

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

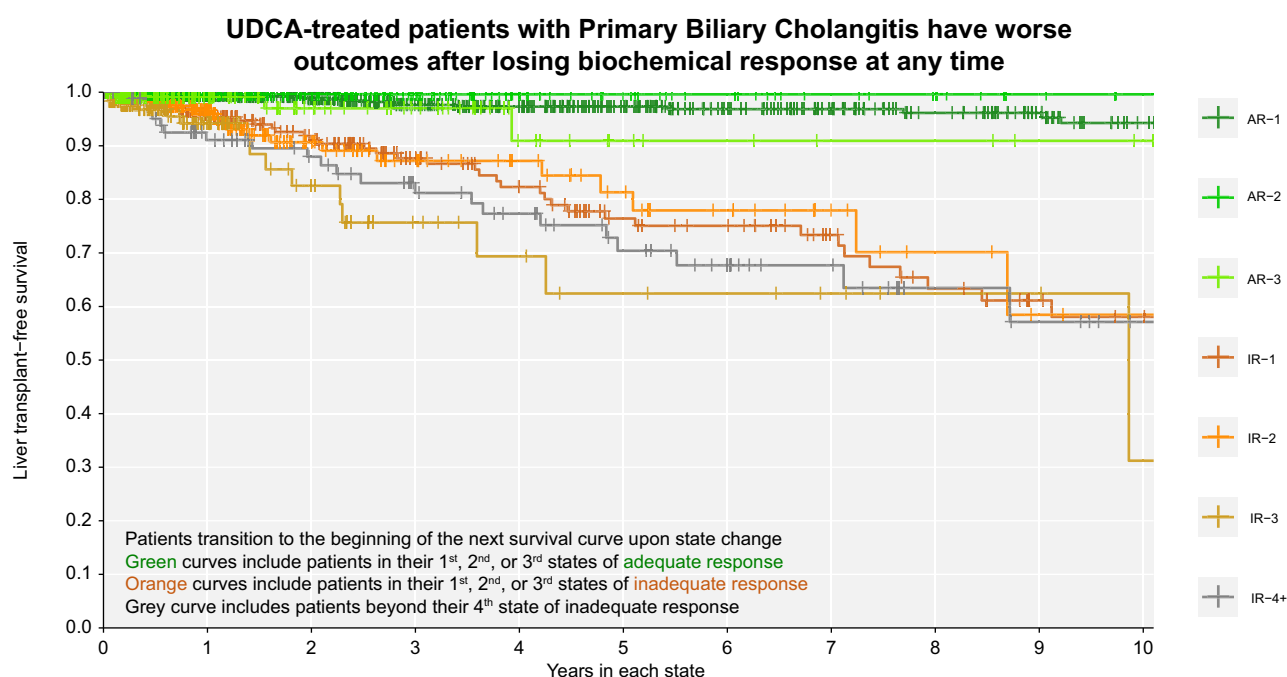
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Graphical abstract



Highlights:

- Biochemical response to therapy is associated with good prognosis in primary biliary cholangitis.
- Patients with primary biliary cholangitis transition between biochemical response states over time.
- There is a survival benefit when a patient transitions from inadequate to adequate response at any time.
- Clinicians should re-evaluate risk and optimize treatment decisions throughout follow-up.

Impact and implications:

Early biochemical response to ursodeoxycholic acid is associated with good prognosis in patients with primary biliary cholangitis (PBC). Our work demonstrates that patients with PBC transition between biochemical response states over time, and that these transitions correspond with changes in risk of liver transplantation or death. Clinicians should re-evaluate risk and optimize treatment decisions for patients with PBC throughout follow-up, regardless of early biochemical response to therapy.

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

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Background & Aims: Biochemical response to ursodeoxycholic acid (UDCA) therapy is associated with good prognosis in people living with primary biliary cholangitis (PBC). Biochemical response is typically assessed early in disease and it is not known what proportion of patients lose previously attained biochemical response, nor whether this impacts long-term liver transplant (LT)-free survival.

Methods: We identified all UDCA-treated patients with PBC from the Canadian Network for Autoimmune Liver disease with biochemical measurements at 1 year, and evaluated their liver biochemistry over time. Inadequate biochemical response was defined as serum alkaline phosphatase $\geq 1.67\times$ the upper limit of normal or abnormal serum total bilirubin at 1 year of UDCA therapy and all time points thereafter. Multistate Markov models were used to estimate transition rates between biochemical response states and from each state to LT or death. Results were validated in an external cohort (GLOBAL PBC registry).

Results: A total of 823 patients from eight centers were included. Mean age at diagnosis was 53 years, 91% were female, 33% had inadequate biochemical response to UDCA at 1 year ($n = 269$). Patients who retained initial adequate response had lower rates of LT or death compared to patients who subsequently lost response (relative rate 0.102, 95% CI 0.047–0.223). Patients who regained adequate response had lower rates than patients who did not (0.016, 95% CI 0.001–0.568), and patients who lost response once more (0.010, 95% CI 0.001–0.340). Patients who regained adequate response for a third time also had lower rates than patients who did not (0.151, 95% CI 0.040–0.566). Analyses in the GLOBAL PBC registry ($n = 2,237$) validated these results.

Conclusion: Loss of biochemical response at any time is associated with heightened risks of LT or death in people living with PBC. Achievement of biochemical response is an important goal throughout follow-up, regardless of biochemical response profile early in therapy.

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Introduction

Primary biliary cholangitis (PBC) is a slowly progressive immune-mediated biliary disease that leads to chronic cholestasis, ductopenia, liver fibrosis, and eventual liver transplantation (LT) or death. However, ursodeoxycholic acid (UDCA) when given as first-line treatment for patients with PBC has been demonstrated to slow histological progression^{1–3} and improve LT-free survival.^{4–7} Many criteria have been proposed to assess biochemical response to UDCA,^{8–13} the early attainment of which is associated with improved long-term clinical outcomes. Most biochemical response criteria include alkaline phosphatase (ALP) and/or total bilirubin because

values of both biomarkers early in treatment have been associated with long-term clinical outcomes in patients with PBC.^{4,14–17} UDCA response is typically assessed between 6–24 months after UDCA initiation,^{8–11,13} with approximately 40% of patients classified as inadequate responders at 1 year.⁸ Importantly, inadequate responders to UDCA experience sub-optimal survival compared to patients who meet response criteria and to matched control populations.^{8,18}

To date, studies have investigated the association between inadequate biochemical response to UDCA and adverse clinical outcomes based on biochemical measurements at discrete time points after UDCA initiation. The decision to evaluate

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UDCA response at pre-specified time points early in therapy is somewhat arbitrary and does not consider that a patient with PBC may transition through different disease states over time, altering their risk of a clinical event.¹⁹ Longitudinal patterns of UDCA response, and how these patterns may relate to risks of adverse clinical events over time, remain unstudied.

We sought to move beyond frameworks that only consider UDCA response at a single time point early in the course of therapy, and describe how patients transition between response states during the course of their disease. We anchor our definition of biochemical response in real-world criteria for the initiation of second-line therapy, and we evaluate how transitions between these biochemical states associate with eventual risks of LT or death.

Materials and methods

Study design, data source and population

Our study involved two large and distinct cohorts of patients with PBC; one as a primary cohort and the other to validate our findings. We included patients from the Canadian Network for Autoimmune Liver disease (CaNAL), a pan-Canadian registry of patients with autoimmune liver disease including long-term retrospective data and detailed prospective follow-up at tertiary care liver clinics. CaNAL data are collected through detailed manual chart review linked to automated extraction from electronic patient records. Further details about CaNAL are available in the public domain.^{20,21} We included patients diagnosed with PBC according to established clinical practice guidelines of the American Association for Liver Disease and the European Association for Study of the Liver.^{22,23} Patients had to be treated with UDCA and have had biochemical measurements at 1 year after UDCA initiation allowing for assessment of UDCA response. We excluded patients who had overlapping clinical diagnoses of autoimmune hepatitis or had end-stage liver disease within the first 6 months of UDCA treatment based on presence of ascites, hepatic encephalopathy, variceal bleeding, hepatorenal syndrome, hepatopulmonary syndrome, gastric antral vascular ectasia, hepatocellular carcinoma, LT, or death. To ensure that patients had adequate opportunity to establish UDCA response, we excluded patients who were treated with UDCA for less than 6 months and defined index date as 1 year after UDCA initiation. Follow-up time was censored at UDCA discontinuation, initiation of second-line therapy (obeticholic acid, bezafibrate, fenofibrate), or the last follow-up. Data from the Global PBC Study Group, an international cohort of patients with PBC,¹⁴ were used for external validation. Patients from Toronto exist in both datasets and were excluded from external validation. Both studies hold relevant ethics approval at participating institutions.

Outcome measures

Biochemical response to UDCA was defined at every biochemical measurement throughout follow-up using the following criterion: ALP $\geq 1.67 \times$ the upper limit of normal (ULN) or abnormal total bilirubin.²⁴ Limits of normal were based on site-specific values. We selected this criterion because right now it determines the clinical labelling of biochemical response and is the indication for reimbursement of second-line

obeticholic acid therapy, which is immediately relevant for real-world clinical decision making. Each patient was assigned an initial state reflecting adequate or inadequate response to UDCA at 1 year after initiation. UDCA response at 1 year was defined using biochemical measurements closest to 1 year. Patients with inadequate response at 1 year were labelled IR-1 (inadequate response #1) and patients with adequate response were labelled AR-1 (adequate response #1). UDCA response was also assessed at all available biochemical measurements from 1 year until end of follow-up. As a patient's biochemical response status changed over time, the patient was assigned a new UDCA response state at the time that transition was observed (Fig. 1). Patients could transition to a composite outcome of LT or death from any state at any point in time, and patients without one of these events were censored at last known date alive.

Statistical analysis

We applied Kaplan Meier curves to investigate the association between each UDCA response state and LT-free survival. Kaplan Meier curves employ a clock-reset approach with respect to follow-up time: patients transition to the beginning of the next survival curve when they change UDCA response state. Patients are censored at the time of state transition or the last known date alive. Survival curves are compared using the log-rank test with *p* values adjusted for multiple comparisons using the Benjamini-Hochberg method.²⁵ We applied time-homogeneous multistate Markov models with progressive state changes to estimate the rate of transition between UDCA response states, and from each state to LT or death. Follow-up time began at 1 year of UDCA therapy and patients entered the model as either adequate responders or inadequate responders at 1 year. Multistate models were fitted without covariates to examine state changes over time for the overall cohort, and with covariates to investigate how patient characteristics were associated with transition between states. Covariates included age at UDCA initiation, sex, ALP \times ULN, total bilirubin \times ULN, and fibrosis-4 (FIB-4) score indicating advanced fibrosis.²⁶ We compared rates of transition between different states using relative rates, calculated as the ratio of instantaneous rates from the fitted transition intensity matrix. We used the fitted transition probability matrix to estimate the percentage of patients occupying each state at any given time under complete follow-up from 1 to 15 years after UDCA initiation. The time a patient is estimated to spend in each state was defined by the integral of the transition probability matrix from 1 to 15 years after UDCA initiation. Missing biochemical values were imputed with multivariate imputation by chained equations (Table S1). Linear mixed-effects regressions with patient-level random intercepts were used to maintain within-patient correlation of imputed biochemical values and predictive mean matching was used to ensure imputed values were within plausible ranges. Imputation models included age at diagnosis, sex, ALP \times ULN, total bilirubin \times ULN, alanine aminotransferase \times ULN, aspartate aminotransferase \times ULN, platelet count, albumin \times LLN, year of diagnosis, year of UDCA initiation, follow-up time, and lag values of all above biochemical parameters to better capture mechanisms of missing data.²⁷ We randomly selected one imputed dataset for

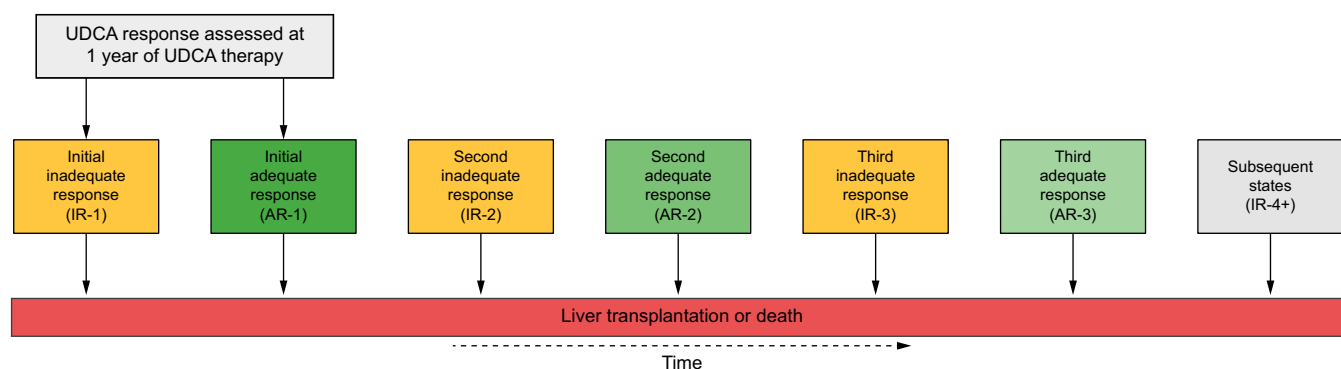


Fig. 1. Multistate model of the transitions between UDCA response states over time. This figure outlines biochemical response states through which patients progressively transition in the multistate model. Patients enter the model as IR-1 or AR-1 and progress through states sequentially or remain in a state if no change. Patients may transition to liver transplantation or death from any state at any point in time. For example, a patient with inadequate response at 1 year will begin as IR-1. This patient will transition to AR-1 when they achieve adequate response. This patient's state will change to IR-2 if they transition back to inadequate response and will change to AR-2 if they achieve adequate response once again. The patient's state will change to IR-3 if they transition back to inadequate response for a third time and will transition to AR-3 if they achieve adequate response for a third time. State changes beyond the fourth instance of inadequate response are absorbed into the IR-4+ state. We applied a composite endpoint of liver transplantation or death and patients without one of these two events were censored at last known date alive. Patients can transition to liver transplantation or death from any state at any point in time. AR-, adequate response; IR-, inadequate response; LT, liver transplantation; UDCA, ursodeoxycholic acid.

our main analyses because we did not have sufficient computational resources to repeatedly fit our multivariable model to 50 multiply imputed datasets as per recommendations.²⁸ Instead, we replicated our analyses in a database of completely external patients (external validation) and within a second randomly selected imputed dataset (sensitivity analysis). Analyses were performed in R version 4.0.2 (R Foundation for Statistical Computing). Multistate models were fit using the *msm* package and imputation was performed using the *mice* package.^{29,30}

Results

Cohort characteristics

A total of 823 patients from eight Canadian sites were included in the primary cohort (CaNAL, Fig. 2). Mean age at UDCA initiation was 53.0 years (SD 11.8), 91.0% were female, 86.8% were positive for anti-mitochondrial antibody, 12.6% initiated second-line therapy during follow-up, and 4.6% discontinued UDCA at a median of 3.9 years after initiation. Median follow-up after censoring was 6.5 years (25th-75th 3.3-11.6) and median

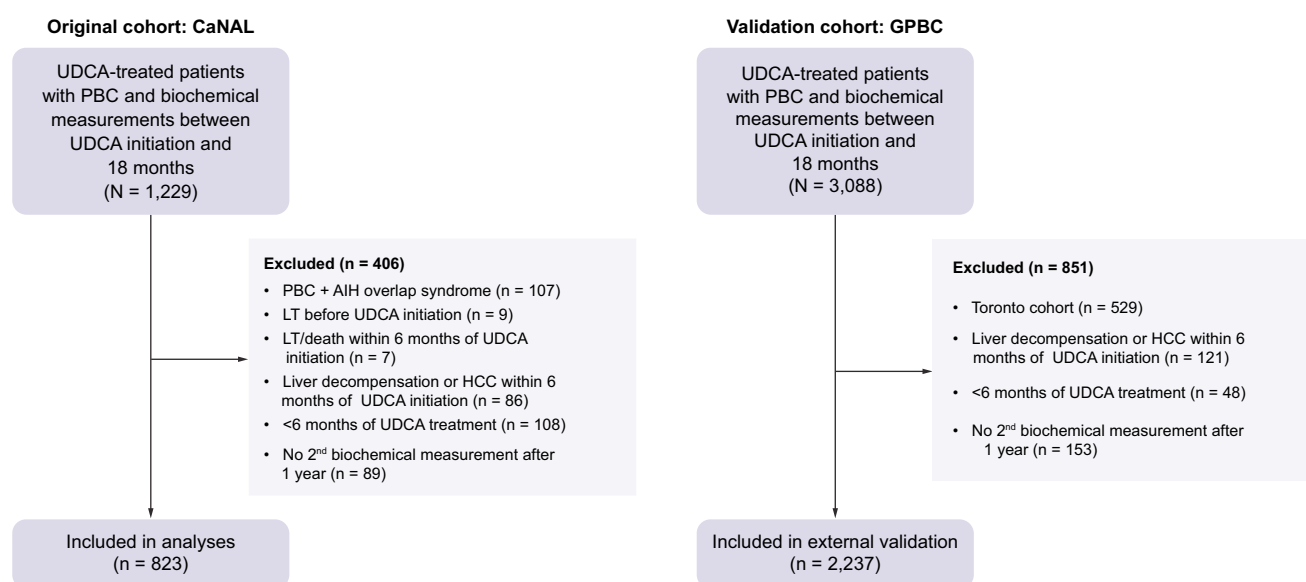


Fig. 2. Study flowchart for the original and validation cohorts. The same exclusion criteria were applied to both cohorts; exclusion criteria which resulted in 0 patients being excluded are not included in the figure for the validation cohort. Patients from Toronto were excluded from the validation cohort because they were present in the original cohort. AIH, autoimmune hepatitis; CaNAL, Canadian Network for Autoimmune Liver disease; GAVE, gastric antral vascular ectasia; GPBC, Global PBC Study group; HCC, hepatocellular carcinoma; HE, hepatic encephalopathy; HPS, hepatopulmonary syndrome; HRS, hepatorenal syndrome; LT, liver transplantation; PBC, primary biliary cholangitis; SBP, spontaneous bacterial peritonitis; UDCA, ursodeoxycholic acid.

Table 1. Patient characteristics.

Characteristic	Main cohort (n = 823)
Age at UDCA initiation, mean (SD)	53.0 (11.8)
Female sex, n (%)	749 (91.0)
AMA positive, n (%)	714 (86.8)
Discontinued UDCA, n (%)	38 (4.6)
Initiated second-line therapy, n (%)	104 (12.6)
Obeticholic acid	60 (7.3)
Bezafibrate	21 (2.6)
Fenofibrate	41 (5.0)
Liver transplantation or death - n (%)	
5 years after UDCA initiation	50 (6.1)
10 years after UDCA initiation	89 (10.8)
15 years after UDCA initiation	104 (12.6)
Serum biochemistry at UDCA initiation	
Alkaline phosphatase x ULN, mean (SD)	2.36 (1.87)
Alkaline phosphatase ≥ 1.67 x ULN, n (%)	450 (54.7)
Total bilirubin x ULN, mean (SD)	0.76 (0.99)
Total bilirubin >1 x ULN, n (%)	125 (15.2)
Platelet count ($\times 10^9/L$), mean (SD)	265 (102)
Platelet count $<150 \times 10^9/L$, n (%)	74 (9.0)
FIB-4 score ≥ 4.03 , n (%)	61 (7.4)
Serum biochemistry at 1 year	
Alkaline phosphatase x ULN, mean (SD)	1.53 (1.30)
Alkaline phosphatase ≥ 1.67 x ULN, n (%)	228 (27.7)
Total bilirubin x ULN, mean (SD)	0.74 (1.25)
Total bilirubin >1 x ULN, n (%)	102 (12.4)
Platelet count ($\times 10^9/L$), mean (SD)	243 (94)
Platelet count $<150 \times 10^9/L$, n (%)	120 (14.6)
FIB-4 score ≥ 4.03 , n (%)	51 (6.2)

ALP, alkaline phosphatase; AMA, anti-mitochondrial antibody; FIB-4, fibrosis-4; UDCA, ursodeoxycholic acid; ULN, upper limit of normal.

year of diagnosis was 2006 (25th-75th 2000-2013). The cohort experienced 54 LTs and 81 deaths: 6.1% of patients had LT or death by 5 years, 10.8% by 10 years, and 12.6% by 15 years. Serum biochemistry at UDCA initiation and 1 year are presented in Table 1.

Transitions through biochemical response states over time

At UDCA initiation, 54.7% of patients had ALP ≥ 1.67 x ULN and 15.2% had total bilirubin >1 x ULN. At 1 year of UDCA therapy, 32.6% of patients had inadequate biochemical response: 27.7% had ALP ≥ 1.67 x ULN and 12.4% had total bilirubin >1 x ULN. Twenty-three percent of patients with normal total bilirubin and 6.7% of patients with ALP <1.67 x ULN were inadequate responders at 1 year. An estimated 10.2% of patients never achieved adequate biochemical response to UDCA by 5 years, 54.1% achieved adequate response and retained their AR-1 state by 5 years, and 7.7% underwent LT or death by 5 years. The remaining 28.0% of patients fluctuated between multiple states: 13.2% lost adequate response and were in IR-2 or IR-3 by 5 years, 14.1% regained adequate response and were in AR-2 or AR-3 by 5 years, and 0.7% transitioned between adequate and inadequate biochemical response at least five times by 5 years (IR-4+ state) (Fig. 3). Patients with inadequate response to UDCA at 1 year were estimated to remain in their IR-1 state for an additional mean of 3.4 years (95% CI 3.0-3.8). If these patients achieved adequate biochemical response, they were expected to retain this response and remain in AR-1 for 4.5 years (95% CI 4.1-4.9). Patients with adequate response at 1 year were estimated to remain in their AR-1 state for an additional 6.6 years (95% CI 6.1-7.0) (Fig. 4).

Associations between biochemical response over time and LT-free survival

Patients with inadequate biochemical response to UDCA at 1 year had significantly worse LT-free survival over time compared to patients with adequate response at 1 year (Fig. 5). Achieving adequate biochemical response was associated with survival benefit regardless of prior history of inadequate response. Patients in their first, second, and third states of adequate response had better LT-free survival than patients in their first, second, and third states of inadequate response (log-rank $p < 0.01$ all pairwise comparisons to the previous state, Fig. 5). At any time, patients who retained their initial adequate response had significantly lower rates of LT or death than patients who never achieved adequate response (AR-1 vs. IR-1: 0.089-fold, 95% CI 0.046-0.170) or who transitioned back to inadequate response (AR-1 vs. IR-2: 0.102-fold, 95% CI 0.047-0.223). Patients who regained adequate response for the second time had significantly lower rates of LT or death than patients who did not regain response (AR-2 vs. IR-2: 0.016-fold, 95% CI 0.001-0.568) or who transitioned to inadequate response for a third time (AR-2 vs. IR-3: 0.010-fold, 95% CI 0.001-0.340). Patients who regained adequate response for a third time also had lower rates of LT or death compared to patients who did not regain adequate response for a third time (AR-3 vs. IR-3: 0.151-fold, 95% CI 0.040-0.566).

Exploratory analysis of associations between patient characteristics and state transitions

Tables S2-S4 present estimates of the association between baseline patient characteristics and state transitions in the main analysis, sensitivity analysis, and external validation. We do not report specific point estimates due to variation between the three analyses and instead comment on associations that were consistent across all analyses (i.e. where 95% CIs exclude 1 in all three analyses). Older age at UDCA initiation was associated with an increased rate of transition from all states of inadequate response to adequate response (Table S2). Higher serum ALP at 1 year was associated with a decreased rate of ever achieving adequate response, an increased rate of losing adequate response, a decreased rate of regaining adequate response again, and an increased rate of losing adequate response again (Table S3). Higher serum total bilirubin at 1 year was also associated with an increased rate of losing adequate response, a decreased rate of regaining adequate response, and an increased rate of losing adequate response again (Table S4). Sex was not associated with rate of initial response, transitions between any response states, or transitions from any state to transplantation or death (all 95% CI exclude 1 in all three analyses). We were unable to comment on FIB-4 score due to too few patients with FIB-4 >4.03 at 1 year.

Study validation and sensitivity analysis

We replicated all analyses in a separate validation cohort of external patients with PBC (n = 2,237, 14 sites, Fig. 2). In the external validation cohort, mean age at UDCA initiation was 54.5 years (SD 11.7), 91.1% were female, mean ALP at 1 year was 1.78x ULN (SD 1.45), mean total bilirubin at 1 year was 0.80 (SD 1.22), and 14.3% had cirrhosis. Median follow-up after censoring was 7.1 years (25th-75th 3.3-11.4) and 7.2% had LT

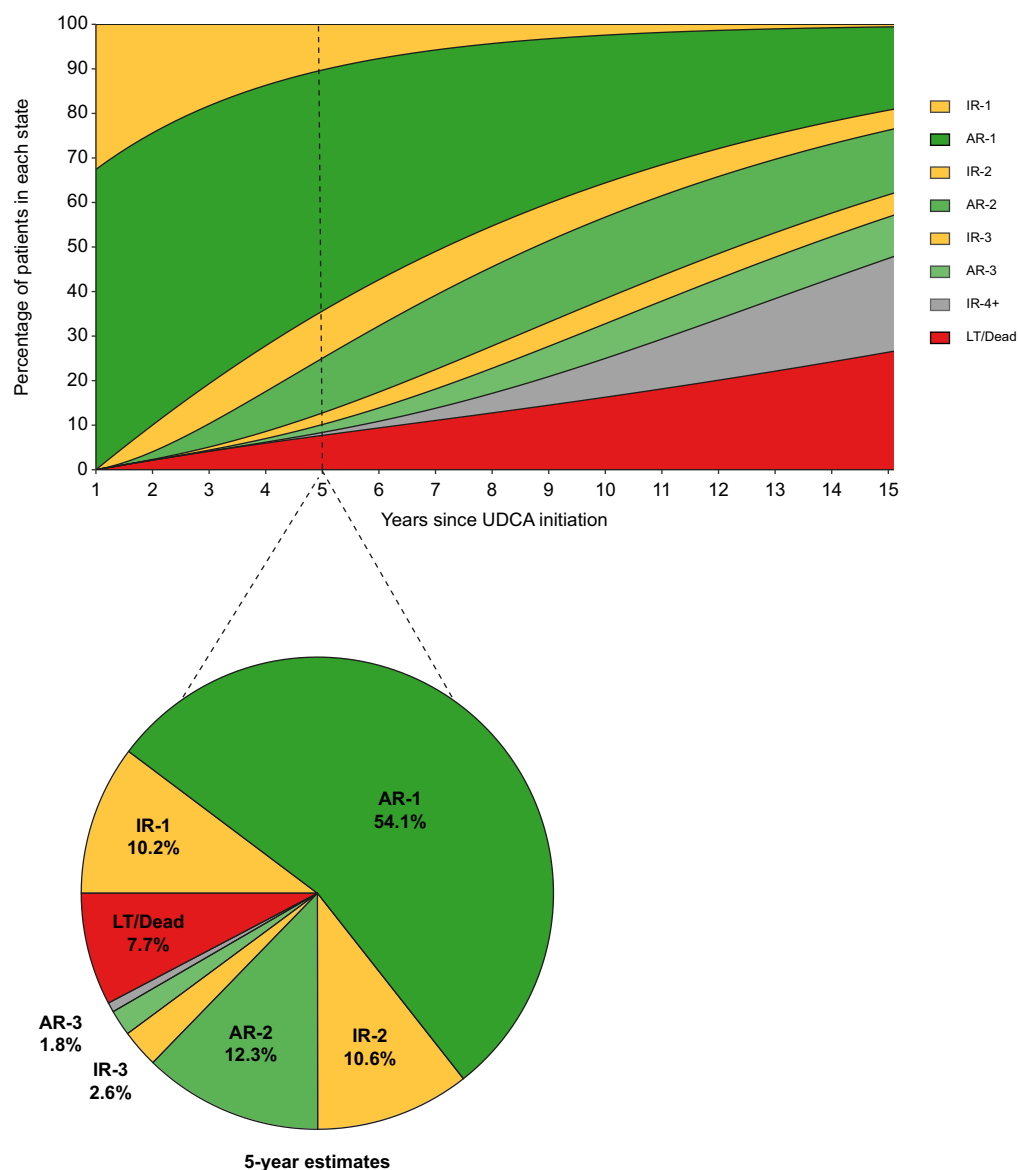


Fig. 3. Estimated percentage of patients in each response state over time, whole cohort. Estimated percentage of patients in each response state over time in the main cohort, derived from the fitted transition probability matrix of the multistate model. Pie chart represents the breakdown of states at 5 years, corresponding to the dashed vertical line in the rectangular figure. The pie chart represents the 5-year values reported in the text. AR-, adequate response; IR-, inadequate response; LT, liver transplantation; UDCA, ursodeoxycholic acid.

or death by 5 years, 14.4% by 10 years, and 18.2% by 15 years. Median year of diagnosis was 1997 (25th–75th 1991–2004). Patients in the external validation cohort who retained their initial adequate response to UDCA had significantly lower rates of LT or death than patients who never achieved adequate response (AR-1 vs. IR-1: 0.061-fold, 95% CI 0.035–0.105) or transitioned back to inadequate response (AR-1 vs. IR-2: 0.061-fold, 95% CI 0.031–0.119, Fig. 5). Patients who achieved adequate response for the second time also had significantly lower rates of LT or death than patients who did not regain adequate response (AR-2 vs. IR-2: 0.077-fold, 95% CI 0.012–0.481) or who transitioned to inadequate response once more (AR-2 vs. IR-3: 0.073-fold, 95% CI 0.001–0.551).

Patients who regained adequate response for a third time also had lower rates of LT or death compared to patients who did not regain adequate response for a third time (AR-3 vs. IR-3: 0.241-fold, 95% CI 0.071–0.823).

Sensitivity analysis in a second imputed dataset selected at random demonstrated the same associations as the main analysis and external validation. Both external validation and sensitivity analysis showed that biochemical states varied during follow-up and often did not reflect biochemical response status at 1 year. All analyses indicated that younger age, higher ALP at 1 year, and higher total bilirubin at 1 year were associated with a tendency towards transitioning to insufficient response throughout follow-up (Tables S2–S4).

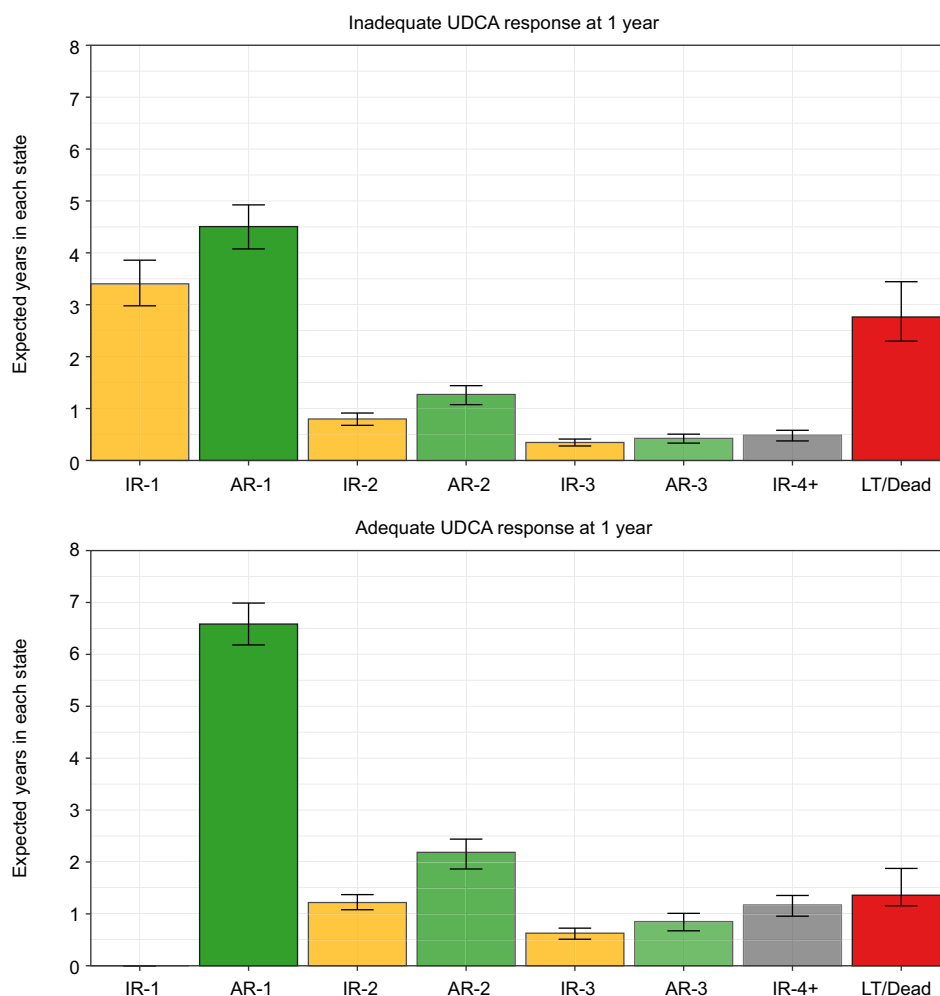


Fig. 4. Estimated mean time spent in each state from 1 to 15 years after UDCA initiation, by UDCA response status at 1 year. Patients with inadequate response to UDCA at 1 year were estimated to remain in their IR-1 state for an additional mean of 3.4 years (95% CI 3.0-3.8). If these patients achieve adequate biochemical response, they were expected to retain this response and remain in AR-1 for 4.5 years (95% CI 4.1-4.9). Patients with adequate response at 1 year were estimated to remain in their AR-1 state for an additional 6.6 years (95% CI 6.1-7.0). A patient with inadequate response to UDCA at 1 year will enter the IR1 state, and any subsequent achievement of biochemical response moves them to the AR-1 state. A patient with adequate response to UDCA at 1 year will enter the AR-1 state, and any subsequent loss of response moves them to the IR-2 state. The time a patient is estimated to spend in each state was defined by the integral of the transition probability matrix from 1 to 15 years after UDCA initiation. AR-, adequate response; IR-, inadequate response; LT, liver transplant; UDCA, ursodeoxycholic acid.

Discussion

PBC is a chronic disease where patients are routinely monitored over time, usually for decades. We investigated longitudinal patterns of biochemical response to UDCA therapy and their association with LT or death, first in a multicenter Canadian cohort of patients with PBC and then in an international cohort. We demonstrated, and subsequently validated, that patients transition between adequate and inadequate response to UDCA such that biochemical response status over time may not reflect status at 1 year after UDCA initiation. These transitions between adequate and inadequate biochemical response over time were associated with a significant change in a patient's risk of LT or death throughout the course of disease. Our findings challenge the current paradigm that long-term risk assessment should be based on biochemical response at 6 months,¹³ 1 year,^{8,10,11} or 2 years.⁹ The presence of insufficient biochemical response is a risk factor for worse outcomes at any

time and is therefore an indication to optimize treatment when a patient's biochemical state worsens.

Our findings support that adequate biochemical response to UDCA treatment is a valid surrogate of prognosis throughout a patient's course of disease. Achievement of adequate biochemical response at any given time was associated with decreased rates of LT or death regardless of a patient's prior history of inadequate response. In other words, when a patient transitions from inadequate to adequate response, they experience a corresponding survival benefit. When a patient loses adequate response, their risk of LT or death increases. These results emphasize the value in regular monitoring of patients' biochemical profile over time to re-evaluate their risk of LT or death and intervene proactively. Continuous re-assessment of biochemical response provides important clinical information about a patient's changing risk profile that may highlight opportunities for intervention to reduce the risk of LT or death.

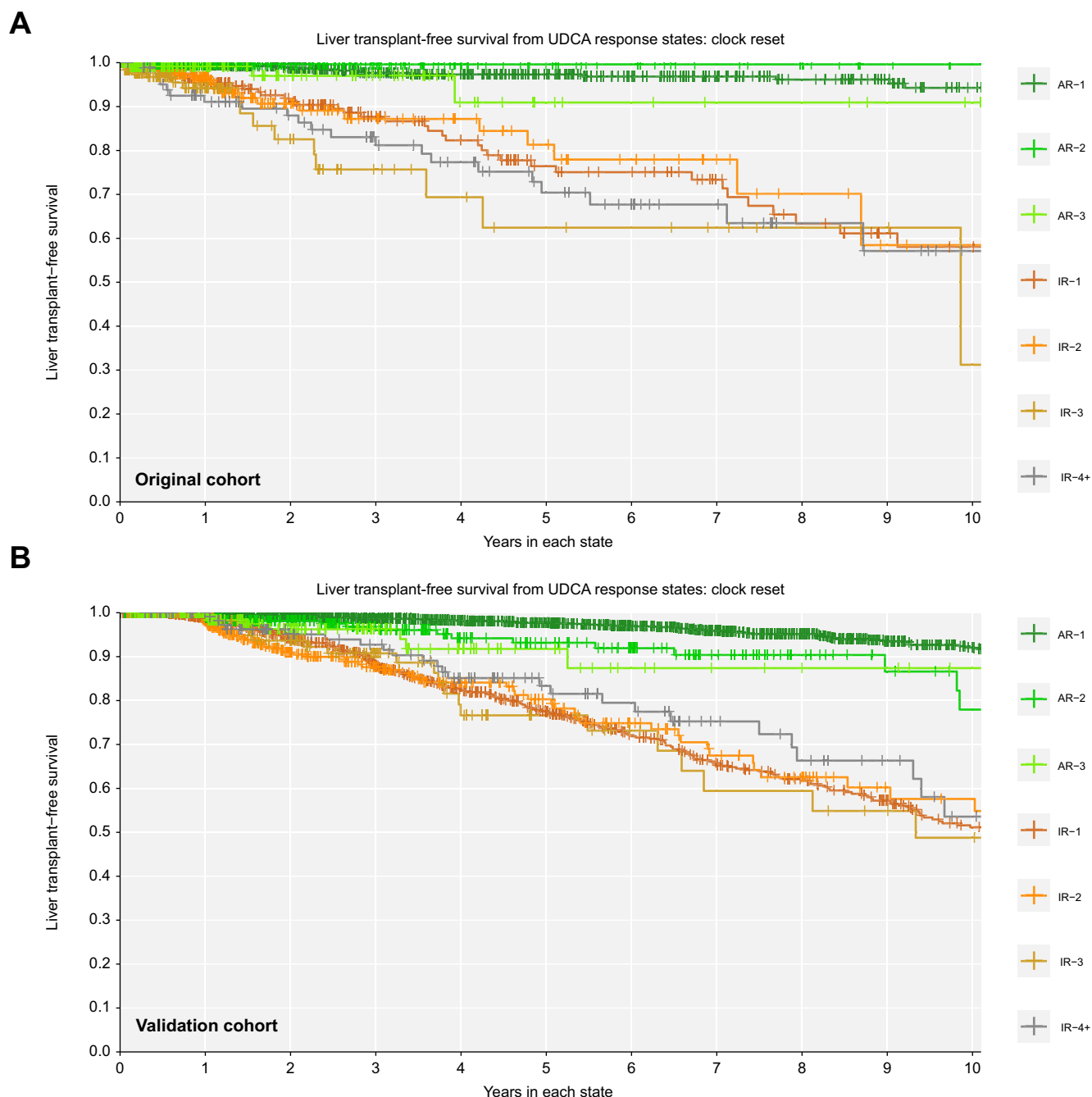


Fig. 5. Over time, adequate response is always associated with better liver transplant-free survival. (A) Original cohort; (B) validation cohort. Clock-reset Kaplan Meier curves of survival probability from each UDCA response state. Follow-up time begins 1 year after UDCA initiation. Patients transition from one curve to the next at the time of their state change. Patients are censored at last date known alive or at the time of state change. Log-rank $p < 0.01$ all pairwise comparisons to previous state. p values are corrected for multiple comparisons using the Benjamini-Hochberg method. AR-, adequate response; IR-, inadequate response; UDCA, urso-deoxycholic acid.

Importantly, our definition of biochemical response reflects widely used criteria for the indication and reimbursement of second-line therapy. We highlight that our study is not about optimal prognostication of patients with PBC. Research on improving prognostication should build on richer continuous scores (e.g. GLOBE, UK-PBC)^{31,32} instead of dichotomous biochemical response criteria. Rather, we aim to confirm and spread a critical message about response-guided clinical

management anchored in the context of current decision-making criteria. Our analyses focus on a dichotomous biochemical response criterion (ALP $\geq 1.67 \times$ ULN or abnormal total bilirubin) instead of richer continuous prognostic scores because this criterion reflects clinical labelling of biochemical response and is the indication and reimbursement criteria for second-line obeticholic acid.^{33–36} Our results support response-guided management of patients with PBC, and are

timely because response-guided management is often poorly implemented in practice (e.g., approximately 1/3 of patients with PBC are under-dosed on UDCA, 1/2 do not receive second-line therapies for insufficient biochemical response).^{37,38} We acknowledge that applying dichotomous response criteria does not consider that patients have a distribution of risk within their dichotomous response categories, but neither do reimbursement criteria for second-line therapy. Our study does not comment on how changes in the magnitude of continuous biochemistry over time may influence state transitions and clinical outcomes in patients with PBC.

Exploratory results demonstrated that younger age, higher ALP at 1 year, and higher total bilirubin at 1 year were associated with a tendency towards transition to inadequate response throughout follow-up. These results align with the current clinical paradigm that young age, high serum ALP at 1 year, and high serum total bilirubin at 1 year are important factors to consider when assessing future risk in patients with PBC. We did not observe an association between sex and biochemical response or LT and death. Earlier studies have reported that males present with more advanced disease and are less likely to respond to UDCA treatment than females.^{39,40} Our results are consistent with recent findings from a large international cohort that reported no association between male sex and probability of treatment failure, LT, or death.⁴¹ The prognostic role of male sex has been an ongoing subject of debate and while our results suggest that male sex does not meaningfully impact risk after consideration of other important variables, this is yet to be resolved in the literature.

A key strength of our study is our use of all available biochemical measurements over time. We investigated associations using serum biochemistry across continuous time, allowing our estimates to consider the natural times at which patients transition between response states and better reflect the continuous nature of disease progression. This approach allowed our analyses to leverage information from all observations and incorporate more information than an analysis of

discrete time points. We were unable to account for adherence to and dose of UDCA therapy.

Our analyses assume that a patient’s future states only depend on their current state and not the time spent in the current state nor previous states (Markov assumption). Our analyses also assume that transition rates between states are consistent across time (time-homogeneity assumption). We were unable to pool results from multiply imputed datasets due to computational limitations. As a result, our 95% CIs are likely underestimated because we were not able to account for between-imputation variability in our data. We remain confident in our results because the external validation was consistent with our main analysis. Our intermittent observation scheme may underestimate the number of true state transitions because patients may transition between response states at times when they are not observed in clinic. This may also contribute to overestimation of the time that patients spend in each state. This limitation is unavoidable and applies to all studies without continuous patient observation. While this may limit our ability to extrapolate our results to the true disease course of PBC, it accurately reflects the information that is available to physicians to evaluate biochemical risk and inform clinical decision making. Second-line therapies are new in PBC; therefore, we were unable to investigate their association with long-term biochemical response and clinical outcomes. As patients accrue more follow-up on second-line therapies, future studies should investigate whether their use has an impact on longitudinal patterns of biochemical response and whether those altered patterns associate with improved clinical outcomes.

In conclusion, achievement of adequate biochemical response to UDCA therapy in people living with PBC is associated with better outcomes at any time during the course of disease. The presence of insufficient biochemical response is a risk factor for worse outcomes and is therefore an indication to optimize treatment throughout follow-up when a patient’s biochemical state worsens. Treatment goals in PBC should target durable biochemical response and move beyond single time point measures early in disease.

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Abbreviations

ALP, alkaline phosphatase; AR-1, adequate response #1; CaNAL, Canadian Network for Autoimmune Liver Disease; FIB-4/Fibrosis-4; IR-1, inadequate response #1; LT, liver transplant; PBC, primary biliary cholangitis; ULN, upper limit of normal; UDCA, ursodeoxycholic acid.

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Conflict of interest

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Authors' contributions

Conceptualization: SBR, GMH, BEH. Data curation: All authors. Formal analysis: SBR, GMH, WJC, ALM, BEH. Funding acquisition: GMH, BEH. Investigation: SBR, GMH, ALM, BEH. Methodology: SBR, WJC, GMH, BEH. Project administration: All authors. Resources: GMH, HLAJ, ALM, BEH. Software: SBR. Supervision: GMH, BEH. Validation: SBR, GMH, BEH. Visualization: SBR, WJC. Writing – original draft: SBR, WJC. Writing – review & editing: all authors.

Data availability statement

These data are not publicly available due to the sensitive nature of patient data. Researchers interested in using these data will need to comply with all relevant REB requirements of these datasets. Contact the corresponding authors for more information.

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Supplementary data

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