have required a liver transplantation (LT), and 21 (2.6%) deaths have been reported from 8 countries, most being reported from Indonesia ($n=7$) and the USA ($n=6$).

A rapid online survey was organized by a group of European clinical trial networks and the pediatric gastroenterology-hepatology and infectious diseases societies to examine case numbers of acute hepatitis of unknown origin among children in 24 countries from 1 January up to 18 April 2022 in comparison with the incidence during the previous 5 years; the investigators identified 5/17 European and 1/7 non-European countries with an elevation in probable cases of unexplained acute hepatitis, and severe cases were elevated in 5 European countries, particularly within the UK.⁵ Based on the ECDC Communicable Disease Threats Report (CDTR) and the Technical Briefing 3 reported by UK Health Security Agency, there has been a surge of new cases since the end of 2021 (Fig. 2).^{4,6} The WHO has assessed the risk at the global level as moderate, considering that recent cases are more clinically severe and a higher proportion develops acute liver failure compared with previous reports of acute hepatitis of unknown origin in children. Although hepatitis of unknown origin has been reported in the past, we still need to be more vigilant and to intensify the investigation.

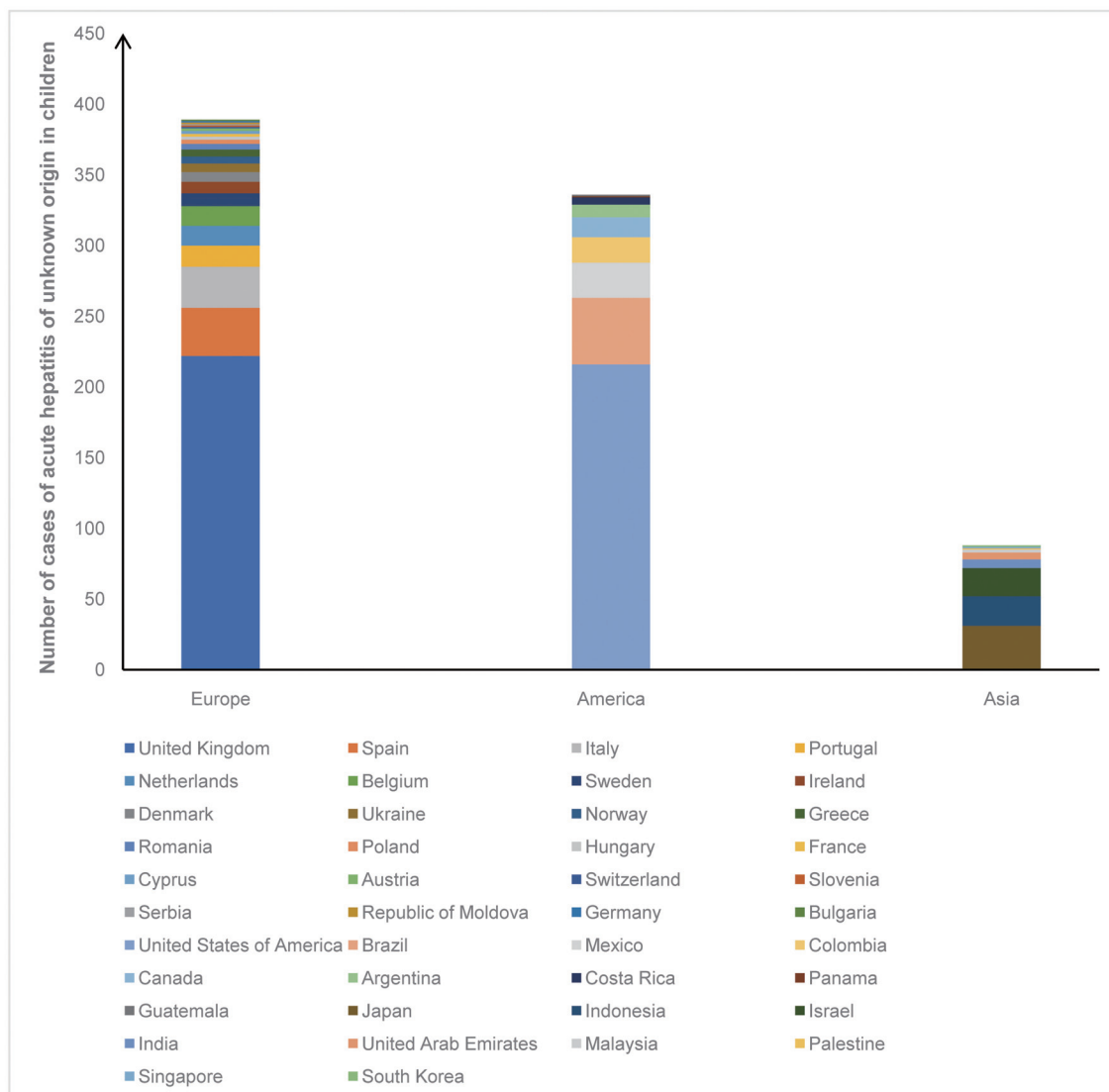


Fig. 1. Cases of acute hepatitis of unknown origin in children reported per country since 1 October 2021, as of 31 May 2022.

Clinical settings and pathology characteristics

Symptoms

These cases occurred in a sporadic manner in countries or regions without defined epidemiological association between cases, as only 3 had a history of close contact. No history of travel to the epidemic area and no defined exposures, such as to specific poisons, medicines, food or water, have been identified. Few affected children had a history of 2019 coronavirus disease (COVID-19) vaccination.

Most children with acute hepatitis of unknown origin were previously healthy children without underlying chronic disease. Therefore, hereditary metabolic diseases or genetic abnormalities may basically be excluded. These children were aged from 1 month to 16 years-old, predominantly aged 5 years or younger (75.4%), with a median age of 3 years (interquartile range: 2 to 4 years) and without sex difference.⁷ The most common presenting symptoms were gastrointestinal, accompanied by systemic symptoms

or respiratory symptoms reported in the preceding weeks of hospital admissions. Most of the cases sought medical attention after presentation of jaundice (yellowing of the eyes or skin, dark urine) (Fig. 3). Among the cases reported from the UK, which has a highest incidence, the rate of jaundice was as high as 68.8%, with pale stools reported in 42.7%.

The second most common reported symptom was vomiting (57.6%), followed by other gastrointestinal symptoms, including abdominal pain (36.1%) and nausea (25.7%). Other nonspecific symptoms included lethargy (48.6%), diarrhea (43.1%), fever (28.5%) and respiratory symptoms (18.1%).⁷ Among the nine cases reported in Alabama (USA), there were 7 cases of hepatomegaly, 1 case of splenomegaly, and 1 case of hepatic encephalopathy. The timing of these nonspecific symptoms and the chronological sequence of liver injury are quite important for etiology. Presenting respiratory and gastrointestinal symptoms commonly preceded the onset of jaundice by several weeks, although symptom onset data were reported in only 55.7% of cases. Current evidence reveals no reproducible pattern

Table 1. Incidence of acute hepatitis of unknown origin in children worldwide as of May 31, 2022

Continent	WHO region	Country	Case, <i>n</i>	Population, millions	Incidence, [<i>n</i> /millions]	LT, <i>n</i>	Death, <i>n</i>
Europe	EUR	Austria	2	8.92	0.22		
Europe	EUR	Belgium	14	11.56	1.21		
Europe	EUR	Bulgaria	1	6.93	0.14		
Europe	EUR	Cyprus	2	1.21	1.65		
Europe	EUR	Denmark	7	5.83	1.20		
Europe	EUR	France	2	67.39	0.03		
Europe	EUR	Germany	1	83.24	0.01		
Europe	EUR	Greece	5	10.80	0.46		
Europe	EUR	Hungary	2	9.75	0.21		
Europe	EUR	Ireland	8	6.20	1.29	1	3
Europe	EUR	Italy	29	59.55	0.49	1	
Europe	EUR	Netherlands	14	17.44	0.80	3	
Europe	EUR	Norway	5	5.38	0.93		
Europe	EUR	Poland	3	37.95	0.08		
Europe	EUR	Portugal	15	10.31	1.45		
Europe	EUR	Republic of Moldova	1	2.62	0.38		1
Europe	EUR	Romania	4	19.29	0.21		
Europe	EUR	Serbia	1	6.91	0.14		
Europe	EUR	Slovenia	1	2.10	0.48		
Europe	EUR	Spain	34	47.35	0.72	1	
Europe	EUR	Sweden	9	10.35	0.87		
Europe	EUR	Switzerland	1	8.64	0.12		
Europe	EUR	Ukraine	6	44.13	0.14		
Europe	EUR	UK	222	67.22	3.30	11	1
Asia	SEAR	India	6	1,357.18	0.00		
Asia	SEAR	Indonesia	21	273.50	0.08		7
Asia	EUR	Israel	20	9.22	2.17	2	
Asia	WPR	Japan	31	125.80	0.25		
Asia	WPR	Malaysia	2	32.37	0.06	1	
Asia	EMR	Palestine	1	4.80	0.21		1
Asia	WPR	Singapore	1	5.69	0.18		
Asia	WPR	South Korea	1	51.78	0.02		
Asia	EMR	United Arab Emirates	5	9.89	0.51		
Americas	AMR	Argentina	9	45.38	0.20	1	
Americas	AMR	Brazil	47	212.60	0.22		1
Americas	AMR	Canada	14	38.01	0.37	2	
Americas	AMR	Colombia	18	50.88	0.35		
Americas	AMR	Costa Rica	5	5.09	0.98		
Americas	AMR	Guatemala	1	16.86	0.06		
Americas	AMR	Mexico	25	128.90	0.19		1
Americas	AMR	Panama	1	3.93	0.25		
Americas	AMR	USA	216	329.50	0.66	15	6

AMR, region of the Americas; EMR, Eastern Mediterranean region; EUR, European region; SEAR, South-East Asian region; WPR, Western Pacific region.

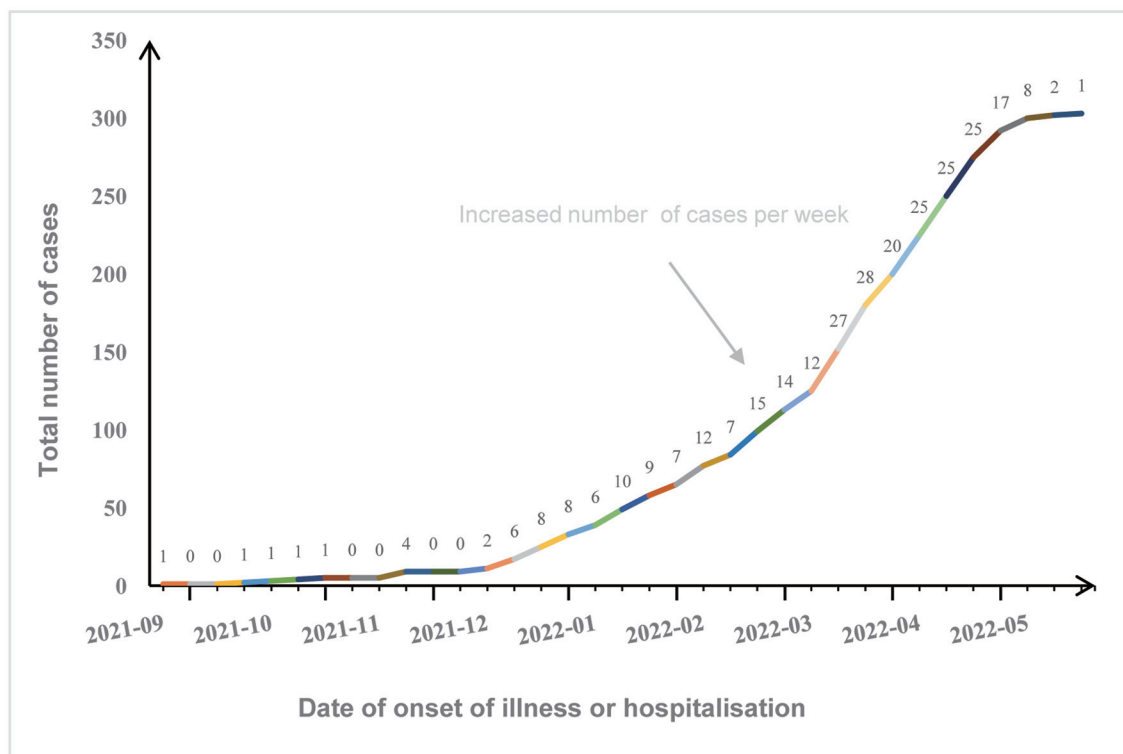


Fig. 2. Total number of cases by date of onset of illness or date of hospitalization according to the ECDC from the 39th week 2021 to the 21st week 2022.

with regard to the relationship between respiratory symptoms and the severity of acute hepatitis of unknown origin. Additional studies are needed to further elucidate the pathophysiological origins and implications on clinical outcomes.

Furthermore, the symptoms described were quite similar

to cases of pediatric acute liver failure (PALF), which have been reported in many countries over the past few years.^{8,9} PALF can be precipitated by disparate etiologies that include drug-induced, metabolic and genetic, infectious, immune-mediated, hemodynamic, and oncologic injuries, depending on the age of the child, and geographic and socioeconomic factors, etc. A definitive diagnosis was not determined in up to 50% of cases.^{10,11} Although it can be said that unexplained hepatitis has always existed, the clusters of cases and the higher than expected numbers in some countries makes this outbreak concerning.

Laboratory changes

Most affected children had abnormal findings on liver function tests (LFTs), with a predominant hepatocellular pattern and with serum alanine aminotransferase (ALT) or aspartate aminotransferase (AST) elevations greater than 500 IU/L, with a subset associated with bilirubin elevation. This pattern is consistent with virally mediated hepatocyte injury observed with hepatotropic and non-hepatotropic viral etiology seen in children, and without corresponding markers for immune-mediated, genetic, or metabolic liver injury. The criteria of case definition is based on 500 IU/L of ALT or AST, but the values reported are not exhaustive. In the nine children in Alabama, serum ALT ranged from 603 to 4,696 IU/L (median: 1,724 IU/L), serum AST ranged from 447 to 4,000 IU/L (median: 1,963 IU/L), and total bilirubin (TB) ranged from 0.23 to 13.5 mg/dL.¹² This indicated that the hepatocytes of affected children may be severely damaged. Except for TB, indicators for liver failure have been rarely reported – for example, albumin indicating liver synthesis, international normalized ratio (INR) indicating coagulation function, blood ammonia warning of hepatic encephalopa-

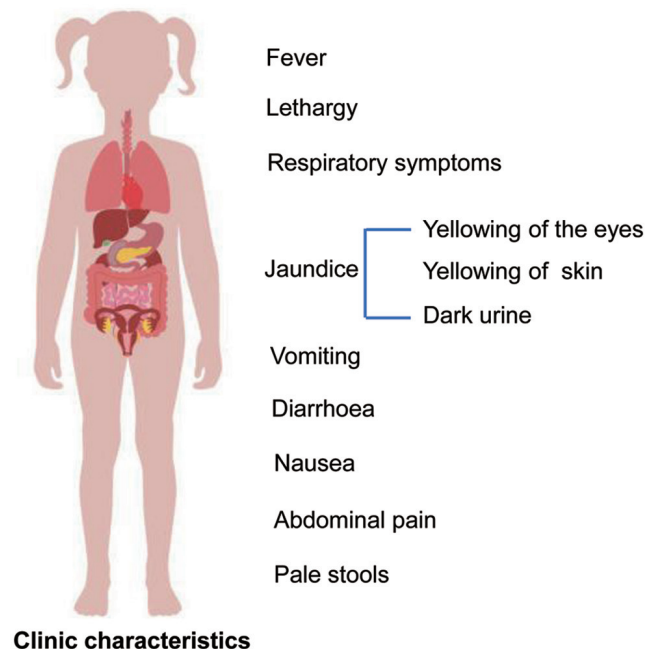


Fig. 3. Clinical characteristics of acute hepatitis of unknown origin in children.

thy, alpha-fetoprotein (AFP) indicating regenerative capacity, etc. Routine tests such as blood routine and those for C-reactive protein, inflammatory factors, immunoglobulin G and other indicators at the time of onset were also rarely reported in the literature. These indicators may help to determine the etiology of infection, inflammation, immune status, etc. The absence of these data will have a certain impact on our ability to identify the etiology. The WHO has advised that available samples should be processed for all cases meeting the case definition to conduct tests for further investigations.

Pathological changes in liver

Liver biopsies have been performed in a limited number of cases and no detailed information have been provided, including presentation of inflammation, degree of liver fibrosis, type of necrosis, infiltrating cells, rosette formation, etc. It is difficult to identify the cause based on limited information of pathology changes. The histopathological changes of acute viral hepatitis are generally extensive degeneration of hepatocytes, necrosis, infiltration of inflammatory cells in the lobule and portal area, and cholestasis and bile embolism. Histopathology from six patients in Alabama demonstrated various degrees of hepatitis, with no viral inclusions, no immunohistochemical evidence of human adenovirus (HAdV), and no viral particles identified on electron microscopy.¹² As so far, there has been no evidence for direct damage of hepatotropic virus, or HAdV, or severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in children with acute hepatitis of unknown origin. There are a few reports of HAdV hepatitis in immunocompetent children, but the HAdV infection was difficult to confirm by histopathology.¹³ Liver injury has been frequently observed in patients with COVID-19 infection with a predominant hepatocellular pattern of injury, but liver failure and obvious intrahepatic cholestasis are rare in the absence of preexisting liver disease.¹⁴ Pathological and electron microscopic findings revealed typical coronavirus particles in the cytoplasm of hepatocytes from two cases of COVID-19. The predominant histological features of SARS-CoV-2-infected liver were massive apoptosis and binuclear hepatocytes, which was inconsistent with the pathology described in recent acute hepatitis of unknown origin.¹⁵

Most of the pathological liver tissue was acquired several weeks after the onset of symptoms, and it probably does not represent the early manifestations of the injury; moreover, the destruction of enterohepatic circulation after abnormal liver function may lead to the translocation of bacteria and viruses from the colonized intestinal tract to the liver, so it is not necessarily the virus present that caused the liver disease. Immune impairment due to viral infection or other etiologies often appears several weeks or months after the recovery of infection. Liver biopsy samples from cases reported by Schneider Children's Medical Center in Israel presented inflammatory cells in the portal area of the liver, indicating an interface hepatitis similar to autoimmune hepatitis (AIH), without the characteristic of autoimmune disease observed in the blood tests.¹⁶ PALF due to type 2 AIH has been reported in the context of SARS-CoV-2 infection.¹⁷ In fact, many hepatotropic viruses may cause hepatocyte damage through immune-mediated inflammatory reactions. Pathological changes caused by SARS-CoV-2-related immune response cannot be excluded as a co-factor or alternatively an independent factor for acute hepatitis of unknown origin in children, which can be commonly seen with hepatotropic virus infections. Since the underlying mechanisms of the hepatitis of unknown origin remain unclear, histopathology of liver requires detailed interpretation.

Case definitions

The definition of acute hepatitis in children in early reports during the 2022 outbreak have not been standardized across countries and regions.¹⁸ On April 23, 2022, the WHO abolished the concept of "confirmed case" in an updated standard and converted it into a definition of "suspected case".¹⁹ There are currently three main case definitions, namely the WHO Working Case Definition, England, Wales, Northern Ireland Case Definition, and Scotland Case Definition (Table 2). They are basically similar with a non-hepA-E acute hepatitis of unknown cause, with serum transaminase greater than 500 IU/L (AST or ALT), and with no consideration of the value of TB. The WHO defines the onset of hepatitis as 1 October 2021 and England as 1 January 2022. The WHO further defines the age of onset as under 16 years for a probable case and England as under 10 years for a confirmed case and 11 to 15 years for a possible case. The definition of "Epi-linked" case depends on an epidemiological history of close contact. Scotland has removed possible and epi-linked cases and added epidemiological history to the definition of confirmed cases. Statistics will vary due to case definitions. In order to obtain more meaningful statistical data, it is recommended to further unify and simplify the case definition worldwide.

Outcomes

To date, cases of acute hepatitis of unknown origin in children has continued to increase in some countries. Most of these cases have required hospitalization and the overall severe rate was as high as 10%. At least 38 children have required a LT due to liver failure, and 21 (2.6%) deaths have been reported. However, limited information on outcome has been reported. The Europe region (EUR), as the WHO region with the largest number of affected cases and involved countries, had provided relatively more information.

According to the latest Joint Surveillance Bulletin by the ECDC-WHO Regional Office for Europe on cases from the EUR which has been reported through the European Surveillance System (TESSy), 180 of the 305 probable cases of acute hepatitis of unknown origin in children aged 16 years and below had reported information on outcome, as of 31 May 2022.⁴ Of these, 148 have recovered, while 31 remain under medical care. Of the 169 cases with information, 23 (13.6%) were admitted to an intensive care unit. Of the 131 cases with available information, 14 (10.7%) have received a LT. There was one death associated with this disease. Due to limited reports on follow-up beyond hospitalization, long-term natural history and outcomes are poorly characterized.

Potential etiology and pathogenesis

Adenovirus-related

Previously, the UK Health Security Agency (UKHSA) suspected a possible association with HAdV infection, as this was the most frequently detected virus in tested samples.²⁰ Experts discussed its precise role in acute hepatitis in immunocompetent individuals.²¹ According to the modified Koch's postulates, we may list the evidence as follows to see whether HAdV is the underlying pathogen.

Supported evidence include the following: (1) HAdV was detected in whole blood specimens, with the highest positivity rate of 68.6% in the EUR, suggesting a role of pathogenic microorganisms; (2) Although a significant in-

Table 2. Three case definitions of acute hepatitis of unknown origin in children

	WHO working case definition	England, Wales, Northern Ireland case definition	Scotland case definition
Confirmed	N/A at present	A person presenting since 1 January 2022 with an acute hepatitis which is not due to hepatitis A–E viruses, or an expected presentation of metabolic, inherited or genetic, congenital or mechanical cause [note 1] with serum transaminase greater than 500 IU/L (AST or ALT), who is 10 years-old and under.	A person presenting with a serum transaminase greater than 500 IU/L (AST or ALT) without any known cause [note 3], who is 10 years of age and under or a contact of any age of a confirmed case, since 1 January 2022.
Probable/ Possible	A person presenting with an acute hepatitis [non-hepA–E (if hepatitis A–E serology results are awaited, but other criteria met, these can be reported and will be classified as “pending classification”. Cases with other explanations for their clinical presentation are discarded)] with serum transaminase >500 IU/L (AST or ALT), who is 16 years or younger, since 1 October 2021.	A person presenting with an acute hepatitis since 1 January 2022 with an acute hepatitis which is not due to hepatitis A–E viruses or an expected presentation of metabolic, inherited/genetic, congenital or mechanical cause [note 1] with serum transaminase greater than 500 IU/L (AST or ALT), who is 11 to 15 years-old.	
Epi-linked	A person presenting with an acute hepatitis [non-hepA–E (if hepatitis A–E serology results are awaited, but other criteria met, these can be reported and will be classified as “pending classification”. Cases with other explanations for their clinical presentation are discarded)] of any age who is a close contact of a probable case, since 1 October 2021.	A person presenting since 1 January 2022 with an acute hepatitis (non-hepatitis A to E) who is a close contact of a confirmed case.	

crease in the rate of HAdV infection was also observed in healthy children in this season, and HAdV detection was significantly higher in patients than in healthy individuals; (3) HAdV infection was detected in all nine children in Alabama, with the DNA levels being 12-times higher in children who received LT than in those who did not, and most of the HAdV stains with typing information were confirmed to be the same: HAdV type 41.

Unsupported evidence includes the following: (1) No information about the levels of specific antibodies during the outbreak; (2) No histological demonstration of pathognomonic lesions, such as inclusions in liver biopsy; (3) Although adenovirus has been detected, the viral load is low, which may due to the detection techniques [such as next-generation sequencing (NGS)]. As a result, it was impossible to analyze the virus mutation or genetic recombination by whole genome sequencing using blood or liver biopsy tissue; (4) Adenovirus hepatitis have been mainly seen in people in a state of immunosuppression, such as those with malignant tumors or who have undergone organ transplantation.²² Seldom cases of adenovirus infection-induced liver failure in healthy children have been reported. However, a vast majority of children with acute hepatitis of unknown origin were previously healthy.

Interestingly, it has been hypothesized that adenovirus may be responsible for severe hepatitis in children with an auxiliary factor affecting children of specific age groups, which might make adenovirus infection more severe or cause some immunopathological changes. Possible ancillary factors include increased susceptibility of children to common childhood viruses due to exposure and lack of ex-

posure related to preventive measures taken during the COVID-19 pandemic, or previous exposure to other viruses, including one or more variants of COVID-19. COVID-19 has exposed children to the childhood virus that “should be exposed to” at a normal age. Some experts have suggested paying attention to the impact of the “immune gap” during the COVID-19 epidemic.²³ There were also differing opinions, however; the current protective measures, such as wearing masks, gathering less, and using alcohol, do not mean that people were no longer exposed to microorganisms, and were insufficient to affect people’s immune system. In addition, it has been almost 2 years since the western countries lifted the large-scale sealing control. Therefore, additional investigation is needed to further examine and validate the etiology, genomics, liver pathology, and immunohistochemistry to clarify the role of HAdV infection in the 2022 outbreak.²⁴ We also recommend conducting a cohort study for comparing the disease manifestations between children with detectable and non-detectable HAdV in blood.

Coronavirus-related

As of 31 May 2022, SARS-CoV-2 was detected (positive result) in 11.8% of the 204 cases tested by PCR and in 67.6% of the 34 cases tested by serology from the EUR, but the data for other countries are incomplete. The first two cases reported by Israel were hospitalized for hepatitis as early as February 2021, and the other two were admitted from August to September 2021, even earlier than

cases in Alabama. If the hepatitis could be explained by viral infection, considering the span expanding 1 year, the first consideration will be SARS-CoV-2 sweeping worldwide. After all, the major instigating infection of the past year has been SARS-CoV-2, and there are grounds for assuming it is connected to these hepatitis cases. Like other RNA viruses, SARS-CoV-2 has evolved rapidly, producing mutants that differ significantly from ancestral strains, and being associated with increased transmissibility and viral virulence, decreased diagnostic sensitivity, and potential influence on vaccination, such as Alpha, Beta, Gamma, Delta and Omicron variants.²⁵ The current endemic variant in Europe and the Americas is the SARS-CoV-2 Omicron variant, which was designated by WHO on 26 November 2021.²⁶ The Omicron variant has a total of 60 mutations and exhibits a higher transmissibility than the Delta variant. At present, the primary mutations of the Omicron variant are in the S1 subunit of S protein, where the virus binds to the human angiotensin converting enzyme 2 (ACE2) receptor and antibody recognition blocks viral invasion, and thus may decrease viral infectivity and transmissibility but increase the degree of immune escape.²⁷ The population infection rate of the Omicron variant is much higher than estimated, especially among unvaccinated children under age 5 years. The surge of acute severe hepatitis happened to coincide with the time when the Delta variant alternated with the Omicron variant. Based on our clinical experience, Chinese children infected with the Omicron variant commonly present with gastrointestinal symptoms, such as vomiting, diarrhea, abdominal pain, and anorexia, potentially reflective of gut tropism of SARS CoV-2 and ACE2 expression within the small intestine. However, despite high ACE2 expression within hepatocytes and cholangiocytes, acute hepatitis and jaundice are rare with COVID-19.²⁸ Therefore, a direct relationship between the COVID-19 Omicron variant and acute non-A-E hepatitis appears unlikely.

Although there is inadequate evidence to support a causative role, an intermediate link between Omicron and hepatocellular injury may be considered, including co-infection with other viruses, such as HAdV type 41. Based on the “superantigen hypothesis” of Petter Brodin, acute hepatitis in children may result from the emergence of a viral reservoir in the intestine after SARS-CoV-2 followed by adenovirus infection, which in turn triggers an aberrant host immune-mediated hepatitis.²⁹ Interestingly, severe hepatitis with abdominal symptoms suggestive of a gastrointestinal virus was reported in 1923 following the 1918 influenza pandemic, which was considered to be related to increased susceptibility to viruses persons had not been exposed to during social containment. Based on portal vein blood flow, directly coming from the intestine, and the described clinical presentation of abdominal pain and vomiting, such a trigger might reasonably stem from enteric viruses, such as the adenovirus type 41.³⁰ This parallelism supports further investigation of a possible role for viral pathogens in the 2022 outbreak, and may additionally account for the absence of acute non-A-E hepatitis in countries which have adopted strict quarantine and masking policies, such as China. In addition, some experts hypothesize that an immune-mediated hepatocyte injury secondary to the infection with SARS-CoV-2 may be possible. According to an Israeli hepatologist, five of the twelve cases were classified as a sequelae of COVID-19, with an interval of approximately 3.5 months from the new coronavirus infection to the onset of hepatitis, which were actually an AIH without atypical serological test results. Most recently, Chinese experts hypothesized that strains infected with the ORF1ab^{VVVNASN} mutation may cause autoimmune T-cell responses in patients through “molecular mimicry” and may be associated with the outbreak of unknown hepatitis. Generally speaking, there are several immune-related hypotheses that need further ex-

perimental verification in order to clarify the pathology of the unexplained hepatitis in children.

Other infections

In addition to HAdV and SARS-CoV-2, other pathogens were also detected and include human herpes virus (HHV) 7, HHV6, Epstein-Barr virus, cytomegalovirus, respiratory syncytial virus, enterovirus, influenza A virus, etc. Adenovirus-associated virus 2 (AAV-2) has also been detected in a small number of cases in the UK by using meta-genomic analysis of liver and blood samples. Multiple viruses detected may indicate colonization of intestinal pathogens or infection secondary to liver failure. Some researchers have speculated the possible emergence of an unidentified new unknown hepatotropic or non-hepatotropic virus, although this has not yet been reported.

Non-infectious factors

Non-infectious factors may include certain toxins, food, drugs, or environmental exposures. However, there has been no confirmed epidemiologic evidence among reported cases across countries or regions. In the UK and USA, no common exposures (such as to paracetamol) have been identified based on toxicology studies. In these cases of hepatitis, no family has been reported. COVID-19 vaccination was considered to have no relation with the acute hepatitis, because the vast majority of children were not vaccinated against COVID-19. However, the possibility of a hepatocyte damage after natural immunity through infection cannot be ruled out.

Management

When children with jaundice or gastrointestinal symptoms seek medical treatment, clinicians should consider prompt laboratory evaluation with LFTs and coagulation markers (prothrombin time/INR) to facilitate timely identification of potential cases of acute hepatitis of unknown origin. Among children with evidence of acute hepatitis, standard diagnostic testing should be pursued, including evaluation for hepatotropic (hepatitis A IgM antibody (Ab), hepatitis B surface antigen (Ag), hepatitis B core Ab IgM, hepatitis C Ab, hepatitis D Ab IgM, hepatitis E Ab IgM) and non-hepatotropic virus infections (e.g., cytomegalovirus, Epstein-Barr virus, herpes simplex virus, adenovirus), as well as alternative etiologies for acute hepatitis, such as drug-induced liver injury, ischemic hepatitis, AIH, etc. If alternative etiologies are not identified, clinicians may consider reporting to public health authorities for investigation of possible acute non-A-E hepatitis of unknown origin. In children with very high elevation of liver transaminases (ALT or AST >500 IU/L) and/or evidence of coagulation dysfunction, consideration should be given for timely referral to a liver specialty center, including those with capacity for LT. Although no evidence-based therapies have been established in the management of acute hepatitis of unknown origin during the 2022 outbreak, supportive measures and close clinical and laboratory monitoring are prudent, including hospitalization for those with evidence of fulminant hepatitis or acute liver failure. In the absence of evidence, clinicians may consider hepatoprotective drugs and/or artificial liver support systems as a bridge to LT, which has represented the only life-saving intervention reported to date. Unfortunately, some children have died before an organ became available.³⁰

Due to incomplete understanding of the origin, transmis-

sion, and pathogenesis of acute hepatitis of unknown origin in children, it remains premature to provide evidence-based guidance on preventive measures. Although a viral origin is suspected, available data do not yet strongly support a highly communicable infection that may be associated with a public health epidemic. However, standard precautions adopted from the COVID-19 pandemic are prudent, including wearing a mask, regular handwashing, respiratory hygiene, and social distancing, as well as adherence to age-appropriate childhood vaccinations. Public health authority initiatives to educate and counsel the general public on the 2022 outbreak of acute hepatitis of unknown origin may help minimize fear and anxiety.³¹

Future perspective

The 2022 outbreak of acute hepatitis of unknown origin has raised global public health attention due to its unusual severity with high rates of hospitalization, liver failure, need for LT, and liver-related mortality. Data emerging from the UK, USA, and WHO confirm an ongoing expansion of cases, with a total of 813 affected children across more than 40 countries as of 31 May 2022, and preliminary investigations have identified a potential association with infection of HAdV, SARS-CoV-2, or other virus. International clinical, epidemiological and virological surveillance data are being collected and will provide vital insights into origin, pathogenesis, natural history, and outcomes, which will collectively inform future guidelines on testing, diagnosis, and treatment. We call for the establishment of a global biological sample bank for children with acute hepatitis of unknown origin, formulation of standardized rules and regulations for the operation and management of the sample bank, and provision of experimental samples and detailed clinical data using standardized definitions, which will facilitate coordinated research across countries and regions. No case has been reported in China to date. However, that does not mean that no cases occurred. Experts in China have already taken steps. On May 25, 2022, experts in mainland China set up a collaborative group for acute severe hepatitis of unknown origin and held a project kick-off meeting. In cases of hepatitis in children, experts from the collaborative group can be invited to consult for probable cases and conduct related clinical examinations and laboratory tests, including genetic tests. Meanwhile, they have compiled a guideline on diagnosis and treatment for clinicians.

Funding

Dr. Jian-Gao Fan wishes to acknowledge support from the National Key Research and Development Program of China (2021YFC2700802) and the National Natural Science Foundation of China (81873565, 82170593).

Conflict of interest

JGF has been an associate editor of *Journal of Clinical and Translational Hepatology* since 2022, JKL has been an executive associate editor of *Journal of Clinical and Translational Hepatology* since 2022. The other authors have no conflict of interests related to this publication.

Author contributions

Writing of the manuscript (LYZ and LSH), analysis and map-

ping (YHY), revision of the manuscript (RF and JKL), and developing the idea for the article and critically reviewing it (JGF). All authors read and approved the final version of the manuscript.

References

- Marsh K, Tayler R, Pollock L, Roy K, Lakha F, Ho A, et al. Investigation into cases of hepatitis of unknown aetiology among young children, Scotland, 1 January 2022 to 12 April 2022. *Euro Surveill* 2022;27(15). doi:10.2807/1560-7917.ES.2022.27.15.2200318, PMID:35426362.
- ecdc.europa.eu [Internet]. Solna: European Centre for Disease Prevention and Control; Newsroom; Epidemiological update issued 19 May 2022: hepatitis of unknown aetiology in children; c2022 [updated 19 May 2022; cited 4 June 2022]. Available from: <https://www.ecdc.europa.eu/en/news-events/epidemiological-update-issued-19-may-2022-hepatitis-unknown-aetiology-children>.
- who.int [Internet]. Geneva: World Health Organization; Disease Outbreak News; Acute hepatitis of unknown aetiology in children - Multi-country; c2022 [updated 27 May 2022; cited 4 June 2022]. Available from: <https://www.who.int/emergencies/disease-outbreak-news/item/DON-389>.
- ecdc.europa.eu [Internet]. Solna: European Centre for Disease Prevention and Control/WHO Regional Office for Europe; Hepatitis of Unknown Aetiology in Children, Joint Epidemiological overview, 31 May, 2022; c2022 [updated 31 May 2022; cited 4 June 2022]. Available from: <https://cdn.ecdc.europa.eu/novhhep-surveillance>.
- van Beek J, Fraaij P, Giaquinto C, Shingadia D, Horby P, Indolfi G, et al. Case numbers of acute hepatitis of unknown aetiology among children in 24 countries up to 18 April 2022 compared to the previous 5 years. *Euro Surveill* 2022;27(19). doi:10.2807/1560-7917.ES.2022.27.19.2200370, PMID:35551703.
- ecdc.europa.eu [Internet]. Solna: European Centre for Disease Prevention and Control; Publications & data; Communicable disease threats report, 15-21 May 2022, week 20; c2022 [updated 20 May 2022; cited 4 June 2022]. Available from: <https://www.ecdc.europa.eu/en/publications-data/communicable-disease-threats-report-15-21-may-2022-week-20>.
- gov.uk [Internet]. London: UK Health Security Agency; Research and analysis; Acute hepatitis: technical briefing. Technical briefing document on the investigation into acute hepatitis cases of unknown aetiology in children in England; c2022 [updated 20 May 2022; cited 4 June 2022]. Available from: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/1077027/acute-hepatitis-technical-briefing_3.pdf.
- Grana A, Aldea CO, Burac L, Delean D, Bulata B, Sirbe C, et al. Etiology and Outcome of Acute Liver Failure in Children-The Experience of a Single Tertiary Care Hospital from Romania. *Children (Basel)* 2020;7(12):E282. doi:10.3390/children7120282, PMID:33317098.
- Chiou FK, Logarajah V, Ho CWW, Goh LS, Karthik SV, Aw MM, et al. Demographics, aetiology and outcome of paediatric acute liver failure in Singapore. *Singapore Med J* 2021. doi:10.11622/smedj.2021138, PMID:34602977.
- Squires JE, McKiernan P, Squires RH. Acute Liver Failure: An Update. *Clin Liver Dis* 2018;22(4):773-805. doi:10.1016/j.cld.2018.06.009, PMID:30266162.
- Mendizabal M, Dip M, Demirdjian E, Lauferman L, Lopez S, Minetto J, et al. Changing Etiologies and Prognostic Factors in Pediatric Acute Liver Failure. *Liver Transpl* 2020;26(2):268-275. doi:10.1002/lt.25658, PMID:31606931.
- Baker JM, Buchfellner M, Britt W, Sanchez V, Potter JL, Ingram LA, et al. Acute Hepatitis and Adenovirus Infection Among Children - Alabama, October 2021-February 2022. *MMWR Morb Mortal Wkly Rep* 2022;71(18):638-640. doi:10.15585/mmwr.mm7118e1, PMID:35511732.
- Matoq A, Salahuddin A. Acute Hepatitis and Pancytopenia in Healthy Infant with Adenovirus. *Case Rep Pediatr* 2016;2016:8648190. doi:10.1155/2016/8648190, PMID:27340581.
- Li J, Fan JG. Characteristics and Mechanism of Liver Injury in 2019 Coronavirus Disease. *J Clin Transl Hepatol* 2020;8(1):13-17. doi:10.14218/JCTH.2020.00019, PMID:32274341.
- Wang Y, Liu S, Liu H, Li W, Lin F, Jiang L, et al. SARS-CoV-2 infection of the liver directly contributes to hepatic impairment in patients with COVID-19. *J Hepatol* 2020;73(4):807-816. doi:10.1016/j.jhep.2020.05.002, PMID:32437830.
- haaretz.com [Internet]. Tel Aviv: Haaretz ; Israel News. Explainer; Everything You Need to Know About the Hepatitis Outbreak Among Children; c2022 [updated 21 April 2022; cited 4 June 2022]. Available from: <https://www.haaretz.com/israel-news/everything-you-need-to-know-about-the-hepatitis-outbreak-among-children-1.10754895>.
- Osborn J, Szabo S, Peters AL. Pediatric Acute Liver Failure Due to Type 2 Autoimmune Hepatitis Associated With SARS-CoV-2 Infection: A Case Report. *JPGN Rep* 2022;3(2):e204. doi:10.1097/PJG9.000000000000204, PMID:35505826.
- Mücke MM, Zeuzem S. The recent outbreak of acute severe hepatitis in children of unknown origin - what is known so far. *J Hepatol* 2022;S0168-8278(22)00271-9. doi:10.1016/j.jhep.2022.05.001, PMID:35533802.
- World Health Organization (23 April 2022). Disease Outbreak News; Multi-Country - Acute, severe hepatitis of unknown origin in children. Available from: <https://www.who.int/emergencies/disease-outbreak-news/item/multi-country-acute-severe-hepatitis-of-unknown-origin-in-children>.

- [20] Iacobucci G. Acute hepatitis is identified in more children, but cause remains elusive. *BMJ* 2022;377:o1156. doi:10.1136/bmj.o1156, PMID:35523450.
- [21] Hakim MS. The recent outbreak of acute and severe hepatitis of unknown etiology in children: A possible role of human adenovirus infection? *J Med Virol* 2022. doi:10.1002/jmv.27856, PMID:35577525.
- [22] Onda Y, Kanda J, Sakamoto S, Okada M, Anzai N, Umadome H, *et al*. Detection of adenovirus hepatitis and acute liver failure in allogeneic hematopoietic stem cell transplant patients. *Transpl Infect Dis* 2021;23(2):e13496. doi:10.1111/tid.13496, PMID:33075208.
- [23] Samarasekera U. Mystery outbreak of severe acute hepatitis in children. *Lancet Gastroenterol Hepatol* 2022:S2468-1253(22)00159-5. doi:10.1016/S2468-1253(22)00159-5, PMID:35500588.
- [24] Zhu Z, Zhang NY, Mao Y, Xu WW. [Consideration on the emerging of severe acute hepatitis cases with of unknown etiology in children worldwide]. *Zhonghua Yu Fang Yi Xue Za Zhi* 2022;56:1-3. doi:10.3760/cma.j.cn112150-20220427-00423, PMID:35484645.
- [25] Ning Q, Wu D, Wang X, Xi D, Chen T, Chen G, *et al*. The mechanism underlying extrapulmonary complications of the coronavirus disease 2019 and its therapeutic implication. *Signal Transduct Target Ther* 2022;7(1):57. doi:10.1038/s41392-022-00907-1, PMID:35197452.
- [26] Wolter N, Jassat W, Walaza S, Welch R, Moultrie H, Groome M, *et al*. Early assessment of the clinical severity of the SARS-CoV-2 omicron variant in South Africa: a data linkage study. *Lancet* 2022;399(10323):437-446. doi:10.1016/S0140-6736(22)00017-4, PMID:35065011.
- [27] Gupta R. SARS-CoV-2 Omicron spike mediated immune escape and tropism shift. *Res Sq* 2022. doi:10.21203/rs.3.rs-1191837/v1, PMID:35075452.
- [28] Louis TJ, Qasem A, Abdelli LS, Naser SA. Extra-Pulmonary Complications in SARS-CoV-2 Infection: A Comprehensive Multi Organ-System Review. *Microorganisms* 2022;10(1):153. doi:10.3390/microorganisms10010153, PMID:35056603.
- [29] Brodin P, Arditi M. Severe acute hepatitis in children: investigate SARS-CoV-2 superantigens. *Lancet Gastroenterol Hepatol* 2022:S2468-1253(22)00166-2. doi:10.1016/S2468-1253(22)00166-2, PMID:35576952.
- [30] de Kleine RH, Lexmond WS, Buescher G, Sturm E, Kelly D, Lohse AW, *et al*. Severe acute hepatitis and acute liver failure of unknown origin in children: a questionnaire-based study within 34 paediatric liver centres in 22 European countries and Israel, April 2022. *Euro Surveill* 2022;27(19). doi:10.2807/1560-7917.ES.2022.27.19.2200369, PMID:35551705.
- [31] Khan YH, Mallhi TH, Alanazi AS, Butt MH, Khan A, Salman M. Outbreak of acute hepatitis of unknown etiology in children: The critical role of health-care professionals in neutralizing misleading narratives during the COVID-19 pandemic. *J Med Virol* 2022. doi:10.1002/jmv.27819, PMID:35488384.