Utility of Matrix Metalloproteinase-7 as a Biomarker in Cholestatic Infants with Congenital Heart Disease

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Background

- Infants with congenital heart disease (CHD) are at risk for cholestasis due to right ventricular hypertension.
- Biliary atresia (BA) is a relatively common, progressive cholangiopathy requiring intervention within 60 days of life.
- Matrix metalloproteinase 7 (MMP-7) is a biomarker which has been shown to differentiate BA from other cholestatic conditions in term infants without congenital anomalies.
- Identifying the etiology of cholestasis in infants with CHD is important because CHD repair can affect outcomes after BA repair.
- Few prior studies report data about MMP-7 in infants with CHD, though other MMP have been associated with pulmonary hypertension (PH).

Methods

- Single-center, retrospective, cross-sectional study from 2019-2022
- Infants with cholestasis evidenced by direct bilirubin ≥ 1 who had serum MMP-7 lab obtained.
- Patients sub-analyzed based on presence or absence of CHD, BA, and PH.
- PH defined by initiation of therapy
- Subgroups compared by demographics, gestational age, TPN exposure, lab studies

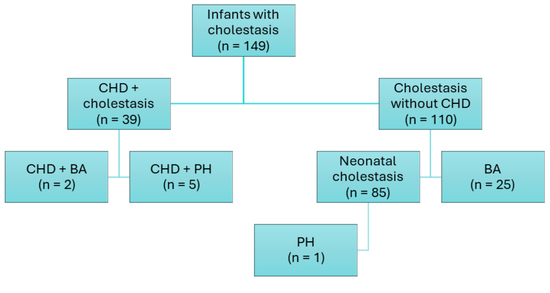

Figure 1. Breakdown of patient subgroups used for analysis

Results

Characteristic	N	Cholestasis Alone, N = 110[1]	CHD-C, N = 39[1]	p-value[2]
Age (mos)	149	31 (17, 58)	30 (17, 48)	0.834
Sex	149			0.945
Male		67 (61%)	24 (62%)	
Female		43 (39%)	15 (38%)	
Ethnicity	145			0.728
Hispanic or Latino		9 (8.5%)	2 (5.1%)	
Non-Hispanic or Latino		97 (92%)	37 (95%)	
Race	143			0.381
White		70 (67%)	21 (54%)	
Black		25 (24%)	13 (33%)	
Asian		3 (2.9%)	1 (2.6%)	
Other/mixed		6 (5.8%)	4 (10%)	

Table 1. Patient demographics: Congenital Heart Disease + Cholestasis vs. Cholestasis alone

Characteristic	N	Cholestasis Alone, N = 110[1]	CHD-C, N = 39[1]	p-value[2]
ALT (U/L)	148	59 (28, 120)	71 (37, 175)	0.561
AST (U/L)	148	91 (44, 193)	114 (73, 240)	0.222
Total bilirubin (mg/dL)	**148**	**7.1 (3.9, 10.8)**	**9.7 (6.2, 13.0)**	**0.034**
Direct bilirubin (mg/dL)	**148**	**2.7 (1.2, 5.1)**	**5.8 (3.1, 8.1)**	**<0.001**
GGT (U/L)	147	172 (86, 409)	111 (56, 339)	0.124
INR	122	1.08 (0.98, 1.20)	1.14 (1.06, 1.28)	0.051
TPN use (%)	**39**	**24 (22%)**	**15 (38%)**	**0.045**
Prematurity	147	29 (27%)	17 (44%)	0.053

Table 2. Clinical and laboratory data CHD-C vs. cholestasis alone

Results

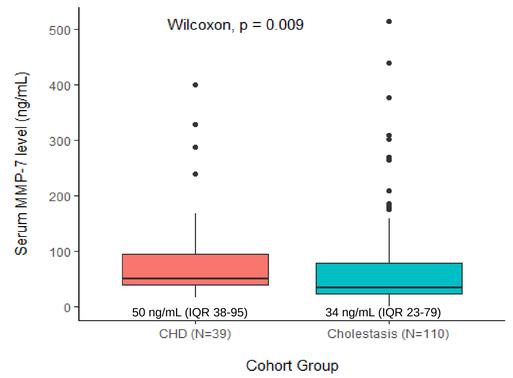

Figure 2. Median serum MMP-7 in patients with CHD + cholestasis compared to patients with cholestasis alone
Not shown: Median CHD-BA MMP-7 (82 ng/mL) was not statistically different from BA alone 146 ng/mL (IQR 113-210) (p=0.09)

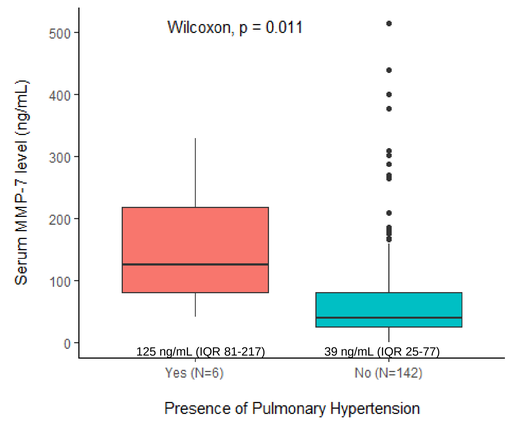

Figure 3. Median serum MMP-7 based on presence of pulmonary hypertension. Excludes one patient with PH and severe right-sided congenital diaphragmatic hernia and omphalocele.

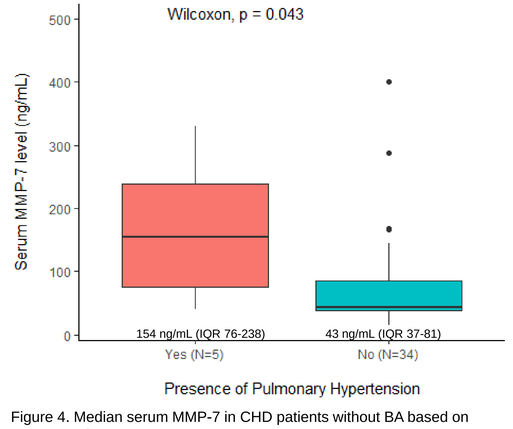

Figure 4. Median serum MMP-7 in CHD patients without BA based on presence of PH

Discussion

- Serum MMP-7 levels in infants with CHD + cholestasis were significantly greater than in those with cholestasis alone.
- MMP-7 levels were significantly higher among infants with CHD who also had clinically significant PH.
- Median MMP-7 levels in infants with CHD + cholestasis remained below standard cut-offs for detecting BA
- Further studies are necessary to determine the utility of MMP-7 as a biomarker for evaluation of biliary atresia in infants with CHD.

Conclusions

- Mild MMP-7 elevation in CHD patients should be interpreted within clinical context and additional studies are needed in this population.
- MMP-7 may be a valuable biomarker of PH in neonates and infants.

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