EE629

Natural History Modeling of All-Cause Decompensated Cirrhosis: Long-Term Clinical and Economic Burden and Considerations for Future Economic Evaluations

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Background

- Decompensated cirrhosis (dF4) is a progressive condition affecting over 10 million people globally that is characterized by recurrent liver-related events, frequent hospitalizations, high mortality, and potential need for liver transplant (LT).[1-3]
- Evaluating emerging dF4 therapies requires a framework that reflects the natural history of dF4, including event types, prior event history, and downstream complications.
- The long-term natural history of dF4 and cumulative impact of recurrent events remain incompletely characterized,[4-8] limiting understanding of lifetime disease burden and potential treatment value.

Objective

- We developed an evidence-based disease model incorporating recurrent decompensation events and progression to advanced liver disease outcomes to characterize the long-term clinical and economic burden of all-cause dF4 and inform future economic evaluations.

Methods

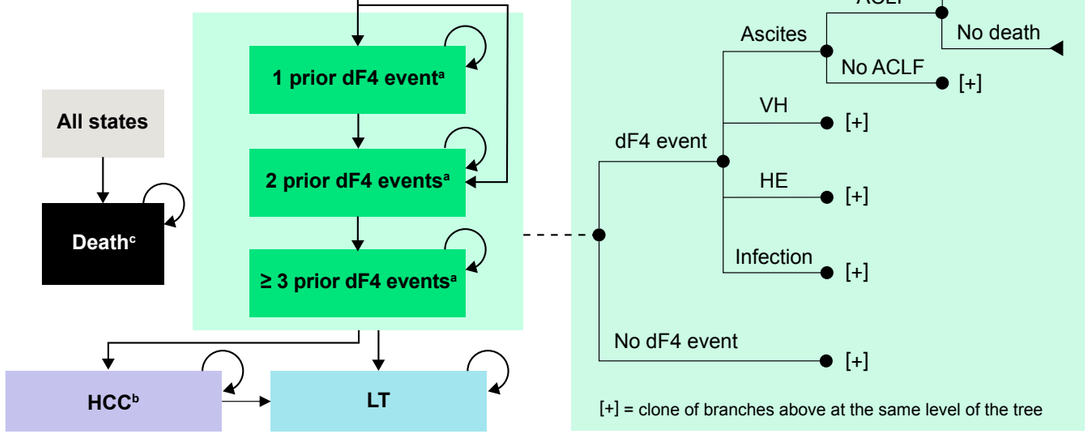
Model Design

- The Markov model included health states for nonacute dF4 (stratified by the number of prior dF4 events), hepatocellular carcinoma (HCC), LT, and death (**Figure 1**).
- A decision tree embedded in each cycle captured the risk of acute dF4 events by type and applied event-specific risks of acute-on-chronic liver failure (ACLF) and subsequent death.
- The base-case population comprised adult patients (aged ≥ 18 years) with nonacute dF4 and 1 prior dF4 event. Patients entered and progressed through the model in 3-month cycles, with half-cycle correction, over a lifetime horizon of up to 40 years.

Model Parameters and Assumptions

- Probabilities of subsequent dF4 events, HCC, LT, and ACLF and the distribution of dF4 event types were derived from the Optum Market Clarity Database using data from January 2006 through May 2022 (**Table 1, Supplementary Table 1**).[10]
- Other natural history model inputs were informed by a targeted literature review of relevant clinical, economic modeling, and burden-of-illness literature (**Table 1, Supplementary Table 1**).[3-4,11-14]
- Costs were based on US claims and inpatient admissions data; utilities and quality-adjusted life-year (QALY) losses were based on published burden-of-illness and economic evaluation studies (**Table 2**).[12,16-20]

Figure 1. Model Structure



HE = hepatic encephalopathy; VH = variceal hemorrhage.
Note: The dF4 health states did not distinguish between prior dF4 event types; event-specific ACLF and mortality risks were captured in the probability tree.
[a] All dF4 states carried risks of dF4 events, ACLF (whether or not precipitated by a dF4 event), and liver-related death, varying by the number of prior events and time in the health state.
[b] The HCC state carried a risk of ACLF.
[c] Patients could transition to death from any health state, reflecting death from liver-related or other causes.

Table 1. Natural History Parameters

Parameter	Time in health state	Value
Transition probability to subsequent dF4 events per cycle[a]		
From 1 prior dF4 event	Year 1	0.281[10]
	Year 2	0.013[10]
	Years 3+	0.005[10]
From 2 and ≥ 3 prior dF4 events	Year 1	0.310[10]
	Year 2	0.014[10]
	Years 3+	0.005[10]
Transition probability to HCC per cycle		
From 1 prior dF4 event	Year 1	0.010[10]
	Years 2+	0.003[10]
From 2 and ≥ 3 prior dF4 events	Year 1	0.008[10]
	Years 2+	0.003[10]
Transition probability to LT per cycle		
From 1 prior dF4 event	Year 1	0.004[10]
	Years 2+	0.002[10]
From 2 and ≥ 3 prior dF4 events	Year 1	0.005[10]
	Years 2+	0.002[10]
From HCC	All years	0.050[4]
Distribution of dF4 events		
Ascites	All years	0.439[10]
VH	All years	0.279[10]
HE	All years	0.203[10]
Infection	All years	0.078[10]

[a] Transitioning to subsequent dF4 event health states is conditional on surviving the event.

Table 2. Costs and Utilities

Parameter	Costs	Utilities
Health state annual costs and utilities		
Any dF4 event state	$54,710[16]	0.570[4,18]
HCC	$118,639[17]	0.496[4,18]
LT (subsequent cycles after the first cycle)	$44,730[17]	0.730[19]
Costs and QALY losses per event[a]		
Ascites	$22,698[12]	0.010[20]
VH	$32,203[12]	0.013[20]
HE	$28,709[12]	0.008[20]
Infection	$38,317[12]	0.010[20]
ACLF	$56,690[12]	0.022[20]
LT (first cycle only)	$259,272[17]	0.070[19]

USD = United States dollar.
Note: Costs from the literature were inflated to 2024 USD using the US medical care consumer price index.
[a] Event costs were applied at the time of the event, independently from underlying health state costs, with a cost-to-charge ratio of 0.4918[21] applied to costs from Afridi et al. (2023).[12] Event-related QALY losses were also applied at the time of the event, independently from underlying health state utilities.

Disclosures

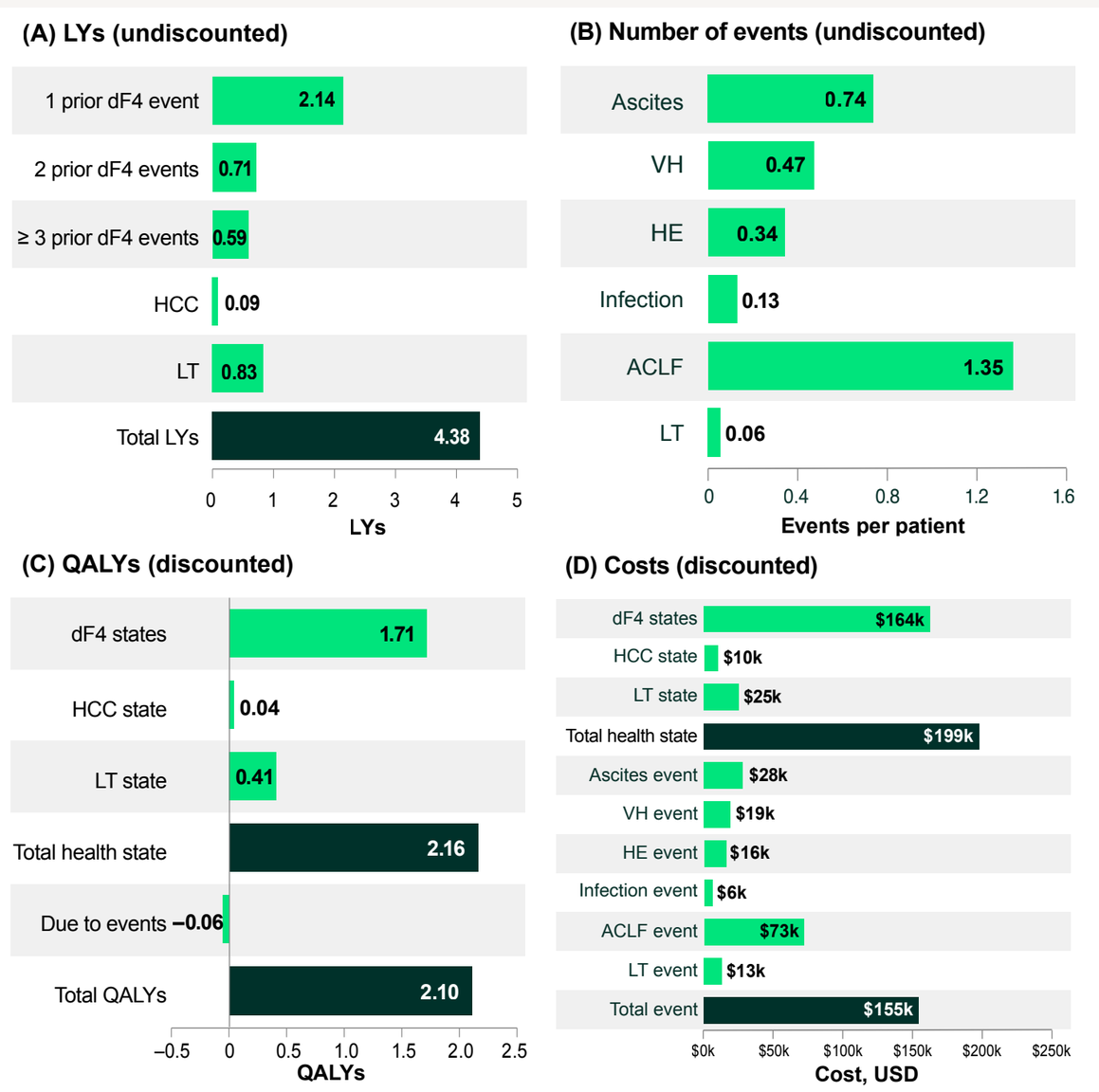
LF and WLH are full-time employees of RTI Health Solutions, an independent research organization. MKS and NG-S are full-time employees of Boehringer Ingelheim International GmbH. CS is an independent contractor to Boehringer Ingelheim International GmbH during model development. RTI Health Solutions provided medical writing support under the authors' guidance, funded by Boehringer Ingelheim International GmbH.

Results

Base-Case Results

- Predicted undiscounted overall survival per patient was 4.38 life-years (LYs), including 1.31 LYs in states with ≥ 2 prior dF4 events and 0.93 LYs with advanced disease (HCC or LT) (**Figure 2A**).
- Over their remaining lifetime, patients experienced a mean of 1.67 dF4 events, 1.35 ACLF events, and 0.06 LT events (**Figure 2B**).
- Total discounted expected lifetime QALYs were 2.10, including a loss of 0.06 QALYs due to events, and total expected disease-related costs were $353,814 (**Figure 2C** and **2D**).

Figure 2. Base-Case Analysis Results, Per Patient



Note: Costs and QALYs were discounted at 3% per year.[9]

Scenario Analyses

- A more advanced disease population at model entry (Scenario 1) resulted in lower LYs, QALYs, costs, and fewer dF4 and ACLF events due to shorter survival (**Table 3**).
- In Scenario 2 (Scenario 3), reduced (increased) subsequent dF4 event risk led to fewer (more) dF4 and ACLF events and correspondingly higher (lower) survival, QALYs, and costs.
- Alternative assumptions regarding LT exclusion and eligibility in Scenarios 4 and 5 substantially impacted LYs, QALYs, and costs.

Table 3. Scenario Analyses Results

Parameter	Base case	Scenario 1: More advanced population	Scenario 2: Reduced dF4 event probabilities	Scenario 3: Increased dF4 event probabilities	Scenario 4: LT excluded	Scenario 5: Proxy for LT eligibility
Number of events per patient (undiscounted)						
dF4	1.67	1.50	1.32	2.00	1.71	1.62
ACLF	1.35	1.17	1.22	1.48	1.40	1.29
LT	0.06	0.04	0.07	0.05	0.00	0.11
LYs per patient (undiscounted)	4.38	2.51	5.49	3.52	3.82	4.71
QALYs per patient (discounted)	2.10	1.28	2.60	1.71	1.81	2.32
Total costs per patient (discounted)	$353,814	$257,858	$379,224	$337,433	$332,097	$367,647

Note: Scenarios assessed included (1) all patients assumed to have 2 prior dF4 events at model entry; 20% (2) decrease and (3) increase in subsequent dF4 event risk; (4) all LT probabilities set to 0%; and (5) alternative LT probabilities as a proxy for early-stage favored LT eligibility (1 prior event: year 1 = 2%, year 2+ = 1%; 2 prior events: base case; ≥ 3 prior events: 0%).

Conclusions

- Results highlight the substantial lifetime burden of dF4, characterized by reduced overall and quality-adjusted survival, recurrent dF4 and ACLF events, and high costs.
- Future evaluations should consider remaining uncertainties, including the role of disease etiology, natural history data differentiated by prior dF4 event type, and the suitability of cost and utility inputs across dF4 event history.
- Whether delaying LT is perceived as beneficial or detrimental to patients remains unclear, and this distinction could change how outcomes like survival and quality of life are weighted when evaluating future treatments for late-stage liver disease.
- To our knowledge, this is the first model to comprehensively capture the natural history of all-cause dF4, including event types, prior event history, and advanced liver disease, providing a foundation for future economic evaluations of emerging dF4 therapies.

Scan the QR code to view supplementary files

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