ACUTE LIVER INJURY IN CHILDREN WITH SARS-CoV-2 INFECTION – TWO DISTINCT CLINICAL PHENOTYPES CAUSED BY THE SAME VIRUS

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Background

- Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) associated acute liver injury (ALI) has been linked to severe disease course and poor outcomes in adults
- Here we compare characteristics and outcomes of children with acute liver injury (ALI) in two distinct manifestations of the same infection
  - multisystem inflammatory disease in children (MIS-C)
  - coronavirus disease 2019 (COVID-19)

Methods

- ***DESIGN***:
- This is a retrospective study of children ≤ 21 years of age who were positive for SARS-CoV-2 between March 14th to June 30th, 2020
- ***PARTICIPANTS***:
- Patients were identified by the international classification of diseases 10th revision (ICD-10) code for a positive COVID-19 test (U07.1) and/or by an institutional COVID-19 or MIS-C database
- Only participants with confirmed SARS-CoV-2 infection with detection of the virus via nasal swab-derived real-time reverse polymerase chain reaction were included in the COVID-19 cohort
- MIS-C was defined by the modified criteria of the Centers for Disease Control and Prevention (CDC)
- ALI was defined by an elevation of alanine aminotransferase (ALT) > 40 U/L
- Children without liver tests were excluded
- ***SETTING***:
- Children were enrolled from the 2 tertiary children's hospitals; Children's Hospital at Montefiore and Morgan Stanley Children's Hospital
- ***ANALYSIS***:
- Bivariate analysis
- Multivariable logistic regression was used to examine the potential ALI risk factors by cohort (COVID-19 and MIS-C) and for the combined data set

Results

- Of the 291 patients, ALI was detected in 36% of children; 31% with COVID-19, and 51% with MIS-C
- ALI in COVID-19 was associated with obesity (p <0.001), immunocompromised status (p=0.04), and chronic liver disease (p=0.01)
- In the regression models, ALI in COVID-19 was also associated with higher C-reactive protein (OR 1.08, p=0.01) after adjusting for common independent predictors
- Children with ALI in the MIS-C subgroup were more often boys (p=0.001), Hispanic (p=0.04), or Black (p<0.001)

Results

- In MIS-C, male gender (OR 5.3, p=0.02) and Black race (OR 4.4, p=0.04) were associated with increased odds of ALI
- Children with ALI in both cohorts had significantly higher multiorgan dysfunction, longer hospitalization, and ICU stay
- Children with MIS-C had a 2.3-fold increased risk of ALI compared to COVID-19. No association was found between ALI and mortality

Table 1. Patient Characteristics in Children with and without ALI

	COVID-19			MIS-C			COVID-19 vs MIS-C†
	ALT ≤ 40 U/L (n=151)	ALT > 40 U/L (n=69)	p-value	ALT ≤ 40 U/L (n=35)	ALT > 40 U/L (n=36)	p-value	p-value
Demographics							
Age (years), median (IQR)	11 (2 – 17)	16 (8-20)	0.001	6 (2-10)	9.5 (6.0-13.5)	0.01	0.01
Male sex, n (%)	87 (58)	49 (71)	0.06	11 (31)	25 (69)	0.001	0.87
Hispanic ethnicity, n (%)	50 (43)	19 (31)	0.13	14 (48)	16 (53)	0.69	0.04
Black race, n (%)	26 (26)	7 (14)	0.08	6 (24)	13 (59)	0.01	<0.001
Comorbidities							
Asthma, n (%)	25 (17)	17 (25)	0.16	2 (6)	6 (17)	0.26	0.35
Chronic liver disease, n (%)	4 (3)	9 (13)	0.01	0	0	-	0.03
Congenital heart disease, n (%)	10 (7)	2 (3)	0.35	0	0	-	0.54
Diabetes mellitus, n (%)	11 (7)	7 (10)	0.48	0	1 (2.8)	1.00	0.26
Immunosuppression, n (%)	9 (6)	11 (16)	0.02	0	0	-	0.01
Malignancy, n (%)	5 (3)	10 (15)	0.01	0	0	-	0.01
Obesity, n (%)	28 (23)	34 (54)	<0.001	6 (19)	11 (31)	0.26	0.02

†compares children with acute liver injury defined as ALT > 40 U/L in COVID-19 vs MIS-C

Table 2. Predictors of ALI among Children comparing *COVID-19 vs MIS-C*

	OR	95% Confidence Interval	p value
Age	1.05	0.99-1.11	0.06
Male sex	**2.33**	**1.22-4.47**	**0.01**
Black race	0.84	0.42-1.69	0.62
Presence of MIS-C	**2.30**	**1.10-4.87**	**0.03**

Multivariable logistic regression comparing ONLY children with acute liver injury defined as ALT > 40 U/L in COVID-19 (n=69) versus MIS-C (n=36). OR: odds ratio.

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Results

Table 3. Predictors of ALI comparing Children with *COVID-19 and MIS-C*

	COVID-19			MIS-C		
	OR	95% Confidence Interval	p-value	OR	95% Confidence Interval	p-value
Age	1.02	0.94-1.11	0.64	1.14	0.97-1.34	0.11
Male sex	2.34	0.73-7.46	0.15	**5.29**	**1.25-22.43**	**0.02**
Black race	0.28	0.06-1.30	0.10	**4.43**	**1.01-18.81**	**0.04**
Obesity	1.67	0.55-5.07	0.37	-	-	-
Chronic liver disease	2.39	0.32-17.95	0.40	-	-	-
ICU admission	2.63	0.66-10.44	0.17	-	-	-
Peak CRP	**1.08**	**1.03-1.15**	**0.01**	1.02	0.96-1.08	0.63

Multivariable logistic regression comparing children without and with ALI. ALI defined as ALT > 40 U/L. Obesity defined as body mass index ≥ 95th percentile in patients <18 years-old or ≥ 30 kg/m2 in patients 19-21 years-old, COVID-19 cohort: ALT ≤ 40 U/L (n=151) and ALT > 40 U/L (n=69)
MIS-C cohort: ALT ≤ 40 U/L (n=35) and ALT > 40 U/L (n=36). CRP: C-reactive protein, OR: odds ratio.

Conclusions

- ALI with SARS-CoV-2 presents as a moderate elevation of aminotransferases without hepatic synthetic dysfunction
- Patients with SARS-CoV-2 infection and ALI are at risk of a more severe disease course including longer hospitalization and ICU stays
- Children require careful management and monitoring throughout their hospitalization and thereafter to establish ALI outcome
- Further studies need to provide mechanistic insights into the pathophysiology of underlying liver injury in both conditions.

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