



Liver abnormalities following SARS-CoV-2 infection in children 1 to 10 years of age

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ABSTRACT

Objective Beginning in October 2021 in the USA and elsewhere, cases of severe paediatric hepatitis of unknown aetiology were identified in young children. While the adenovirus and adenovirus-associated virus have emerged as leading aetiological suspects, we attempted to investigate a potential role for SARS-CoV-2 in the development of subsequent liver abnormalities.

Design We conducted a study using retrospective cohorts of deidentified, aggregated data from the electronic health records of over 100 million patients contributed by US healthcare organisations.

Results Compared with propensity score matched children with other respiratory infections, children aged 1–10 years with COVID-19 had a higher risk of elevated transaminases (HR (95% CI) 2.16 (1.74 to 2.69)) or total bilirubin (HR (95% CI) 3.02 (1.91 to 4.78)), or new diagnoses of liver diseases (HR (95% CI) 1.67 (1.21 to 2.30)) from 1 to 6 months after infection. Patients with pre-existing liver abnormalities, liver abnormalities surrounding acute infection, younger age (1–4 years) or illness requiring hospitalisation all had similarly elevated risk. Children who developed liver abnormalities following COVID-19 had more pre-existing conditions than those who developed abnormalities following other infections.

Conclusion These results indicate that SARS-CoV-2 may prime the patient for subsequent development of liver infections or non-infectious liver diseases. While rare (~1 in 1000), SARS-CoV-2 is a risk for subsequent abnormalities in liver function or the diagnosis of diseases of the liver.

INTRODUCTION

In early 2022, reports emerged of clusters of severe hepatitis not associated with any of the usual viruses in young children in Scotland and soon after, the USA and elsewhere in the UK.^{1–4} The coincidence in timing of this outbreak with the rise of childhood cases of COVID-19 as the Omicron variant spread made SARS-CoV-2 a tempting explanation for this new disease. For other viral infections, such as influenza, Epstein-Barr virus, Coxsackie B and SARS/MERS, damage to the liver is well documented and is often considered to result from T-cell-mediated

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Clusters of severe hepatitis in children in 2022 coincident with the increase in COVID-19 infections in children raised the question of the contribution of SARS-CoV-2 to the hepatitis outbreak, though it was soon determined that SARS-CoV-2 was not the primary aetiological agent.

WHAT THIS STUDY ADDS

⇒ SARS-CoV-2 may prime the patient for subsequent development of liver infections or non-infectious liver diseases.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Despite the mild initial disease in children, there may be longer-term consequences of COVID-19, such as liver abnormalities, which warrant further investigation.

attack without necessarily the presence of the virus or viral antigens in the liver.⁵ In addition, many viruses are known to leave patients vulnerable to secondary invaders. However, it soon became apparent that, although SARS-CoV-2 antibodies could be demonstrated in over half the patients, it was not possible to implicate the virus directly in severe liver damage.⁶ Subsequent studies have suggested that the culprit in the outbreak of severe hepatitis might be adenovirus type 41 species F (Ad-F41) or Ad-F41 plus adeno-associated virus 2.^{7,8} Some series indicate that as many as 80% of patients have evidence of infection with Ad-F41,⁹ so despite the absence of the usual pathologic signature of adenoviral hepatitis, inclusion bodies, this explanation seems the most likely. The reason for the sudden outbreak at widely separated geographical locations, however, is unclear. Concern persists that our lack of understanding of this outbreak may leave us less able to cope effectively with another such episode, should it occur.

The timing of the hepatitis outbreak coincident with the surge in COVID-19 in children suggested some role for SARS-CoV-2 in priming children for the devastating outbreak.¹⁰ In adults, SARS-CoV-2 is known to produce lingering alterations in the immune system that can also lead to autoimmune phenomena.^{11 12} In children, viral persistence has been detected in the gut with prolonged shedding in stool. This ongoing shedding has been postulated as a possible trigger for immune activation that may have affected the response to subsequent adenovirus infection.^{10 13–15}

To investigate the possible role of SARS-CoV-2 in liver dysfunction in children, we examined the risk for protracted abnormalities in liver enzymes or bilirubin, or new diagnoses of hepatitis or liver disease, in children following diagnosis of COVID-19 compared with children who had other respiratory infections (ORIs).

METHODS

We conducted a study using retrospective cohorts of aggregated and deidentified electronic health record (EHR) data from over 100 million patients on the TriNetX analytics platform contributed by 59 healthcare organisations (HCOs) in the USA representing a diverse population geographically, demographically and in insurance status. We employed the US Collaborative Network for the primary analyses. For additional privacy protection, some HCOs that contribute to the network date-shift individual EHRs from 1 to 365 days on the calendar while maintaining the relative timing of clinical data within each EHR. Analyses investigating secular trends during the pandemic or comparing periods predominated by SARS-CoV-2 variants (Delta, Omicron) were performed in the Research USA Minimal Date Shift Network including only HCOs that contributed minimally shifted EHR data (0–7 days). Built-in analytical functions allow for analysis of patient-level data in aggregate form only, without individual protected health information. See online supplemental eMethods for details. The Metro-Health System Institutional Review Board has designated the use of deidentified aggregated data on the TriNetX platform in ways such as described in this manuscript as not involving human participants. The study design and results reporting followed the guidelines of the Strengthening the Reporting of Observational Studies in Epidemiology.

Cohorts

The study population was composed of children aged 1–10 years at the time of the diagnosis of a respiratory infection (COVID-19 or a non-COVID-19 respiratory infection) between 1 January 2020 and 31 December 2022. The lower age limit was selected to avoid perinatal complications and upper age limit was selected because reports of the surge in hepatitis of unknown origin in children reported very few cases above the age of 10 years. A subpopulation of children aged 1–4 years was

also analysed because most cases described during the outbreak were in this age range. Criteria for inclusion in the COVID-19 cohort had either International Statistical Classification of Diseases and Related Health Problems, 10th Revision (ICD-10) code for COVID-19 (U07.1), J12.81 (pneumonia due to SARS-associated COVID-19) or J12.82 (pneumonia due to COVID-19) as an encounter diagnosis, or a positive laboratory result for SARS-CoV-2 RNA detection (see online supplemental eMethods for codes included in the composite code). Inclusion in the non-COVID-19 ORI cohort required an encounter diagnosis of J00–J06 (other acute upper respiratory infections), J20–J22 (other acute lower respiratory infections) or J09–J18 (influenza and pneumonia) and no record of COVID-19, positive SARS-CoV-2 RNA detection nor SARS-CoV-2 antibodies during the prevaccine period (see online supplemental eMethods for details). Patients were excluded from both cohorts for pre-existing liver disease documented by an ICD-10 encounter diagnosis of E88.01 (alpha-1-antitrypsin deficiency), B15–B19 (viral hepatitis), K70–K77 (diseases of the liver) or elevated serum laboratory values (aspartate aminotransferase (AST) ≥ 110 units per litre (U/L), alanine aminotransferase (ALT) ≥ 100 U/L or total bilirubin (TBil) ≥ 2 mg/deciliter (mg/dL)) up until 1 month prior to the first record of the respiratory infection encounter diagnosis. To further investigate whether COVID-19 impacts patients with pre-existing liver disease, additional cohorts were constructed without excluding patients with pre-existing conditions. See online supplemental eMethods for details.

To further examine the subset of patients in the cohorts with disease severity sufficient to require hospitalisation, subcohorts were constructed including only patients with a documented inpatient stay during the acute period (from 1 month prior to 1 month after) the COVID-19 or ORI diagnosis. Additionally, the subset of patients who had AST/ALT or TBil measured during the acute period was compared with controls for access to laboratory testing.

Using the Research USA Minimal Date Shift network, five serial 6-month cohorts were constructed: 1 April 2020 to 30 September 2020; 1 October 2020 to 31 March 2021; 1 April 2021 to 30 September 2021; 1 October 2021 to 31 March 2022; 1 April 2022 to 30 September 2022 to evaluate secular trends. Additional cohorts corresponding to patients with infections that occurred during variant waves were constructed to index a patient's first documented COVID-19 infection or corresponding non-COVID-19 infection occurring when virological surveillance data showed a prevalence of $>90\%$ for the respective virus variant: Delta, 1 August 2021 to 30 November 2021; Omicron, 26 December 2021 to 30 September 2022.

To describe and compare the baseline characteristics of patients who developed liver complications during the 1–6 months follow-up period, additional inclusion criteria were added to existing cohort definitions: ICD-10 codes for the outcomes under study (K70–K77 or B15–B19) occurring during the 1–6 months follow-up period.

See below for more details on these outcome diagnostic codes.

Outcomes

Evidence of liver disease was identified by ICD-10 encounter diagnoses: K70–K77 (diseases of the liver), B15–B19 (viral hepatitis) or elevation in serum laboratory values reflecting transaminitis ($AST \geq 110$ U/L or $ALT \geq 100$ U/L) or cholestasis ($TBil \geq 2$ mg/dL). These outcomes were intended to be comprehensive to capture all acute hepatic complications. Subsets of these outcomes were further analysed by grouping specific ICD-10 codes. The National Syndromic Surveillance Programme and the Premier Healthcare Database Special Release used the following codes to identify hepatitis of unspecified aetiology¹⁶: B17.8 (other specified acute viral hepatitis); B17.9 (acute viral hepatitis, unspecified); B19.0 (unspecified viral hepatitis with hepatic coma); B19.9 (unspecified viral hepatitis without hepatic coma); K71.6 (toxic liver for liver disease with hepatitis, not elsewhere classified); K72.0 (acute or subacute hepatic failure); K75.2 (non-specific reactive hepatitis). We used those codes as a composite outcome with one additional code used for outbreak case finding: K75.9 (inflammatory liver disease, unspecified).² Other composite outcome subsets included K70–K77 (diseases of the liver), B15–B19 (viral hepatitis) and specific codes for acute hepatic complications for which counts were sufficient for analysis: K72 (hepatic failure, not elsewhere classified); K75 (other inflammatory liver diseases); K76 (other diseases of liver).

Statistical analysis

Statistical analyses were performed during August to September 2023, using the TriNetX analytics platform. We compared outcomes between cohorts after propensity score matching (1:1 matching using a nearest neighbour greedy algorithm with a calliper of 0.25 times the SD) for demographic factors including age, sex, race and ethnicity; paediatric body mass index; encounter for preventive medicine services (based on CPT codes); encounter for immunisations (based on CPT codes) and SARS-CoV-2 vaccination as recorded 1 day prior to the first encounter for the respiratory illness. See online supplemental eMethods for specific codes used for matching. A standard mean difference of ≤ 0.1 was considered a good match. Reports of COVID-19 vaccination status are likely incomplete as many patients received vaccination in other settings, which may not be recorded in the EHR.

We compared outcomes between matched cohorts during the period of 1–6 months following the index event (COVID-19 or ORI) after excluding patients with the outcome during the acute period (from 1 month prior to 1 month after the encounter diagnosis of COVID-19 or ORI). Built-in TriNetX analytics use the Cox proportional hazard model to calculate HRs and 95% CIs. The proportional hazard assumption is tested using the generalised Schoenfeld approach. To protect patient privacy when the aggregate counts for a reported outcome are small,

that is, ≤ 10 , the TriNetX platform reports the count as 10. However, in generating the Kaplan-Meier curves and calculating HRs, the TriNetX platform uses actual counts in calculating the rates even when the count is less than 10. Patients are censored from the survival analysis after the last clinical fact in the EHR. Since patients in the study cohorts who had outcomes recorded during both the acute period and also during the follow-up period of 1–6 months were excluded in the primary analysis, an additional comparison was made without excluding those patients to determine whether the elevated liver enzymes or bilirubin values could have been persistent from the acute phase. Relative risks (RRs) and 95% CI for the outcomes during the follow-up period of 1–6 months were calculated (Kaplan-Meier survival analysis and HR was not used because the outcome may have already occurred during the acute period). Small counts ≤ 10 are reported as 10. The RR calculation uses 10 (in contrast to the Kaplan-Meier survival analysis that uses actual counts), so may underestimate RR when one of the cohorts has a count of less than 10. Additional analyses comparing cohorts without excluding those with pre-existing liver abnormalities employed RR as well because the outcome may have occurred previously.

Patient and public involvement

Patients and the public were not involved in this study.

RESULTS

The overall study population was composed of children 1–10 years of age without pre-existing liver disease with EHR-documented COVID-19 (263 069) or a non-COVID-19 respiratory infection (1 111 362) between 1 January 2020 and 31 December 2022. The study population was drawn from 5 660 153 similarly aged children with at least one encounter during the study period. Prior to matching, patients in the COVID-19 cohort were significantly older than patients in the ORI cohort (table 1). After propensity matching on baseline characteristics (table 1), 2 60 132 patients were in each cohort. Tables summarising baseline characteristics for the subset of children aged 1–4 years, and the subsets of children in both age groups with a record of hospitalisation during the acute period (from 1 month prior to 1 month after the respiratory infection encounter diagnosis) can be found in online supplemental eTables 1–3.

Table 2 summarises the counts and hazard of hepatic complications after COVID-19 versus ORI for both age groups (1–4 years, 1–10 years) for all cases and for the subset with an associated hospitalisation. During the 1–6 months after the encounter diagnosis for the respiratory infection, patients with COVID-19 had a significantly greater hazard of elevated AST or ALT, and TBili with HR point estimates ranging from 2.13 to 4.40. HR point estimates were significantly increased for the composite outcome of diseases of the liver or viral hepatitis (K70–K77, B15–19: HR point estimate range, 1.48–4.50), and

Table 1 Baseline characteristics of study population before and after matching (age 1–10 years)

	Unmatched cohort, no (%)			Matched cohort, no (%)		
	COVID-19 n=263 069	ORI n=1 111 362	SMD	COVID-19 n=260 132	ORI n=260 132	SMD
Age at Index in years, mean (SD)	5.17±3.00	4.46±2.87	0.24	5.17±3.00	5.16±3.00	0.003
Sex						
Male	137 041 (52.7)	572 243 (52.1)	0.01	137 041 (52.7)	136 860 (52.6)	0.001
Female	122 928 (47.3)	525 718 (47.9)	0.01	122 928 (47.3)	123 177 (47.4)	0.002
Unknown	165 (0.1)	346 (<0.1)	0.01	163 (0.1)	95 (<0.1)	0.012
Ethnicity						
Not Hispanic	159 371 (61.3)	677 379 (61.7)	0.01	159 369 (61.3)	159 841 (61.4)	0.004
Hispanic	43 986 (16.9)	187 765 (17.1)	<0.01	43 986 (16.9)	44 086 (16.9)	0.001
Unknown	56 777 (21.8)	233 163 (21.2)	0.01	56 777 (21.8)	56 225 (21.6)	0.005
Race						
White	138 595 (53.3)	598 920 (54.5)	0.03	138 595 (53.3)	139 075 (53.5)	0.004
Black	52 889 (20.3)	198 847 (18.1)	0.06	52 887 (20.3)	52 317 (20.1)	0.006
Asian	8989 (3.5)	40 190 (3.7)	0.01	8989 (3.5)	8949 (3.4)	0.001
Native American or Alaska Native	1229 (0.5)	6154 (0.6)	0.01	1229 (0.5)	1166 (0.5)	0.004
Native Hawaiian or other Pacific Islander	526 (0.2)	2677 (0.2)	0.01	526 (0.2)	477 (0.2)	0.004
Unknown race	57 906 (22.3)	251 519 (22.9)	0.02	57 906 (22.3)	58 148 (22.4)	0.002
BMI, paediatric						
Measured	36 455 (14.0)	165 475 (15.1)	0.03	36 455 (14.0)	36 692 (14.1)	0.003
<5th percentile	2753 (1.1)	11 853 (1.1)	<0.01	2735 (1.1)	2576 (1.0)	0.006
5th to <85th percentile	24 003 (9.2)	116 910 (10.6)	0.05	24 003 (9.2)	24 124 (9.3)	0.002
85th to <95th percentile	7742 (3.0)	32 619 (3.0)	<0.01	7742 (3.0)	7714 (3.0)	0.001
≥95th percentile	10 623 (4.1)	38 525 (3.5)	0.03	10 623 (4.1)	10 660 (4.1)	0.001
Preventive medicine services	99 104 (38.1)	450 554 (41.0)	0.06	99 104 (38.1)	99 720 (38.3)	0.005
Encounter for immunisation	88 630 (34.1)	417 136 (38.0)	0.08	88 630 (34.1)	88 873 (34.2)	0.002
SARS-CoV-2 vaccination	2365 (0.9)	6463 (0.6)	0.04	2365 (0.9)	2065 (0.8)	0.013

BMI, body mass index; ORI, other respiratory infection; SMD, standard mean difference.

for diseases of the liver alone (K70–K77: HR point estimate range, 1.67–4.38). Few encounters were coded with the following ICD-10 encounter diagnoses: alcoholic liver disease (K70); toxic liver disease (K71); hepatic failure, not elsewhere classified (K72) (except for all patients aged 1–10 years with 12 in the COVID-19 cohort and 10 in the ORI cohort (HR (CI) 11.42 (1.49 to 87.83))); chronic hepatitis, not elsewhere classified (K73); fibrosis and cirrhosis of liver (K74). ICD-10 terms with sufficient counts to allow comparison had elevated HRs: other inflammatory diseases of the liver (K75: HR point estimate range, 2.85–9.85) which includes autoimmune hepatitis (K75.4) and other specified inflammatory liver diseases (K75.8); and other diseases of the liver (K76: HR point estimate range, 1.46–3.97) which includes fatty change of liver, not elsewhere classified (K76.0). The composite outcome of ICD-10 codes used for surveillance of hepatitis of unspecified aetiology surveillance also had significantly elevated HRs (HR point estimate range, 2.62–6.23). All HRs had

95% CIs that were greater than 1 except the outcome of other inflammatory diseases of the liver in the 1–4 years age group. The Cox proportionality assumption at $p \geq 0.05$ was met for all comparisons except elevated ALT/AST for 1–4 years age group with inpatient stay ($p=0.049$), and elevated TBil for 1–10 years age group with inpatient stay ($p=0.01$). A comparison of these outcomes without excluding patients with the encounter diagnosis for one of these outcomes during the acute period had increased RR estimates for all comparisons. See online supplemental eTable 4. Analyses conducted with cohorts of patients without excluding patients with pre-existing liver abnormalities showed similar results. Furthermore, additional ICD-10 terms had sufficient counts to report from this analysis, showing an elevated risk in the COVID-19 cohort for viral hepatitis (B15–B19) and hepatic failure, not otherwise classified (K72). See online supplemental eTable 5.

Table 2 Comparison of clinical outcomes during 1–6 months after COVID-19 versus ORI among matched cohorts of patients aged 1–10 years (1 January 2020–31 December 2022)

n, All 1–4=1 19 379 n, All 1–10=2 60 132 n, Inpt 1–4=5575 n, Inpt 1–10=10 256		Age group (years)	COVID-19 Cohort no	ORI Cohort no	HR (95% CI)
Elevated AST* or ALT†	All	1–4	139	62	2.13 (1.58 to 2.87)
		1–10	264	117	2.16 (1.74 to 2.69)
	Inpt	1–4	82	27	2.87 (1.86 to 4.43)
		1–10	132	44	2.87 (2.04 to 4.04)
Elevated TBil‡	All	1–4	38	10	4.48 (2.09 to 9.60)
		1–10	76	24	3.02 (1.91 to 4.78)
	Inpt	1–4	19	10	2.82 (1.12 to 7.05)
		1–10	34	10	4.40 (1.95 to 9.93)
Diseases of the liver (K70–K77) OR viral hepatitis (B15–B19)	All	1–4	50	16	2.94 (1.68 to 5.16)
		1–10	112	72	1.48 (1.10 to 1.98)
	Inpt	1–4	23	10	3.39 (1.38 to 8.32)
		1–10	40	10	4.50 (2.11 to 9.61)
Diseases of the liver (K70–K77)	All	1–4	41	11	3.51 (1.81 to 6.83)
		1–10	102	58	1.67 (1.21 to 2.30)
	Inpt	1–4	22	10	3.24 (1.31 to 7.99)
		1–10	39	10	4.38 (2.05 to 9.38)
Other inflammatory disease of the liver (K75)	All	1–4	10	10	4.25 (0.92 to 19.66)
		1–10	18	10	2.85 (1.13 to 7.18)
	Inpt	1–4	10	10	5.30 (0.64 to 43.99)
		1–10	11	10	9.85 (1.27 to 76.31)
Other diseases of the liver (K76)	All	1–4	31	10	2.92 (1.43 to 5.96)
		1–10	83	54	1.46 (1.03 to 2.05)
	Inpt	1–4	16	10	2.83 (1.04 to 7.71)
		1–10	31	10	3.97 (1.75 to 9.01)
Hepatitis of unspecified aetiology§	All	1–4	13	10	6.11 (1.38 to 27.10)
		1–10	22	10	2.62 (1.16 to 5.88)
	Inpt	1–4	11	10	4.82 (1.07 to 21.77)
		1–10	14	10	6.23 (1.42 to 27.43)

Cohorts matched on factors listed in table 1. Patients with pre-existing disease and outcomes from 0 to 1 month after respiratory illness are excluded from this analysis.

*AST≥110 units per litre.

†ALT≥100 units per litre.

‡TBil≥2 mg per deciliter.

§Surveillance codes include B17.8, B17.9, B19.0, B19.9, K71.6, K72.0, K72.9, K75.2, K75.9.

ALT, alanine aminotransferase; AST, aspartate aminotransferase; ORI, other respiratory infection; TBil, total bilirubin.

When comparison was restricted to patients with AST, ALT or TBil measured, but not shown to be elevated during the acute period, patients with COVID-19 had a greater hazard for elevated AST, ALT or TBil during the 1–6 months follow-up period in both age groups (table 3). Similarly, a comparison was made between patients with labs measured during the acute period, but without excluding those who may have had elevated labs during the acute period. The RR for persistent or newly incident lab elevations was greater for patients after COVID-19

(online supplemental eTable 6). Among patients aged 1–10 years with persistent lab elevations into the 1–6 months follow-up period after COVID-19, the most recent elevated lab value mean U/L (SD) were as follows: AST 236 (1760), ALT 133 (260) and TBil 2.16 (2.89).

The prevalence of pre-existing conditions (documented at least a month before the respiratory diagnosis) among patients who, during the 1–6 months follow-up period, had encounter diagnoses for diseases of the liver (K7–K77) or viral hepatitis (B15–B19) following

Table 3 Comparison of elevated laboratory values during 1–6 months after COVID-19 versus ORI among matched cohorts of paediatric patients with laboratory values measured during the acute period of infection (1 January 2020–31 December 2022)

n, 1–4=5513 n, 1–10=11 308	Age group (years)	COVID-19 cohort no	ORI cohort no	HR (95% CI)
Elevated AST* or ALT†	1–4	82	37	2.23 (1.50 to 3.27)
	1–10	144	56	2.59 (1.90 to 3.53)
Elevated TBil‡	1–4	19	10	3.61 (1.35 to 9.66)
	1–10	39	10	4.17 (2.02 to 8.60)

Cohorts matched on factors listed in [table 1](#). Patients with elevated labs from 0 to 1 months after respiratory illness are excluded from this analysis.

*AST≥110 units per litre.
†ALT≥100 units per litre.
‡TBil≥2 mg per deciliter.

ALT, alanine aminotransferase; AST, aspartate aminotransferase; ORI, other respiratory infection; TBil, total bilirubin.

COVID-19 versus ORI were compared. Cases with hepatic complications that followed COVID-19 versus ORI were older (mean, 5.51 vs 4.42 years) and had a higher prevalence of pre-existing conditions. However, when limiting the comparison to cases who were hospitalised during the acute phase of the respiratory infection, the prevalence of pre-existing conditions among COVID-19 or ORI-associated cases varied by condition. See online supplemental eTable 7 for details.

Analyses comparing shorter time periods yielded smaller total counts and did not uncover any temporal or variant-related trends. These analyses were conducted using the Research USA Minimally Shifted Network which has approximately 35% fewer records. When comparing COVID-19 to ORI during five serial 6-month time blocks from 1 March 2020 to 30 September 2022, there were no significant secular trends. Elevations in liver enzymes and bilirubin were evident in all time periods. Liver-related complications were seen in each time period, however, the relatively small counts when divided over five time periods made the comparison between COVID-19 and ORI underpowered. When restricting analyses to infections that occurred during COVID-19 waves in which either the Delta or the Omicron variant was predominant, results for liver enzymes and bilirubin were similar for the COVID-19 to ORI cohort comparison during each wave as when comparing the results over the entire study period. No differences in liver enzyme and bilirubin elevation were found when comparing COVID-19 cohorts between waves.

DISCUSSION

In a large population sample from across the USA, children who had COVID-19 were at significantly higher risk for elevated liver enzymes and bilirubin or a new diagnosis of hepatitis of various types in the following 6 months. These elevations were observed for children aged 1–10 years and also for younger children aged 1–4 years when compared with patients with a non-COVID-19 respiratory infection, and it was true for patients with COVID-19 of

unspecified severity, as well as for those with an associated hospitalisation. The risk was increased during the period 1–6 months after COVID-19 diagnosis whether or not patients with pre-existing liver disease were excluded or whether or not patients with liver abnormalities during the acute illness period were excluded from the sample. The risk was also noted when comparing only patients with normal labs measured during the acute phase of the illness. The increased risk for elevated transaminases or bilirubin was evident following a COVID-19 diagnosis during each time period of the pandemic. Because the surge in severe hepatitis among paediatric patients occurred coincident with the Omicron variant surge in the pandemic, we directly compared the time when the Delta variant predominated to the time when over 90% of sequenced viruses were the Omicron variant. No difference in the risk of subsequent liver enzyme or bilirubin elevations was found between variant waves.

Since several respiratory infections are known to be associated with subsequent liver abnormalities, the excess of new cases among children who contracted SARS-CoV-2 compared with those with prior respiratory infections may be especially telling. Indeed, the excess risk of elevated transaminases or bilirubin was much higher when children diagnosed with COVID-19 were compared with children who had a medical encounter for any reason, but this category could include well-child visits, fractures or allergies, diagnoses much less likely to display liver abnormalities than children who had viral respiratory infections. However, even compared with ORIs, COVID-19 posed more of a risk for subsequent liver diagnoses, suggesting that it does impose particular vulnerability. While elevated transaminases and bilirubin could reflect pathology of non-hepatic aetiology such as haemolysis or myositis and should prompt a clinical investigation that considers these other causes, the increased risk of these lab abnormalities in the COVID-19 population in comparison to non-COVID-19 respiratory infection population was mirrored by the elevated risk of encounter diagnoses for hepatic complications. The physician must be alert

to ongoing vulnerability to other viral infections, or to lingering inflammatory damage following COVID-19.

We tested whether prior infection with SARS-CoV-2 is associated with subsequent diagnoses of hepatitis of known viral origin (hepatitis A–E), unspecified viral hepatitis, or cases of acute liver complications for which an infectious origin was not diagnosed, including toxic liver disease, hepatic failure, other inflammatory diseases of the liver (including autoimmune hepatitis) or other diseases of the liver (including fatty change). We reasoned that if COVID-19 conferred vulnerability by any of the mechanisms involving the immune system, this vulnerability may extend to many infectious or even non-infectious disorders of the liver. For all acute disease, ICD-10 codes examined for which there was a large enough number of cases for comparison, the risk was higher among children 1–6 months following COVID-19 than it was following ORIs. For the following codes: viral hepatitis (B15–B19); toxic liver disease (K71); hepatic failure, not elsewhere classified (K72); the number of cases was too small for the primary analysis. We speculate that ongoing low-grade liver inflammation following COVID-19, though rare (approximately 10 in 10 000) among children without a history of liver abnormalities, leaves children vulnerable to either develop liver disease or to acquire an additional infection. Nevertheless, if 10 million children were infected, 10 000 or more might be left at risk.

Children were more likely to have liver enzymes or bilirubin measured during the following 1–6 months if they were diagnosed with COVID-19 at the index encounter (RR, 1.8) even though the risk of a follow-up visit for any reason was only modestly increased for children with COVID-19 (RR, 1.07). This probably speaks to the index of suspicion in the physicians caring for these children. However, this excess of sampling might create some bias of ascertainment in detecting liver abnormalities among children following COVID-19. Therefore, we compared only those children who had blood drawn to measure liver enzymes or bilirubin around the time of the diagnosis of COVID-19 or ORI. For this comparison, laboratory measurements showing liver enzymes and bilirubin were also elevated among children following COVID-19.

How COVID-19 might predispose to later liver abnormalities is a matter for speculation. For adults, four mechanisms have been suggested: direct infection, toxicity from cytokine storm or hypoxic injury associated with severe COVID-19, toxicity from the drugs used to treat COVID-19 and immune phenomena.¹⁷ Direct infection of hepatocytes is unlikely because viral receptors are sparse on hepatocytes, although they do occur in abundance on cholangiocytes. However, there are case reports of acute hepatitis associated with COVID-19, some of them accompanying multisystem inflammatory syndrome in children (MIS-C), and others, without significant respiratory involvement.¹⁸ Though in adults, worse acute liver injury is associated with more severe COVID-19, we did not observe an association with severity of COVID-19 as assessed by need for hospitalisation. Moreover, children

tend to have less severe disease than adults. Therefore, it is less likely that cytokine storm, vascular injury or hypoxia during the acute illness account for our findings. Few antiviral drugs are approved for children under 10 years of age (paxlovid has not been approved for children <12 years of age and remdesivir has been seldom used), so drug-induced hepatotoxicity is also less likely than in adults. Therefore, immune phenomena seem the most likely explanation. Many autoimmune phenomena have been documented following SARS-CoV-2 infection, so an autoimmune mechanism of liver damage is possible.¹⁹ MIS-C is thought to be a result of immune dysregulation following SARS-CoV-2 infection.²⁰ Case reports of autoimmune hepatitis following COVID-19 in adults have appeared.^{12 21 22} In addition, for other viruses, T-cell-mediated damage to the liver has been observed even in the absence of persistence of the virus or viral antigens in the liver.⁵ Further work is needed to sort out these possibilities.

Limitations

This study has several limitations. Its retrospective observational design precludes determination of causality, only association. Especially during the later time periods of the pandemic, it is likely that some patients with COVID-19 were not medically attended nor tested for SARS-CoV-2 in a way recorded in the EHR. Therefore, some patients who had COVID-19 may have been included with the ORI control group. However, such an error would tend to reduce the group differences rather than create them. Not all patients diagnosed with liver diseases had liver enzymes or bilirubin recorded in TriNetX, either because the tests were performed outside of the HCO, or because at some HCOs, laboratory databases are not included in the TriNetX uploads. Therefore, an exact match of the biochemical abnormalities and the diagnoses is not possible. In addition, the TriNetX database, though quite large and covering about 28% of the US population, may not be entirely representative. Further studies focusing in on the key issues raised by this report are warranted.

For patients hospitalised around the time of the encounter diagnosis for COVID-19 or non-COVID-19 encounter diagnosis, the indication for hospitalisation cannot be ascertained, but likely represents severe COVID-19. Nevertheless, hospitalised patients with these concurrent respiratory infections had a similar prevalence of common underlying conditions, but a substantial difference in the subsequent risk for persistent liver disease as documented by encounter diagnoses or elevation of AST/ALT or TBil.

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Data availability statement No data are available. We used a cloud-based database and cannot download the data set. In addition, the database is constantly being upgraded with new information, so the actual data from which the analysis was done will not be available at a subsequent time. That is why we indicate when the database was accessed and which specific data set was used. The EMR data are deidentified and so individual data cannot be made available to us or anyone else.

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