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Short Communication

Liver transaminase concentrations in children with acute SARS-CoV-2 infection

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ABSTRACT

Objective: To evaluate the relationship between SARS-CoV-2 infection and liver injury by comparing transaminase concentrations among children tested for SARS-CoV-2 and other respiratory viruses in pediatric emergency departments.

Design & methods: Eligible children were <18 years with suspected SARS-CoV-2, tested using molecular approaches in emergency departments between March 7, 2020, and June 15, 2021 (Pediatric Emergency Research Network), and between August 6, 2020, and February 22, 2022 (Pediatric Emergency Research Canada). We compared aspartate (AST) and alanine aminotransferase (ALT) concentrations at presentation for SARS-CoV-2 and other respiratory viruses through a multivariate linear regression model, with the natural log of serum transaminase concentrations as dependent variables.

Results: Of 16,892 enrolled children, 2,462 (14.6%) had transaminase concentrations measured; 4318 (25.6%) were SARS-CoV-2 positive, and 3932 (23.3%) were tested for additional respiratory viruses. Among study participants who had additional respiratory virus testing performed, the most frequently identified viruses were enterovirus/rhinovirus [8.7% (343/3,932)], respiratory syncytial virus [4.6% (181/3,932)], and adenovirus [2.6% (103/3,932)]. Transaminase concentrations were elevated in 25.6% (54/211) of children with isolated SARS-CoV-2 detection and 21.6% (117/541) of those with no virus isolated; P = 0.25. In the multivariable model, isolated SARS-CoV-2 detection was not associated with elevated ALT (adjusted geometric mean ratio (IU/L): 0.96; 95%Confidence Interval (CI): 0.84, 1.08) or AST (adjusted geometric mean ratio (IU/L): 1.03; 95%CI: 0.92, 1.16) concentrations, with negative respiratory panel as the referent group. Ninety-day follow-up was completed in 82.2% (3,550/4,318) of SARS-CoV-2 positive children; no cases of new-onset liver disease were reported.

Conclusion: Among those tested, transaminase concentrations did not vary between SARS-CoV-2-positive children and those with a negative respiratory viral panel. In multivariate analysis, SARS-CoV-2 infection was not associated with increased initial transaminase concentrations compared to other respiratory viruses.

Abbreviations: ALT, alanine transaminase; AST, aspartate aminotransferase; CI, Confidence Interval; ED, emergency department; MIS-C, multisystem inflammatory syndrome in children; OR, Odds Ratio; PERC, Pediatric Emergency Research Canada; PERN, Pediatric Emergency Research Network; RSV, Respiratory Syncitial Virus; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

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1. Introduction

Gastrointestinal manifestations such as diarrhea, nausea, vomiting, and abdominal pain are common presentations of pediatric SARS-CoV-2 infection. Previous reports estimate that between 29 and 44% of SARS-CoV-2 infected children have elevated transaminases during acute illness [1–3]; this proportion may exceed 50% in patients affected by the multisystem inflammatory syndrome in children (MIS-C). However, few studies have conducted focused evaluations of the impact of SARS-CoV-2 infection on liver enzymes. Recent concerns regarding rare but severe cases of hepatitis and acute liver failure occurring in children, potentially associated with SARS-CoV-2 infection, have highlighted the importance of this issue. A recent electronic health record study reported that SARS-CoV-2 infected children were twice as likely to have elevated transaminases compared to children infected with other respiratory viruses [4].

Although the pathology remains unclear, children <5 years of age appear to be at increased risk of COVID-19 associated liver injury [1,3]. Liver injury may be due to immune effects, endothelial damage, vascular thrombosis or from direct cytotoxicity from the SARS-CoV-2 virus [5]. In most cases, the transaminase elevation is mild and self-limited, normalizing within four months of onset with no effect on synthetic liver function [6].

The studies to date however are limited in the number of children included, testing and comparison to other viruses, and lack clinical data. To further interrogate the relationship between SARS-CoV-2 infection and liver injury, we evaluated serum transaminase concentrations among children tested for SARS-CoV-2 and other respiratory viruses in a multinational, prospective, pediatric emergency department (ED)-based cohort study.

2. Methods

Data collected as part of the Pediatric Emergency Research Network (PERN) [7] and Pediatric Emergency Research Canada (PERC) COVID-19 cohort studies were analyzed. These studies prospectively recruited children <18 years with suspected SARS-CoV-2 who had a nasopharyngeal swab collected and tested for SARS-CoV-2 using molecular approaches. The studies were conducted in 41 EDs in 10 countries between March 7, 2020, and June 15, 2021 (PERN), and 14 Canadian EDs between August 6, 2020, and February 22, 2022 (PERC), respectively. The indications for testing varied by institution and over time. Although children may have presented for symptoms not directly related to COVID-19 (e.g. abdominal pain), in general all tested participants either had symptoms of COVID-19 infection (e.g. fever, rhinorrhea, vomiting) or epidemiologic risk factors (e.g. close contact). Liver transaminase, hepatitis virus, and additional respiratory viral testing was at the discretion of the clinical team. For the latter, a variety of testing approaches were used across participating sites (e.g. isolated respiratory syncytial virus (RSV) and influenza or extensive multiplex viral platforms). The results of all viral testing performed were documented. Participants were contacted 90 days following their index ED visit by phone and asked if their child had any new, recurrent, or persistent symptoms, or diagnoses that were not present prior to the illness prompting the index ED visit. Ethics approval and participant consent and assent was obtained at all study sites in accordance with local ethics

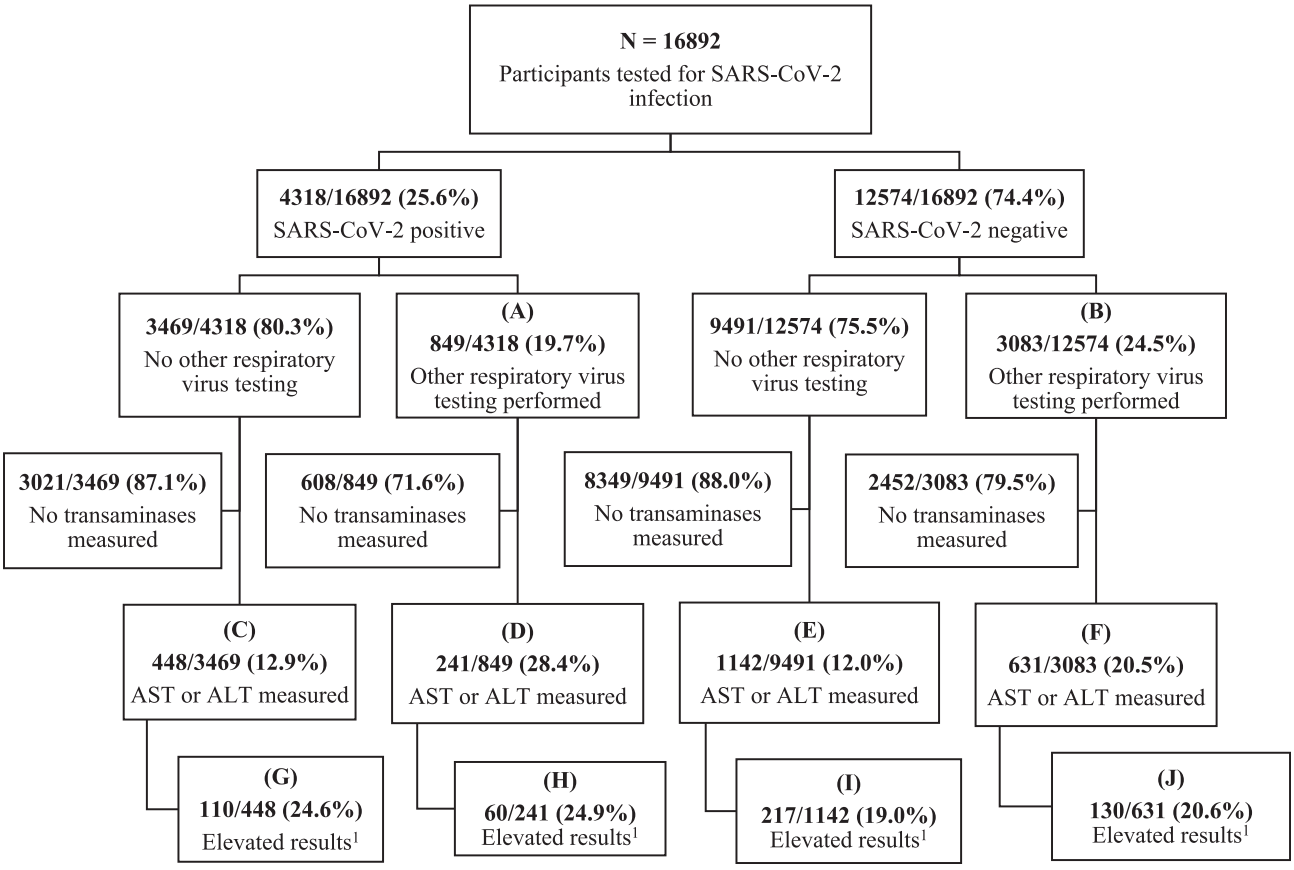

Fig. 1. Description of SARS-CoV-2 test results and liver transaminase measurements within the cohort. AST, Aspartate Aminotransferase; ALT, Alanine Aminotransferase.[1]>97th percentile in AST and/or ALT for age and sex. Total number who had transaminase concentrations measured = C + D + E + F = 2462. Total number who additional respiratory virus testing performed = A + B = 3932. Total number of SARS-CoV-2 positive children who had elevated transaminases = G + H = 170.Total number of SARS-CoV-2 positive children who had transaminase testing performed = C + D = 689. Total number of SARS-CoV-2 negative children who had elevated transaminases = I + J = 347. Total number of SARS-CoV-2 negative children who had transaminase testing performed = E + F = 1773.

Table 1
Aspartate aminotransferase and alanine aminotransferase values in participants reported based on virus detected, and multivariable linear regression models, with alanine aminotransferase (n = 705 patients) and aspartate aminotransferase (n = 532 patients) as the dependent variables.[6]

	Alanine Aminotransferase				Aspartate Aminotransferase					
	Number of Participants	Geometric mean[4] (IU/L) (SD)	Median (IQR)	P Value	Number of Participants	Geometric mean[4] (IU/L) (SD)	Median (IQR)	P Value	Elevated ALT or AST Concentration, n (%)	P Value
All participants	867	25.4 (2.2)	20 (15, 32)	0.36[3]	685	42.9 (1.9)	39 (28, 55)	0.99[3]	190/873 (21.8%)	0.16[5]
No respiratory viruses identified	536	26.4 (2.3)	21 (15, 34)		433	43.3 (2.0)	39 (28, 55)		117/541 (21.6%)	
SARS-CoV-2 only	210	25.3 (2.1)	21 (15, 32)		176	43.0 (2.1)	40 (27, 58)		54/211 (25.6%)	
Respiratory Adenovirus only	17	21.7 (1.9)	18 (13, 28)		14	41.6 (1.4)	40 (34, 52)		3/17 (17.6%)	
RSV only	17	18.4 (1.4)	17 (14, 25)		5	43.1 (1.1)	42 (38, 48)		0/17 (0%)	
Rhinovirus/ Enterovirus only	38	24.6 (2.1)	19 (14, 36)		26	39.6 (1.6)	37 (29, 53)		8/38 (21.1%)	
Other virus (single - no co-detection)[1]	7	17.4 (1.5)	19 (10, 23)		3	34.3 (1.4)	30 (min 25, max 49)		0/7 (0%)	
More than one virus detected[2]	42	21.2 (1.6)	20 (16, 27)		28	40.5 (1.7)	42 (26, 51)		8/42 (19.0%)	
Regression Model										
	Number of Participants	Adjusted geometric mean ratios of natural log (IU/L)		P Value	Number of Participants	Adjusted geometric mean ratios of natural log (IU/L)		P Value		
Age, per year increased	866	1.00 (0.99, 1.01)		0.78	684	0.98 (0.97, 0.99)		<0.001		
Sex										
Female	395	0.95 (0.86, 1.05)		0.33	296	0.96 (0.87, 1.06)		0.45		
Male	471	reference			388	reference				
Country										
Canada	307	0.91 (0.81, 1.03)		0.13	146	1.07 (0.95, 1.22)		0.28		
Costa Rica	26	0.86 (0.63, 1.16)		0.31	25	1.11 (0.85, 1.45)		0.46		
Singapore	17	0.78 (0.53, 1.13)		0.19	17	0.75 (0.54, 1.04)		0.08		
Other (Australia, Spain, Argentina, Italy)	17	0.91 (0.63, 1.32)		0.61	11	0.85 (0.58, 1.26)		0.42		
United States	499	reference			485	reference				
Admitted to ICU										
Yes	146	1.15 (0.99, 1.33)		0.07	137	1.13 (0.99 1.29)		0.07		
No	720	reference			547	reference				
Hospitalization										
Yes	590	1.16 (1.03, 1.31)		0.02	507	1.02 (0.91, 1.15)		0.72		
No	276	reference			177	reference				
Virus detected										
SARS-CoV-2 only	210	0.96 (0.84, 1.08)		0.47	176	1.03 (0.92, 1.16)		0.62		
More than one virus co-detected	42	0.83 (0.65, 1.06)		0.14	28	0.92 (0.71, 1.18)		0.50		
Rhinovirus/ Enterovirus only	38	0.94 (0.73, 1.21)		0.65	26	0.88 (0.68 1.13)		0.31		
Respiratory Adenovirus only	17	0.83 (0.57, 1.19)		0.31	14	0.94 (0.66, 1.32)		0.71		
RSV only	17	0.72 (0.49, 1.04)		0.08	5	0.90 (0.51, 1.60)		0.72		

(*continued on next page*)

Table 1 (*continued*)

	Alanine Aminotransferase				Aspartate Aminotransferase					
	Number of Participants	Geometric mean[4] (IU/L) (SD)	Median (IQR)	P Value	Number of Participants	Geometric mean[4] (IU/L) (SD)	Median (IQR)	P Value	Elevated ALT or AST Concentration, n (%)	P Value
Other virus (single - no co-detection)	7	0.72 (0.41, 1.28)		0.26	3	0.74 (0.35, 1.54)		0.42		
None	535	reference			432	reference				

RSV, Respiratory Syncytial Virus; ALT, Alanine Aminotransferase; AST, Aspartate Aminotransferase; ICU, Intensive Care Unit; SD, Standard Deviation; IQR, Interquartile Range.

The multiple regression coefficients and 95% CI were backtransformed by applying the inverse natural log function to yield the adjusted geometric mean ratios (AGMR) reported here. For example, the AGMR of 0.71 reported in the Alanine Aminotransferase model for RSV indicates that, compared to no infection, RSV is associated with a 29% lower geometric mean ALT value, holding other variables constant.

[1] Parainfluenza Type 3n = 1, influenza A n = 1, metapneumovirus n = 1, other coronavirus n = 4.

[2] SARS-CoV-2 and rhinovirus/enterovirus n = 14, SARS-CoV-2 and adenovirus n = 3, SARS-CoV-2 and RSV n = 1, SARS-COV-2 and parainfluenza type3 n = 1, SARS-CoV-2 and parainfluenza type4n = 1, SARS-CoV-2 and metapneumovirus n = 2, SARS-CoV-2 and other coronavirus n = 3, RSV and influenza n = 2, parainfluenza type4 and rhinovirus/enterovirus n = 1, rhinovirus/enterovirus and other coronavirus n = 1, rhinovirus/enterovirus and adenovirus n = 5, rhinovirus/enterovirus and parainfluenza type 4n = 1, adenovirus and human bocavirus n = 1, adenovirus and metapneumovirus n = 1, adenovirus and other coronavirus n = 1; rhinovirus/enterovirus, parainfluenza type 4 and SARS-CoV-2n = 1,; rhinovirus/enterovirus, adenovirus and SARS-CoV-2n = 5.

[3] Within groups using Kruskal Wallis test.

[4] Geometric mean and standard deviations were calculated by exponentiating the means and standard deviations of the alanine aminotransferase and aspartate aminotransferase natural log values.

[5] Within groups comparison using Fisher's exact test.

[6] For each transaminase, a multiple linear regression model was fit with the natural log transformed transaminase concentration as the dependent variables. The model included age, sex, country of enrolment, hospitalization, intensive care unit admission, and virus detected.

requirements.

For patients in whom transaminase testing was performed, we analyzed the first aspartate (AST) and alanine aminotransferase (ALT) concentrations available. Values >97.5 percentile for age and sex were classified as elevated [8]. In all analyses, participants with >1 virus detected were analyzed as a single group regardless of the virus-virus combination. Fisher's Exact and Kruskal-Wallis tests were used to compare dichotomous and continuous values, respectively. We constructed linear regression models fit with generalized estimating equations to account for correlations within sites, with the natural log of serum transaminase concentrations as continuous dependent variables. Models included age, sex, country of recruitment, hospitalization, intensive care unit admission, and virus detected [i.e., adenovirus, influenza, RSV, SARS-CoV-2, other viruses (i.e. influenza, metapneumovirus, parainfluenza, other coronavirus), multiple viruses, no virus detected].

3. Results

Of 16,892 enrolled children, 14.6% (2462) had transaminase concentrations measured and 23.3% (3,932/16,892) had additional respiratory virus testing performed; 25.6% (4318/16,892) and 74.4% (12,574/16,892) were SARS-CoV-2 positive and negative, respectively; Fig. 1. Among SARS-CoV-2 positive children, 19.7% (849/4318) had other respiratory virus testing performed; 28.4% (241/849) of these children had transaminase levels measured. Of the 12,574 children who tested negative for SARS-CoV-2 infection, 24.5% (3083/12,574) had other respiratory virus testing performed and 20.5% (631/3083) of these children had transaminase levels measured; Fig. 1.

Among study participants who had additional respiratory virus testing performed, the most frequently identified viruses were enterovirus/rhinovirus [8.7% (343/3,932)], RSV [4.6% (181/3,932)], and adenovirus [2.6% (103/3,932)]. Home medication use prior to the ED visit differed between children who were SARS-CoV-2 positive and the 2,740 children who were negative for both SARS-CoV-2 and other respiratory testing. Specifically, the latter group were more likely to have been administered an antibiotic (7.0% vs. 3.0%), acetaminophen (55.2% vs. 42.6%), and ibuprofen (29.1% vs. 19.7%); all P < 0.001. Of those who were SARS-CoV-2 positive, 6 (0.1%) had pre-existing liver disease based on caregiver report (N = 4313) at the time of enrollment.

Transaminase concentrations were elevated in 24.7% (170/689) of SARS-CoV-2-positive children overall (i.e. including those with co-detections) compared to 19.6% (347/1773) of SARS-CoV-2 test-negative children who had transaminase testing performed; difference = 5.1%; 95 %Confidence Interval (CI) of the difference = 1.4%, 8.8%; Fig. 1. Serum ALT or AST levels were elevated in 25.6% (54/211) of children with isolated SARS-CoV-2 infection and 21.6% (117/541) of those with no virus isolated; Table 1, P = 0.25. None of the 17 children with RSV and transaminases performed demonstrated elevations in ALT or AST. Median (interquartile range) ALT values were 21 (15, 32), 18 (13, 27.5), 19 (14, 36), 17 (14, 25), 21 (15, 34) and AST values were 40 (27, 58), 40 (34, 52), 37 (29, 53), 42 (38, 48), and 39 (28, 55) for children with isolated SARS-CoV-2, adenovirus, enterovirus/rhinovirus, RSV detection, and no virus detected, respectively; Table 1.

In the multivariable model, SARS-CoV-2 detection was not associated with elevated ALT (adjusted geometric mean ratio (IU/L): 0.96; 95 %CI: 0.84, 1.08) or AST (adjusted geometric mean ratio (IU/L): 1.03; 95 %CI: 0.92, 1.16) concentrations (with no respiratory virus detected as the referent group); Table 1. None of the other respiratory viruses were associated with higher ALT and AST concentrations compared to those with a negative respiratory panel. Children with >1 virus detected similarly had no trend towards higher liver transaminases. However, hospitalization was associated with increased ALT levels; OR 1.16 (95 % CI: 1.03, 1.31).

Of the 15 children with initial ALT or AST concentrations >500 U/L, four tested positive for SARS-CoV-2 (0.09% of SARS-CoV-2 positive children). Eight of these children were tested for other respiratory virus in addition to SARS-CoV-2; six were negative for all respiratory viruses and two were SARS-CoV-2 positive only. Discharge diagnoses for the SARS-CoV-2-positive children with transaminases >500 U/L were trauma (N = 3) and pre-existing autoimmune hepatitis (N = 1). Ninety-day follow-up was completed in 82.2% (3550/4318) of SARS-CoV-2 positive children; no cases of new-onset liver disease or elevated transaminase concentrations were reported.

4. Conclusions

Among those tested, transaminase concentrations did not vary in a clinically relevant or statistically significant manner between SARS-CoV-2-positive children and those whose tests were negative for all

viral respiratory pathogens. Although SARS-CoV-2 positive participants were more likely than those who were test-negative to have an elevated transaminase test, in multivariate analysis, acute SARS-CoV-2 infection was not independently associated with increased initial transaminase concentrations. There were only a handful of SARS-CoV-2 positive children with severe ALT/AST elevation (>500 U/L), all of whom had alternate explanations for their liver injury. Our data, which include only a limited post-infectious assessment, provide no indication that acute SARS-CoV-2 infection is associated with elevated transaminase concentrations in children in whom AST and ALT were quantified as part of their clinical evaluation as compared with other respiratory viruses. The other respiratory viruses that we examined (adenovirus, RSV, enterovirus/rhinovirus) similarly showed no trend towards higher serum transaminase levels.

In our cohort, 25% of SARS-CoV-2 positive children with AST/ALT evaluated had elevated transaminases, which closely mirrors other published estimates [1,2]. Unlike prior reports [4], we did not identify a greater association between SARS-CoV-2 infection and elevated transaminases compared with other respiratory viruses, or among those who have respiratory symptoms with no pathogen identified. We believe our findings, which are derived from a smaller but well described cohort, include more appropriate controls with well described alternative viral infections [4].

The fact that 21% of all eligible children in our cohort had elevated transaminase concentrations, compared with only 11% in a prior study in children with acute respiratory tract infections [9], suggests that our cohort is limited by selection bias based on illness severity or presence of preexisting comorbidities (Table A1). However, our study population differs from the prior study which focused on outpatient pediatric patients and excluded those with severe respiratory illness or symptoms lasting >5 days [9]; our study described patients presenting for ED care and selected for aminotransferase testing based on clinical discretion. We did not specifically examine patients with MIS-C, as our focus was on acute infection rather than the well-established liver toxicity associated with the post-infectious hyperinflammation syndrome [10]. Interpretation of our results is limited by the retrospective nature of our analysis, our relatively small sample size, non-sequential sampling, and the various respiratory virus testing approaches used across study sites. Assay bias could also have played a role as our results include analyses performed on a variety of platforms which may lead to analytic variability [11]. However, this variability is likely clinically insignificant and our approach of using a standardized, age-specific, upper limit of normal across all study sites likely introduces less bias than using site-specific, age-based, upper limits of normal [11]. Lastly, although we accounted for confounding through the inclusion of *a priori* identified variables in our regression analysis, other potentially relevant variables such as obesity were unavailable. The symptoms present at the time of the ED visit differed between those who did and those who did not have transaminase testing performed, but there was no clear, consistent pattern (Table A2). Therefore, we cannot specify what drove the clinical care team to measure transaminases on a given patient.

In conclusion, although we found transaminases to be elevated in a quarter of all SARS-CoV-2 positive children who had such testing performed in the ED, we found no independent association between acute SARS-CoV-2 infection and elevated transaminase concentrations in our study population. Notably, the association with elevated transaminases was no different among SARS-CoV-2 infected children compared to those who tested negative or had other respiratory viruses identified.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

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