Loss of biochemical response at any time worsens outcomes in UDCA-treated patients with primary biliary cholangitis

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Table S1: Percent of Missing Values in Imputation: CaNAL Cohort

Variable	Percent Missing
Alkaline Phosphatase	17.3%
Total Bilirubin	21.3%
Aspartate Aminotransferase	29.2%
Alanine Aminotransferase	16.8%
Platelet Count	14.4%
Albumin	33.3%

Variables not included in this table had no missing values.

Table S2: Association between Age at UDCA Initiation and Rates of Biochemical State Transition

Main Analysis (n=823)		**Sensitivity Analysis** (n=823)		**External Validation** (n=2237)	
State Transition	**HR (95%CI)**	**State Transition**	**HR (95%CI)**	**State Transition**	**HR (95%CI)**
IR1 → AR1	1.03 (1.01-1.04)	IR1 → AR1	1.03 (1.01-1.04)	IR1 → AR1	1.01 (1.01-1.02)
AR1→ IR2	1.00 (0.99-1.01)	AR1→ IR2	0.99 (0.98-1.00)	AR1→ IR2	1.00 (0.99-1.00)
IR2 → AR2	1.04 (1.03-1.05)	IR2 → AR2	1.04 (1.03-1.05)	IR2 → AR2	1.02 (1.01-1.03)
AR2 → IR3	1.00 (0.99-1.01)	AR2 → IR3	1.00 (0.99-1.02)	AR2 → IR3	0.98 (0.97-0.99)
IR3 → AR3	1.04 (1.02-1.06)	IR3 → AR3	1.03 (1.02-1.05)	IR3 → AR3	1.01 (1.01-1.03)
AR3 → IR4+	1.04 (1.01-1.06)	AR3 → IR4+	1.03 (1.01-1.05)	AR3 → IR4+	0.99 (0.97-1.01)
Transition to Liver Transplant or Death:					
IR1 → LTx/D	0.99 (0.96-1.02)	IR1 → LTx/D	0.98 (0.95-1.02)	IR1 → LTx/D	1.04 (1.03-1.05)
AR1 → LTx/D	1.12 (1.06-1.18)	AR1 → LTx/D	1.14 (1.06-1.23)	AR1 → LTx/D	1.22 (1.12-1.33)
IR2 → LTx/D	1.01 (0.97-1.05)	IR2 → LTx/D	1.00 (0.96-1.04)	IR2 → LTx/D	1.06 (1.03-1.08)
AR2 → LTx/D	0.77 (0.46-1.29)	AR2 → LTx/D	1.15 (1.03-1.29)	AR2 → LTx/D	1.27 (1.12-1.43)
IR3 → LTx/D	0.99 (0.95-1.04)	IR3 → LTx/D	1.06 (0.99-1.03)	IR3 → LTx/D	1.05 (1.01-1.10)
AR3 → LTx/D	0.97 (0.85-1.10)	AR3 → LTx/D	0.78 (0.50-1.21)	AR3 → LTx/D	1.18 (1.03-1.35)
IR4+ → LTx/D	1.05 (1.01-1.09)	IR4+ → LTx/D	1.05 (1.01-1.09)	IR4+ → LTx/D	1.03 (0.99-1.08)

Hazard ratios are per one-year increase in age at UDCA initiation. Hazard ratios are derived based on the fitted multistate model, by exponentiating the estimated covariate effects on the log-transition intensities.

Abbreviations: Initial inadequate response, IR1; 1st adequate response, AR1; 2nd inadequate response, IR2; 2nd adequate response, AR2; 3rd inadequate response, IR3; 3rd adequate response, AR3; 4th inadequate response and all states thereafter, IR4.Liver transplant or dead, LTx/D; Hazard Ratio, HR.

Table S3: Association between ALP at UDCA 1-year and Rates of Biochemical State Transition

Main Analysis (n=823)		**Sensitivity Analysis** (n=823)		**External Validation** (n=2237)	
State Transition	**HR (95%CI)**	**State Transition**	**HR (95%CI)**	**State Transition**	**HR (95%CI)**
IR1 → AR1	0.55 (0.40-0.74)	IR1 → AR1	0.53 (0.39-0.71)	IR1 → AR1	0.21 (0.17-0.27)
AR1→ IR2	2.20 (1.83-2.65)	AR1→ IR2	2.09 (1.75-2.50)	AR1→ IR2	3.01 (2.61-3.48)
IR2 → AR2	0.65 (0.52-0.80)	IR2 → AR2	0.73 (0.58-0.92)	IR2 → AR2	0.58 (0.48-0.70)
AR2 → IR3	1.54 (1.18-1.99)	AR2 → IR3	1.88 (1.44-2.46)	AR2 → IR3	1.38 (1.10-1.74)
IR3 → AR3	0.69 (0.51-0.93)	IR3 → AR3	0.92 (0.68-1.25)	IR3 → AR3	1.15 (0.84-1.57)
AR3 → IR4+	1.96 (1.36-2.83)	AR3 → IR4+	1.21 (0.86-1.70)	AR3 → IR4+	0.69 (0.49-0.99)
Transition to Liver Transplant or Death					
IR1 → LTx/D	0.86 (0.46-1.61)	IR1 → LTx/D	0.70 (0.40-1.23)	IR1 → LTx/D	1.02 (0.80-1.21)
AR1 → LTx/D	0.33 (0.06-1.80)	AR1 → LTx/D	0.32 (0.04-2.93)	AR1 → LTx/D	4.30 (1.33-13.9)
IR2 → LTx/D	1.69 (0.94-3.03)	IR2 → LTx/D	1.09 (0.62-1.92)	IR2 → LTx/D	0.49 (0.31-0.77)
AR2 → LTx/D	15.32 (0.0-10^5)	AR2 → LTx/D	1.10 (0.03-44.26)	AR2 → LTx/D	0.48 (0.07-3.37)
IR3 → LTx/D	0.79 (0.41-1.54)	IR3 → LTx/D	0.59 (0.23-1.49)	IR3 → LTx/D	0.55 (0.19-1.55)
AR3 → LTx/D	0.30 (0.02-3.63)	AR3 → LTx/D	1.38 (0.01-163.4)	AR3 → LTx/D	4.61 (0.27-77.7)
IR4+ → LTx/D	1.14 (0.54-2.38)	IR4+ → LTx/D	0.98 (0.50-1.93)	IR4+ → LTx/D	0.94 (0.36-2.42)

Hazard ratios are per one unit increase in $\log_e$(ALP) at UDCA initiation. Hazard ratios are derived based on the fitted multistate model, by exponentiating the estimated covariate effects on the log-transition intensities.

Abbreviations: Initial inadequate response, IR1; 1st adequate response, AR1; 2nd inadequate response, IR2; 2nd adequate response, AR2; 3rd inadequate response, IR3; 3rd adequate response, AR3; 4th inadequate response and all states thereafter, IR4.Liver transplant or dead, LTx/D; Hazard Ratio, HR.

Table S4: Association between Total Bilirubin at UDCA 1-year and Rates of Biochemical State Transition

Main Analysis (n=823)		**Sensitivity Analysis** (n=823)		**External Validation** (n=2237)	
State Transition	**HR (95%CI)**	**State Transition**	**HR (95%CI)**	**State Transition**	**HR (95%CI)**
IR1 → AR1	0.99 (0.78-1.27)	IR1 → AR1	0.88 (0.69-1.13)	IR1 → AR1	0.48 (0.41-0.56)
AR1→ IR2	1.41 (1.18-1.67)	AR1→ IR2	2.08 (1.69-2.56)	AR1→ IR2	1.63 (1.37-1.94)
IR2 → AR2	0.69 (0.56-0.85)	IR2 → AR2	0.66 (0.52-0.84)	IR2 → AR2	0.75 (0.61-0.91)
AR2 → IR3	1.98 (1.52-2.57)	AR2 → IR3	1.78 (1.28-2.46)	AR2 → IR3	1.90 (1.45-2.50)
IR3 → AR3	0.80 (0.57-1.11)	IR3 → AR3	0.73 (0.50-1.06)	IR3 → AR3	0.99 (0.74-1.32)
AR3 → IR4+	1.52 (1.10-2.10)	AR3 → IR4+	1.96 (1.27-3.01)	AR3 → IR4+	1.21 (0.83-1.78)
Transition to Liver Transplant or Death					
IR1 → LTx/D	3.04 (2.03-4.56)	IR1 → LTx/D	3.37 (2.18-5.21)	IR1 → LTx/D	2.91 (2.48-3.42)
AR1 → LTx/D	1.20 (0.55-2.60)	AR1 → LTx/D	1.05 (0.28-3.98)	AR1 → LTx/D	8.84 (1.04-75.3)
IR2 → LTx/D	1.63 (0.95-2.78)	IR2 → LTx/D	1.92 (1.07-3.44)	IR2 → LTx/D	1.18 (0.67-2.06)
AR2 → LTx/D	0.01 (0.01-64.9)	AR2 → LTx/D	0.41 (0.03-6.40)	AR2 → LTx/D	0.09 (0.02-0.33)
IR3 → LTx/D	2.28 (1.29-4.02)	IR3 → LTx/D	5.07 (1.66-15.47)	IR3 → LTx/D	0.90 (0.45-1.83)
AR3 → LTx/D	0.27 (0.01-6.28)	AR3 → LTx/D	0.01 (0.01-7.77)	AR3 → LTx/D	1.18 (0.23-6.10)
IR4+ → LTx/D	2.07 (1.12-3.83)	IR4+ → LTx/D	3.22 (1.72-6.04)	IR4+ → LTx/D	1.01 (0.48-2.09)

Hazard ratios are per one unit increase in $\log_e$(Total Bilirubin) at UDCA initiation. Hazard ratios are derived based on the fitted multistate model, by exponentiating the estimated covariate effects on the log-transition intensities.

Abbreviations: Initial inadequate response, IR1; 1st adequate response, AR1; 2nd inadequate response, IR2; 2nd adequate response, AR2; 3rd inadequate response, IR3; 3rd adequate response, AR3; 4th inadequate response and all states thereafter, IR4.Liver transplant or dead, LTx/D; Hazard Ratio, HR.