Supplemental Material

Prognostic roles of tetrahydroxy bile acids in infantile intrahepatic cholestasis

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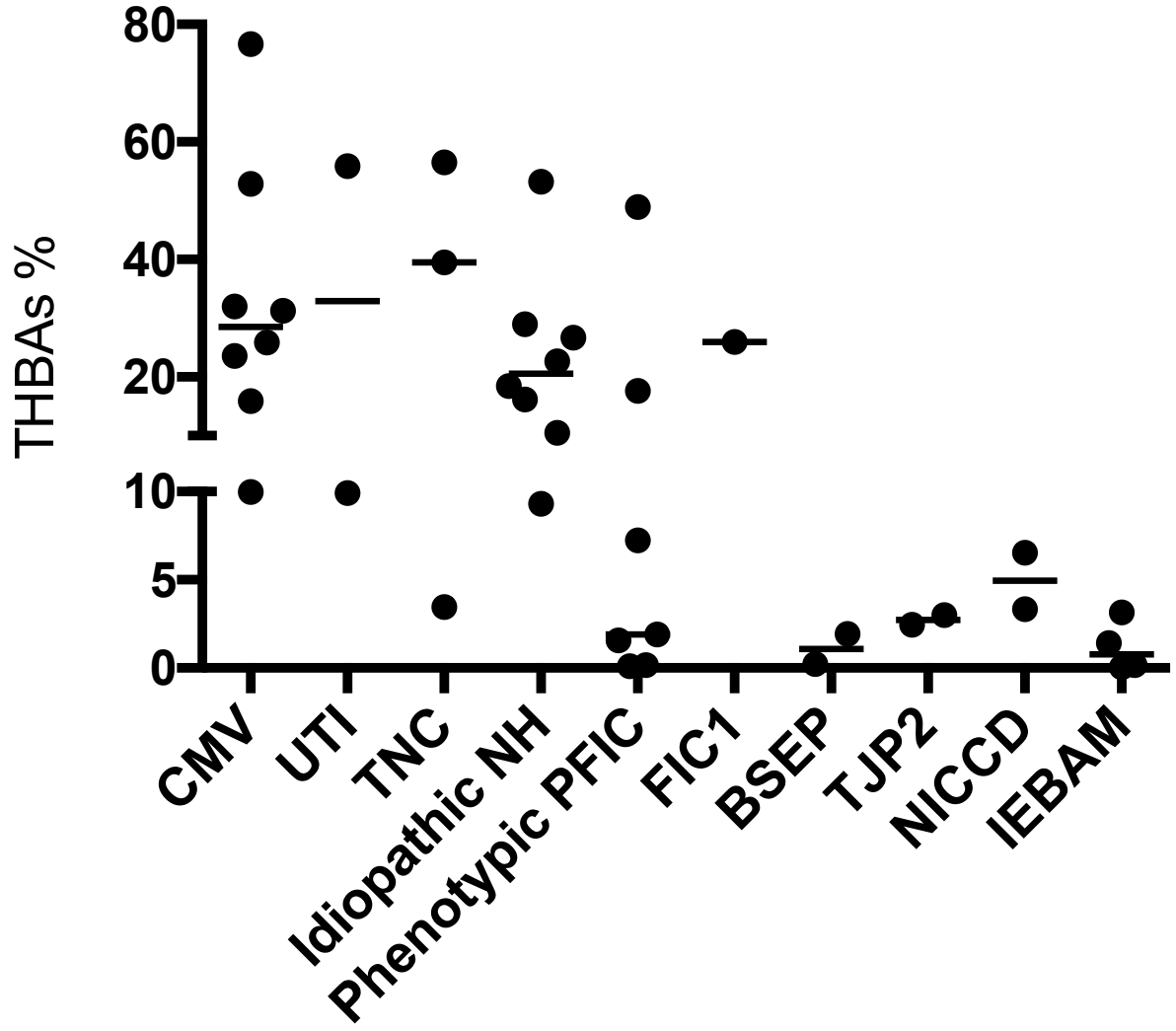
Running title:

Association of tetrahydroxy bile acids with good outcome

Supplemental Figure S1. Urinary tetrahydroxy bile acids (THBAs) proportion in patients with different etiologies of infantile cholestasis



CMV, cytomegalovirus; UTI, urinary tract infection; TNC, transient neonatal cholestasis (*SLC25A13* heterozygous mutation or *VPS33B* heterozygous mutation); NH, neonatal hepatitis; PFIC, progressive familial intrahepatic cholestasis; FIC1, familial intrahepatic cholestasis 1 deficiency; BSEP, bile salt export pump deficiency; TJP2, tight junction protein 2 deficiency; NICCD: neonatal cholestasis caused by citrin deficiency, IEBAM: inborn error of bile acid metabolism (*CYP7B1* mutation or *AKR1D1* mutation), PNAC: parenteral nutrition-associated cholestasis

Supplemental Table S1. The urinary bile acids analysed between good prognosis (jaundice free before one-year-old) patients and poor prognosis (persistence of jaundice after one-year-old) patients.

	Good prognosis	Poor prognosis	*P* value*
	μmole/mmole Cre (% over UTBA)	μmole/mmole Cre (% over UTBA)	
UTBAs	37.16(7.08-193.14)	87.26(16.17-571.06)	0.0153
CBAs	15.75(1.99-147.65)	15.75(1.99-147.65)	0.7349
	41.15(13.52-76.45)	41.15(13.52-76.45)	
CA	9.64(0.67-140.85)	8.18(0.38-371.47)	0.0409
	22.35(6.47-72.92)	11.82(0.91-65.05)	
CDCA	5.56(0.22-20.02)	14.20(0.31-185.79)	0.3673
	11.25(1.2-44.28)	20.57(0.37-52.99)	
DCA	0(0-0.03)	0(0-0.31)	0.0058
	0(0-0.09)	0(0-0.32)	
LCA	0(0-0.1)	0(0-0.4)	0.7202
	0(0-0.2)	0(0-0.66)	
THBAs	13.17(0.82-92.43)	1.22(0.05-83.67)	<0.0001
	25.89(3.45-76.73)	1.93(0.05-48.90)	
CA-1β-ol	10.13(0.51-65.26)	0.85(0.03-67.64)	<0.0001
	19.63(2.15-64.15)	1.57(0.03-39.53)	
CA-2β-ol	0.1(0-4.22)	0(0-0.87)	0.0088
	0.21(0-2.55)	0(0-0.72)	
CA-3β,4β-diol	0(0-0.25)	0(0-0.54)	0.3359
	0(0-0.94)	0(0-0.32)	
CA-4β-ol	0.16(0-8.21)	0(0-1.01)	0.0024
	0.28(0-4.97)	0(0-1.17)	
CA-6α-ol	2.24(0.21-14.74)	0.29(0-13.61)	<0.0001
	5.8(0.88-20.52)	0.39(0-11.65)	
TRHBAs	5.66(1.56-22.8)	3.46(0.09-21.36)	0.0053
	14.1(4.48-36.58)	2.95(0.1-31.99)	
UBAs	1.41(0.17-8.70)	4.60(0.79-99.28)	0.0206
	4.21(0.54-13.89)	6.62(0.5-97.74)	
KBAs	3.83(0-15.99)	12.7(0.19-115.00)	0.0165
	8.28(0-18.56)	20.66(0.21-95.04)	

UTBAs, urinary total bile acids; CBAs, common bile acids; CA, Cholic acid; CDCA, chenodeoxycholic acid; DCA, deoxycholic acid; LCA, lithocholic acid; THBAs, tetrahydroxy bile acids; CA-1β-ol, 1β, 3α,7α,12α-hydroxylated bile acid; CA-2β-ol, 2β, 3α,7α,12α-hydroxylated bile acid; CA-3β-4β-diol, 3β,4β,7α,12α-hydroxylated bile acid; CA-4β-ol, 3α, 4β,7α,12α-hydroxylated bile acid; CA-6α-ol, 3α, 6α,7α,12α-hydroxylated bile acid; TRHBAs, trihydroxy bile acids; UBAs, unsaturated bile acids; KBAs, ketonic bile acids; [%], proportion over urinary total bile acids; * *p* value of [%] of urine bile acids between two group of patients.

Supplemental Table S2. Urinary bile acid compositions in patients with genetic cholestatic diseases.

	FIC1 deficiency (n=3)	BSEP deficiency (n=4)	TJP2 deficiency (n=3)
	μmole/mmole Cre [% of UTBA]	μmole/mmole Cre [% of UTBA]	μmole/mmole Cre [% of UTBA]
UTBA	59.47(57.05-73.78)	91.07(57.74-176.13)	41.46(30.27-93.30)
CBAs	32.48(26.06-40.56)	65.17(13.92-104.32)	28.40(21.49-35.90)
	[44.03(43.82-71.10)]	[68.66(59.23-75.08)]	[68.66(38.48-71.00)
CA	16.47(14.59-25.08)	43.98(6.88-68.38)	7.87(6.43-15.20)
	[27.69(19.77-43.96)]	[37.54(35.60-54.18)]	[16.29(15.51-25.99)]
CDCA	15.40(9.48-17.83)	20.98(6.95-35.62)	20.60(10.57-21.97)
	[24.17(15.59-27.00)]	[24.28(20.23-36.62)]	[34.93(22.08-52.99)]
THBAs	19.18(4.28-22.16)	1.62(0.40-2.40)	1.24(0.12-19.00)
	[26.00(7.51-37.26)]	[2.94(0.23-5.06)]	[2.47(0.38-2.99)]
TRHBAs	6.09(3.35-16.86)	0.58(0.45-6.20)	1.10(0.30-16.70)
	[10.24(5.87-22.85)]	[1.62(0.45-2.37)]	[2.65(0.98-17.90)]
UBAs	5.06(3.00-5.06)	7.88(1.66-12.27)	3.90(1.23-8.00)
	[8.51(4.07-8.82)]	[8.27(6.97-10.49)]	[8.57(4.07-9.41)]
KBAs	2.07(0.05-3.79)	12.27(1.96-58.18)	6.74(6.20-30.40)
	[2.81(0.08-6.64)]	15.41(10.21-33.03)	[20.49(16.26-32.58)]

FIC1, familial intrahepatic cholestasis 1; BSEP, bile salt export pump; TJP2, tight junction protein 2; IEBAM, inborn error of bile acid metabolism (7α-hydroxylase deficiency and Δ4-3-oxosteroid 5β-reductase deficiency); UTBA, urinary total bile acid; CBAs, common bile acid; CA, cholic acid; CDCA, chenodeoxycholic acid; THBAs, tetrahydroxy bile acids; TRHBAs, trihydroxy bile acids; UBAs, unsaturated bile acids; KBAs, ketonic bile acids.