

Title: Prediagnostic Concentrations of Circulating Bile Acids and Hepatocellular Carcinoma Risk: REVEAL-HBV and HCV Studies

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Supplemental Table S1. Spearman correlation coefficients for bile acids¹ among included controls from the REVEAL-HBV and REVEAL-HCV cohorts.

	Primary Bile Acids						Secondary Bile Acids							Bile Acid Ratios			
	CA	GCA	TCA	CDCA	GCDCA	TCDC	DCA	GDCA	TDCA	LCA	GLCA	TLCA	UDCA	GUDCA	TUDCA	LCA/CDCA	DCA/CA
Cholic Acid (CA)	1.000	0.349	0.230	0.800	0.356	0.224	0.360	0.221	0.138	0.068	0.141	0.039	0.564	0.340	0.152	-0.895	-0.761
Glycocholic Acid (GCA)		1.000	0.881	0.283	0.869	0.841	0.225	0.683	0.679	0.212	0.348	0.353	0.147	0.596	0.456	-0.297	-0.195
Taurocholic Acid (TCA)			1.000	0.142	0.714	0.896	0.128	0.566	0.766	0.242	0.315	0.376	0.046	0.448	0.570	-0.182	-0.150
Chenodeoxycholic Acid (CDCA)				1.000	0.396	0.247	0.418	0.150	0.059	0.066	0.040	0.044	0.806	0.454	0.192	-0.716	-0.510
Glycochenodeoxycholic Acid (GCDCA)					1.000	0.838	0.200	0.674	0.587	0.134	0.408	0.315	0.250	0.786	0.550	-0.316	-0.208
Taurochenodeoxycholic Acid (TCDC)						1.000	0.145	0.618	0.780	0.260	0.330	0.410	0.124	0.596	0.683	-0.141	-0.107
Deoxycholic Acid (DCA)							1.000	0.583	0.310	0.384	0.297	0.304	0.335	0.101	-0.026	-0.352	0.262
Glycodeoxycholic Acid (GDCA)								1.000	0.790	0.255	0.567	0.435	-0.034	0.375	0.246	-0.193	0.181
Taurodeoxycholic Acid (TDCA)									1.000	0.253	0.423	0.554	-0.035	0.346	0.400	-0.079	0.095
Lithocholic Acid (LCA)										1.000	0.455	0.427	0.001	0.005	0.121	0.337	0.123
Glycolithocholic Acid (GLCA)											1.000	0.643	-0.073	0.200	0.300	0.030	0.073
Taurolithocholic Acid (TLCA)												1.000	0.143	0.283	0.364	0.176	0.194
Ursodexoycholic Acid (UDCA)													1.000	0.555	0.232	-0.572	-0.366
Glycoursodeoxycholic Acid (GUDCA)														1.000	0.646	-0.292	-0.249
Tauroursodeoxycholic Acid (TUDCA)															1.000	-0.101	-0.134
LCA/CDCA																1.000	0.877
DCA/CA																	1.000

¹All bile acid concentrations were log₂ transformed for normality.

Supplemental Table S2. Multivariate adjusted odds ratios (OR) and 95% confidence intervals (CI) for the associations between bile acid scores and hepatocellular carcinoma among participants of the REVEAL-HBV and REVEAL-HCV cohorts.

	REVEAL-HBV (N=346)				REVEAL-HCV (N=192) ¹			
	Controls n=161	Cases n=185	OR ²	95% CI	Controls n=96	Cases n=96	OR ³	95% CI
Bile Acid Scores								
Primary								
Quartile 1	42	23	1.00		24	13	1.00	
Quartile 2	41	37	1.01	(0.43, 2.33)	24	12	0.77	(0.20, 3.02)
Quartile 3	39	54	1.39	(0.62, 3.10)	24	29	2.45	(0.84, 7.14)
Quartile 4	39	71	1.85	(0.84, 4.05)	24	42	4.06	(1.26, 13.04)
P-value for trend ⁴				0.07				0.004
Continuous (log ₂)			1.34	(1.07, 1.69)			1.95	(1.30, 2.94)
Secondary								
Quartile 1	41	32	1.00		24	15	1.00	
Quartile 2	41	59	3.00	(1.32, 6.80)	24	18	1.23	(0.41, 3.71)
Quartile 3	40	37	0.86	(0.37, 2.00)	24	27	1.52	(0.59, 3.88)
Quartile 4	39	57	1.61	(0.73, 3.54)	24	36	3.69	(1.22, 11.15)
P-value for trend ⁴				0.8				0.02
Continuous (log ₂)			1.09	(0.81, 1.47)			1.55	(1.01, 2.38)
All								
Quartile 1	42	24	1.00		24	10	1.00	
Quartile 2	41	39	1.56	(0.68, 3.58)	24	16	1.40	(0.37, 5.22)
Quartile 3	39	52	1.82	(0.80, 4.17)	24	31	3.87	(1.23, 12.20)
Quartile 4	39	70	2.13	(0.96, 4.74)	24	39	5.54	(1.57, 19.57)
P-value for trend ⁴				0.1				0.005
Continuous (log ₂)			1.32	(1.03, 1.70)			2.10	(1.32, 3.36)

¹Models with categories of <5 cases are suppressed.

²Unconditional logistic regression, adjusted for age (5-year categories), sex, baseline cirrhosis status, and HBV DNA copies at baseline (<10,000, 10,000- <1,000,000, ≤1,000,000), smoking status, HbeAg (negative, positive), alcohol habit (no, yes), BMI (continuous), education level, ALT (continuous), and diabetes status at baseline.

³Conditional logistic regression, adjusted for matching factors (age (5-year categories), sex, baseline cirrhosis status, and HCV-RNA-positive rate), smoking status, alcohol habit (no, yes), BMI (continuous), education status, HCV genotype, ALT (continuous), and diabetes status at baseline.

⁴P-value for trend calculated using the Wald test.

Supplemental Table S3. Multivariate adjusted odds ratios (ORs) and 95% confidence intervals (CIs) for the associations between bile acid concentration quartiles and hepatocellular carcinoma among participants of the REVEAL-HBV and REVEAL-HCV cohorts, excluding those below the lower limit of quantitation.

	REVEAL-HBV (N=346)				REVEAL-HCV (N=192) ¹			
	Controls	Cases	OR ²	95% CI	Controls	Cases	OR ³	95% CI
Primary Bile Acids								
Cholic Acid (CA)								
Quartile 1	41	38	1.00		24	15	1.00	
Quartile 2	40	38	1.11	(0.50, 2.50)	24	23	1.84	(0.61, 5.56)
Quartile 3	39	47	0.92	(0.40, 2.11)	24	20	1.48	(0.50, 4.34)
Quartile 4	40	62	1.76	(0.83, 3.75)	24	38	3.40	(1.16, 9.97)
P-value for trend ⁴				0.1				0.03
Glycocholic Acid (GCA)								
Quartile 1	42	16	1.00		24	9	1.00	
Quartile 2	40	39	1.68	(0.71, 4.00)	24	14	2.77	(0.67, 11.43)
Quartile 3	41	47	1.51	(0.64, 3.53)	24	18	1.78	(0.45, 7.09)
Quartile 4	38	83	3.38	(1.48, 7.71)	24	55	8.16	(2.21, 30.18)
P-value for trend ⁴				0.004				<0.001
Taurocholic Acid (TCA)								
Quartile 1	37	20	1.00		21	9	1.00	
Quartile 2	38	35	1.86	(0.78, 4.43)	21	8	0.86	(0.20, 3.75)
Quartile 3	38	37	1.64	(0.71, 3.81)	21	28	2.60	(0.63, 10.64)
Quartile 4	34	88	2.96	(1.28, 6.83)	20	45	8.03	(2.09, 30.78)
P-value for trend ⁴				0.02				<0.001
Chenodeoxycholic Acid (CDCA)								
Quartile 1	40	36	1.00		24	14	1.00	
Quartile 2	40	42	0.86	(0.38, 1.96)	23	27	2.49	(0.86, 7.20)
Quartile 3	41	51	1.62	(0.74, 3.54)	24	15	1.35	(0.41, 4.40)
Quartile 4	39	56	1.53	(0.70, 3.32)	23	40	3.92	(1.41, 10.85)
P-value for trend ⁴				0.1				0.02
Glycochenodeoxycholic Acid (GCDCA)								
Quartile 1	42	24	1.00		24	8	1.00	
Quartile 2	41	45	1.32	(0.58, 2.97)	24	14	2.38	(0.50, 11.25)

Quartile 3	41	41	1.28	(0.56, 2.93)	24	36	11.94	(2.55, 55.99)
Quartile 4	37	75	2.20	(0.99, 4.88)	24	38	7.61	(1.73, 33.44)
P-value for trend ⁴				0.05				0.007
Taurochenodeoxycholic Acid (TCDCA)								
Quartile 1	41	21	1.00		24	6	1.00	
Quartile 2	40	40	1.59	(0.70, 3.65)	24	11	1.80	(0.45, 7.23)
Quartile 3	42	37	1.03	(0.44, 2.43)	24	30	4.67	(1.26, 17.29)
Quartile 4	36	87	2.60	(1.16, 5.83)	24	49	7.27	(1.99, 26.62)
P-value for trend ⁴				0.01				0.001
Secondary Bile Acids								
Deoxycholic Acid (DCA)								
Quartile 1	39	54	1.00		22	18	1.00	
Quartile 2	36	47	0.79	(0.37, 1.68)	21	15	0.61	(0.18, 2.02)
Quartile 3	36	39	0.59	(0.27, 1.30)	22	26	1.08	(0.38, 3.07)
Quartile 4	38	32	0.37	(0.16, 0.82)	21	28	1.79	(0.51, 6.27)
P-value for trend ⁴				0.02				0.2
Glycodeoxycholic Acid (GDCA)								
Quartile 1	40	34	1.00		22	19	1.00	
Quartile 2	38	40	1.10	(0.49, 2.44)	22	13	1.02	(0.34, 3.07)
Quartile 3	38	33	0.65	(0.28, 1.52)	22	22	1.38	(0.43, 4.38)
Quartile 4	37	68	1.47	(0.68, 3.17)	22	38	1.78	(0.61, 5.20)
P-value for trend ⁴				0.4				0.3
Taurodeoxycholic Acid (TDCA)								
Quartile 1	31	18	1.00		15	9	1.00	
Quartile 2	31	30	1.73	(0.66, 4.54)	15	16	0.92	(0.13, 6.48)
Quartile 3	32	36	1.36	(0.53, 3.46)	15	21	1.30	(0.20, 8.47)
Quartile 4	29	61	1.88	(0.75, 4.74)	15	28	3.63	(0.58, 22.86)
P-value for trend ⁴				0.3				0.1
Lithocholic Acid (LCA)								
Quartile 1	22	30	1.00		11	8	1.00	
Quartile 2	19	26	1.51	(0.50, 4.59)	11	16	3.86	(0.04, 335.38)
Quartile 3	20	24	0.35	(0.11, 1.13)	11	12	0.47	(0.00, 2752.14)

Quartile 4	21	27	0.41	(0.13, 1.30)	11	22	1.10	(0.01, 199.00)
P-value for trend ⁴				0.02				0.7
Glycolithocholic Acid (GLCA)								
Quartile 1	26	24	1.00		11	8	—	
Quartile 2	24	35	2.14	(0.77, 5.93)	10	18	—	
Quartile 3	25	33	1.82	(0.66, 5.03)	10	15	—	
Quartile 4	24	32	1.54	(0.58, 4.08)	10	17	—	
P-value for trend ⁴				0.9				0.1
Taurolithocholic Acid (TLCA)								
Quartile 1	9	27	1.00		3	4	—	
Quartile 2	9	10	0.03	(0.00, 0.46)	3	12	—	
Quartile 3	8	17	0.18	(0.02, 1.35)	3	5	—	
Quartile 4	7	13	0.10	(0.01, 0.92)	3	12	—	
P-value for trend ⁴				0.1				<0.001
Ursodexoycholic Acid (UDCA)								
Quartile 1	41	38	1.00		22	9	1.00	
Quartile 2	35	46	1.62	(0.75, 3.53)	21	21	5.58	(1.28, 24.32)
Quartile 3	38	35	1.21	(0.54, 2.71)	22	48	7.81	(2.14, 28.48)
Quartile 4	37	52	1.78	(0.83, 3.80)	21	10	2.39	(0.58, 9.87)
P-value for trend ⁴				0.3				0.8
Glycoursodeoxycholic Acid (GUDCA)								
Quartile 1	41	26	1.00		23	14	1.00	
Quartile 2	40	47	1.73	(0.75, 3.99)	23	23	1.29	(0.45, 3.72)
Quartile 3	41	44	1.84	(0.80, 4.22)	23	33	1.91	(0.74, 4.88)
Quartile 4	37	68	2.61	(1.15, 5.93)	23	24	1.75	(0.53, 5.79)
P-value for trend ⁴				0.06				0.3
Tauroursodeoxycholic Acid (TUDCA)								
Quartile 1	24	27	1.00		12	16	1.00	
Quartile 2	24	15	0.47	(0.16, 1.44)	12	12	0.32	(0.00, 43.26)
Quartile 3	23	53	2.31	(0.92, 5.80)	12	16	1.89	(0.06, 64.31)
Quartile 4	23	47	1.32	(0.52, 3.34)	12	23	50.98	(0.06, 44024.85)
P-value for trend ⁴				0.3				0.2

Secondary/Primary Ratios**LCA/CDCA**

Quartile 1	21	37	1.00		11	13	1.00	
Quartile 2	19	28	0.49	(0.17, 1.37)	11	20	2.23	(0.12, 40.14)
Quartile 3	20	27	0.67	(0.22, 2.08)	11	9	1.40	(0.03, 56.19)
Quartile 4	22	15	0.28	(0.09, 0.89)	11	16	0.70	(0.04, 12.08)
P-value for trend ⁴				0.06				0.6

DCA/CA

Quartile 1	38	64	1.00		21	26	1.00	
Quartile 2	36	41	0.64	(0.30, 1.36)	22	20	0.44	(0.14, 1.41)
Quartile 3	37	47	0.58	(0.28, 1.20)	21	21	1.11	(0.36, 3.40)
Quartile 4	38	20	0.24	(0.10, 0.59)	22	20	0.48	(0.15, 1.59)
P-value for trend ⁴				0.005				0.4

¹Models with categories of <5 cases are suppressed.

²Unconditional logistic regression, adjusted for age (5-year categories), sex, baseline cirrhosis status, and HBV DNA copies at baseline (<10,000, 10,000- <1,000,000, ≤1,000,000), smoking status, HbeAg (negative, positive), alcohol habit (no, yes), BMI (continuous), education level, ALT (continuous), and diabetes status at baseline.

³Conditional logistic regression, adjusted for matching factors (age (5-year categories), sex, baseline cirrhosis status, and HCV-RNA-positive rate), smoking status, alcohol habit (no, yes), BMI (continuous), education status, HCV genotype, ALT (continuous), and diabetes status at baseline.

⁴P-value for trend calculated using the Wald test.

Supplemental Table S4. Multivariate adjusted odds ratios (ORs) and 95% confidence intervals (CIs) for the associations between bile acid concentration quartiles and hepatocellular carcinoma among participants of the REVEAL-HBV and REVEAL-HCV cohorts, excluding those diagnosed with hepatocellular carcinoma within 5 years of the study baseline.

	REVEAL-HBV (N=346)				REVEAL-HCV (N=192) ¹			
	Controls	Cases	OR ²	95% CI	Controls	Cases	OR ³	95% CI
Primary Bile Acids								
Cholic Acid (CA)								
Quartile 1	42	37	1.00		24	14	1.00	
Quartile 2	40	37	1.22	(0.54, 2.73)	24	21	1.67	(0.55, 5.13)
Quartile 3	39	45	1.05	(0.46, 2.39)	24	20	1.52	(0.51, 4.52)
Quartile 4	40	56	1.80	(0.84, 3.86)	24	38	3.85	(1.25, 11.87)
P-value for trend ⁴				0.1				0.02
Glycocholic Acid (GCA)								
Quartile 1	42	15	1.00		24	9	1.00	
Quartile 2	40	37	1.83	(0.75, 4.45)	24	14	2.73	(0.66, 11.28)
Quartile 3	41	44	1.51	(0.63, 3.60)	24	17	1.93	(0.49, 7.60)
Quartile 4	38	79	3.70	(1.59, 8.61)	24	53	8.11	(2.20, 29.99)
P-value for trend ⁴				0.002				<0.001
Taurocholic Acid (TCA)								
Quartile 1	51	23	1.00		34	15	1.00	
Quartile 2	38	32	1.83	(0.80, 4.18)	21	8	0.97	(0.29, 3.30)
Quartile 3	38	35	1.69	(0.76, 3.75)	21	28	2.58	(0.81, 8.15)
Quartile 4	34	85	3.26	(1.50, 7.08)	20	42	5.01	(1.84, 13.65)
P-value for trend ⁴				0.007				0.001
Chenodeoxycholic Acid (CDCA)								
Quartile 1	41	36	1.00		26	11	1.00	
Quartile 2	40	39	0.75	(0.33, 1.74)	23	27	3.89	(1.21, 12.50)
Quartile 3	41	49	1.55	(0.71, 3.42)	24	15	2.41	(0.72, 8.15)
Quartile 4	39	51	1.51	(0.69, 3.28)	23	40	5.53	(1.88, 16.27)
P-value for trend ⁴				0.1				0.01
Glychenodeoxycholic Acid (GCDCA)								
Quartile 1	42	22	1.00		24	8	1.00	
Quartile 2	41	43	1.37	(0.60, 3.13)	24	14	2.90	(0.61, 13.78)
Quartile 3	41	38	1.28	(0.55, 2.98)	24	35	16.50	(3.16, 86.14)

Quartile 4	37	72	2.41	(1.07, 5.42)	24	36	8.29	(1.83, 37.58)
P-value for trend ⁴				0.03				0.009
Taurochenodeoxycholic Acid (TCDCA)								
Quartile 1	43	19	1.00		24	6	1.00	
Quartile 2	40	36	1.83	(0.78, 4.28)	24	11	1.92	(0.48, 7.72)
Quartile 3	42	36	1.27	(0.54, 3.03)	24	30	5.09	(1.36, 19.03)
Quartile 4	36	84	3.24	(1.44, 7.33)	24	46	7.21	(1.96, 26.51)
P-value for trend ⁴				0.005				0.002
Secondary Bile Acids								
Deoxycholic Acid (DCA)								
Quartile 1	51	66	1.00		32	25	1.00	
Quartile 2	36	41	0.86	(0.42, 1.76)	21	15	0.56	(0.19, 1.66)
Quartile 3	36	36	0.66	(0.31, 1.40)	22	25	1.14	(0.46, 2.84)
Quartile 4	38	32	0.41	(0.19, 0.89)	21	28	2.29	(0.86, 6.09)
P-value for trend ⁴				0.02				0.06
Glycodeoxycholic Acid (GDCA)								
Quartile 1	48	44	1.00		30	22	1.00	
Quartile 2	38	35	0.92	(0.43, 1.97)	22	13	0.86	(0.31, 2.37)
Quartile 3	38	31	0.60	(0.27, 1.33)	22	21	1.21	(0.43, 3.45)
Quartile 4	37	65	1.36	(0.66, 2.79)	22	37	2.47	(0.98, 6.23)
P-value for trend ⁴				0.3				0.04
Taurodeoxycholic Acid (TDCA)								
Quartile 1	69	54	1.00		51	30	1.00	
Quartile 2	31	26	1.43	(0.66, 3.09)	15	16	1.47	(0.53, 4.12)
Quartile 3	32	36	1.08	(0.51, 2.26)	15	21	1.96	(0.71, 5.43)
Quartile 4	29	59	1.52	(0.74, 3.13)	15	26	3.47	(1.16, 10.38)
P-value for trend ⁴				0.3				0.03
Lithocholic Acid (LCA)								
Quartile 1	101	102	1.00		63	44	1.00	
Quartile 2	19	24	1.44	(0.63, 3.28)	11	16	2.37	(0.82, 6.81)
Quartile 3	20	24	0.54	(0.23, 1.29)	11	12	1.59	(0.51, 4.95)
Quartile 4	21	25	0.52	(0.22, 1.24)	11	21	3.36	(1.15, 9.76)
P-value for trend ⁴				0.06				0.04

Glycolithocholic Acid (GLCA)

Quartile 1	88	80	1.00		66	45	1.00	
Quartile 2	24	34	1.31	(0.59, 2.92)	10	17	2.51	(0.83, 7.60)
Quartile 3	25	32	1.20	(0.55, 2.62)	10	15	2.19	(0.69, 6.99)
Quartile 4	24	29	1.09	(0.51, 2.34)	10	16	4.79	(1.30, 17.69)

P-value for trend⁴

0.9

0.02

Taurolithocholic Acid (TLCA)

Quartile 1	137	137	1.00		87	66	—	
Quartile 2	9	9	0.64	(0.20, 2.05)	3	11	—	
Quartile 3	8	17	1.25	(0.40, 3.89)	3	5	—	
Quartile 4	7	12	0.80	(0.23, 2.76)	3	11	—	

P-value for trend⁴

0.9

0.003

Ursodexoycholic Acid (UDCA)

Quartile 1	51	49	1.00		32	15	1.00	
Quartile 2	35	45	1.74	(0.82, 3.68)	21	20	2.75	(0.85, 8.88)
Quartile 3	38	31	1.20	(0.54, 2.65)	22	48	5.01	(1.79, 14.02)
Quartile 4	37	50	1.96	(0.94, 4.07)	21	10	2.01	(0.59, 6.87)

P-value for trend⁴

0.2

0.7

Glycoursodeoxycholic Acid (GUDCA)

Quartile 1	43	26	1.00		27	15	1.00	
Quartile 2	40	40	1.68	(0.73, 3.89)	23	23	1.50	(0.57, 3.99)
Quartile 3	41	44	2.12	(0.93, 4.84)	23	32	2.34	(0.94, 5.82)
Quartile 4	37	65	3.09	(1.37, 6.97)	23	23	2.04	(0.66, 6.34)

P-value for trend⁴

0.009

0.2

Tauroursodeoxycholic Acid (TUDCA)

Quartile 1	91	63	1.00		60	45	1.00	
Quartile 2	24	15	0.70	(0.28, 1.75)	12	12	0.94	(0.33, 2.68)
Quartile 3	23	53	3.31	(1.60, 6.83)	12	15	1.31	(0.46, 3.74)
Quartile 4	23	44	1.96	(0.94, 4.09)	12	21	3.41	(1.16, 10.08)

P-value for trend⁴

0.01

0.03

Secondary/Primary Ratios**LCA/CDCA**

Quartile 1	100	107	1.00		63	50	1.00	
Quartile 2	19	27	0.83	(0.37, 1.87)	11	19	1.43	(0.47, 4.31)

Quartile 3	20	26	1.02	(0.45, 2.33)	11	9	1.73	(0.55, 5.45)
Quartile 4	22	15	0.35	(0.13, 0.95)	11	15	1.38	(0.50, 3.80)
P-value for trend ⁴				0.07				0.5
DCA/CA								
Quartile 1	50	73	1.00		31	34	1.00	
Quartile 2	36	37	0.70	(0.34, 1.45)	22	19	0.55	(0.20, 1.46)
Quartile 3	37	45	0.66	(0.33, 1.32)	21	20	1.45	(0.55, 3.83)
Quartile 4	38	20	0.28	(0.12, 0.67)	22	20	0.69	(0.26, 1.80)
P-value for trend ⁴				0.006				0.7

¹Models with categories of <5 cases are suppressed.

²Unconditional logistic regression, adjusted for age (5-year categories), sex, baseline cirrhosis status, and HBV DNA copies at baseline (<10,000, 10,000- <1,000,000, ≤1,000,000), smoking status, HbeAg (negative, positive), alcohol habit (no, yes), BMI (continuous), and education level.

³Conditional logistic regression, adjusted for matching factors (age (5-year categories), sex, baseline cirrhosis status, and HCV-RNA-positive rate), smoking status, alcohol habit (no, yes), BMI (continuous), education status, and HCV genotype.

⁴P-value for trend calculated using the Wald test.