How Does the Source of Transition Probabilities Influence Natural History Simulation and Economic Evaluation in Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD)?

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MSR121

INTRODUCTION

MASLD is a chronic liver condition linked to obesity, type 2 diabetes, and metabolic syndrome.

MASLD includes a spectrum of liver damage, progressing from simple steatosis to metabolic dysfunction–associated steatohepatitis (MASH) and ultimately fibrosis and cirrhosis.

Accurate modelling of fibrosis progression is essential for evaluating long-term outcomes and cost-effectiveness of emerging MASH therapies.

Transition probabilities (TPs) are key drivers in natural history and economic models, yet published TPs vary significantly depending on their source—randomized controlled trials (RCTs) vs. real-world evidence (RWE).

Although differences between RCT and RWE data are well recognized, **limited research has quantified how these differences affect modelled outcomes in MASLD**, especially in terms of **fibrosis progression and health economic conclusions**.

This study addresses that gap by directly comparing model outputs using TPs derived from both RCTs and RWE.

OBJECTIVES

To evaluate how the choice of transition probability data source—RCTs versus RWE—impacts fibrosis progression projections and health economic modelling Quality adjusted Life Years (QALY) in MASLD, in order to inform future model development and policy decisions.

METHODS

A patient-level microsimulation model was developed in R to simulate the natural history of MASLD and estimate progression from fibrosis stages F0–F3 to cirrhosis (F4) using annual TPs.

- Individuals entered the model at diagnosis across fibrosis stages F0 to F3 (Figure 1).
- In each annual cycle, patients could remain stable, progress, or regress within early fibrosis stages.
- From F4 (cirrhosis), regression to F3 was not permitted; Moreover, patients could also progress to decompensated cirrhosis (DCC) or hepatocellular carcinoma (HCC), where further progression was assumed.
- Patients with DCC or HCC could transition to liver transplantation (LT) or death.
- Microsimulation was used to apply stage-specific transition probabilities from external sources to a heterogeneous patient population, enabling accurate tracking of individual disease trajectories and time-dependent outcomes like cirrhosis-free survival.

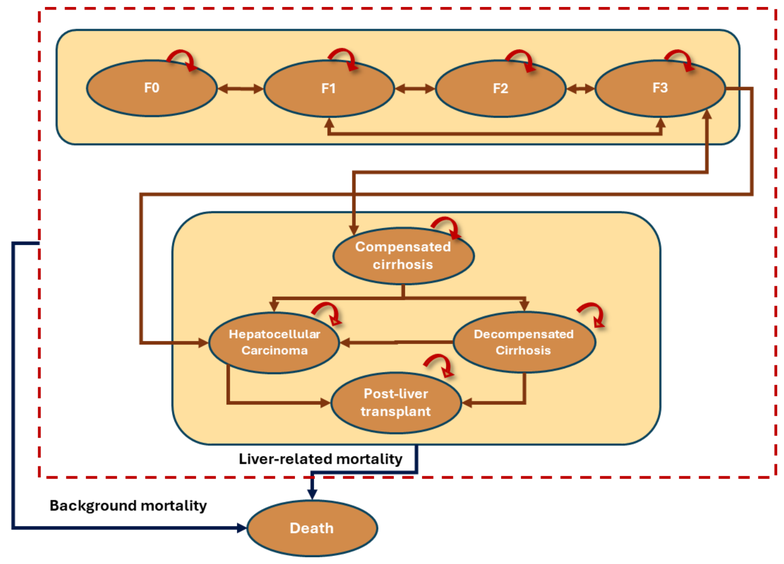
Annual TPs were sourced from a published meta-analysis[1] (Le et al., 2023; PMC9898457), reported separately for:

- Placebo arms of RCTs using biopsy-confirmed fibrosis
- Placebo arms of RWE using non-invasive tests

Although the meta-analysis reported some regression from F4 (cirrhosis), we assumed no regression from F4 in order to estimate unbiased time to progression to cirrhosis.

A synthetic patient cohort was generated using baseline characteristics from Angulo et al.[2] (2015; PMC4516664). The model simulated outcomes under RCT-derived and RWE-based TPs.

Figure 1. Natural history model structure



Simulations were run in annual cycles until death or liver transplantation. The primary outcome was cirrhosis-free survival, stratified by baseline fibrosis stage and data source.

We simulated 10,000 patients with baseline fibrosis stages F0–F3 (53.6% F0, 23.5% F1, 14.0% F2, 8.9% F3), and the mean age of 48 years.

We further performed analyses stratified by fibrosis stage, with all patients at baseline entering the model in one of the F0, F1, F2, or F3 health states to estimate cirrhosis-free survival within each subgroup.

The health state utility values were sourced from NG49. We used 3.5% discount rate per year to calculate the total QALYs, and the 2017-2019 UK life tables for the background mortality.

RESULTS

As shown in **Figure 2A**, models using RWE-derived TPs project longer cirrhosis-free survival (median: 27.0 years) compared to RCT-derived TPs (median: 18.4 years). This difference indicates that RWE inputs lead to slower modelled disease progression, likely due to lower progression rates reported in observational studies using non-invasive diagnostics. The difference of nearly 9 years is clinically meaningful and has implications for how treatment benefits may be evaluated.

In **Figure 2B**, survival curves stratified by baseline fibrosis stage (F0–F3) show that: The survival gap between RCT and RWE expands at earlier stages (e.g., F0/F1). Patients starting at F0 had ~9 more cirrhosis-free years under RWE vs. RCT inputs (28.53 vs. 19.68 years). This gap narrows at F3 (20.23 vs. 14.66), indicating that differences in TP sources have less influence in advanced fibrosis, likely due to shorter remaining time horizons and converging risks.

In **Figure 3**, the state occupancy plots (**Panel A**: RWE, **Panel B:** RCT) visually demonstrate that: A higher proportion of patients remain in lower fibrosis stages (F0–F2) for a longer duration under the RWE scenario. In contrast, the RCT-based model shows earlier and steeper transitions into advanced disease states like F4, DCC, HCC, and LT. The result is a more accelerated disease burden under RCT TPs, with greater cumulative time in costly and low-utility health states.

In **Figure 4**, mean QALYs were higher under RWE-derived TPs (14.00) compared to RCT-derived TPs (12.44), **a difference of +1.56 QALYs**. This is driven by longer duration in early fibrosis stages, which have higher utility weights. The distribution of QALYs is wider under RWE, reflecting greater heterogeneity in modelled outcomes — potentially due to slower progression and more individual variation. This difference is critical from a value assessment perspective, especially in early HTA or cost-effectiveness modelling of new therapies, where QALY gains are key drivers of ICERs.

Figure 2. Cirrhosis-Free Survival by Transition Probability Source: RCT vs. RWE, Overall (A) and Stratified by Baseline Fibrosis Stage (B).

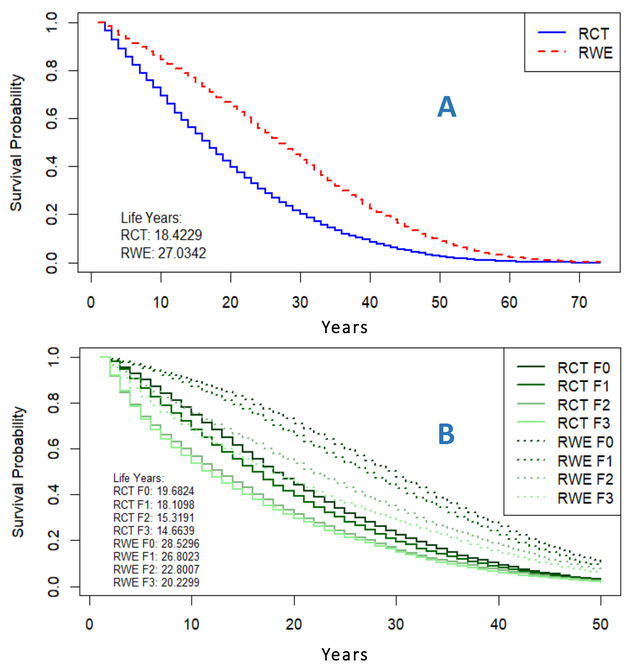


Figure 3. Impact of Transition Probability Source on Fibrosis Progression and Liver-Related Outcomes in MASLD using data from (A) RWE, and (B) RCTs

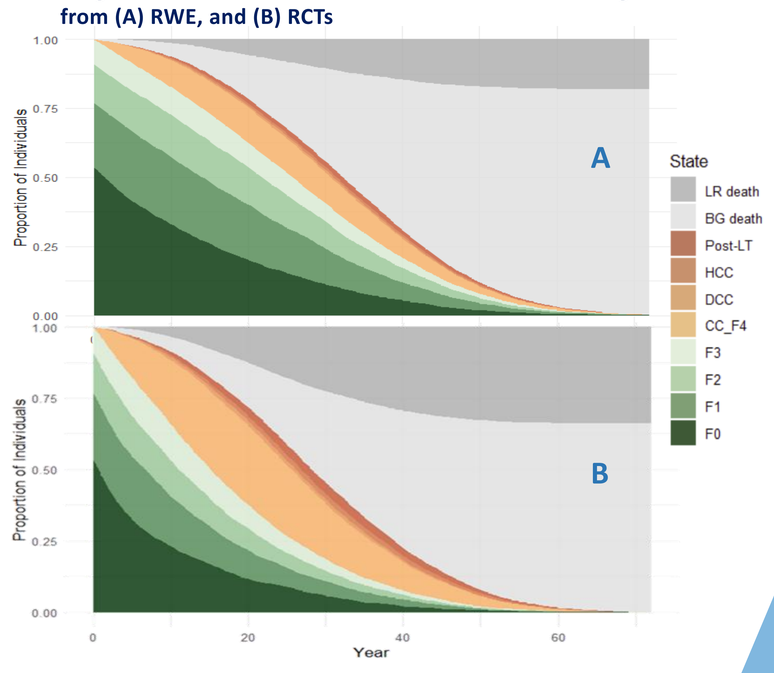
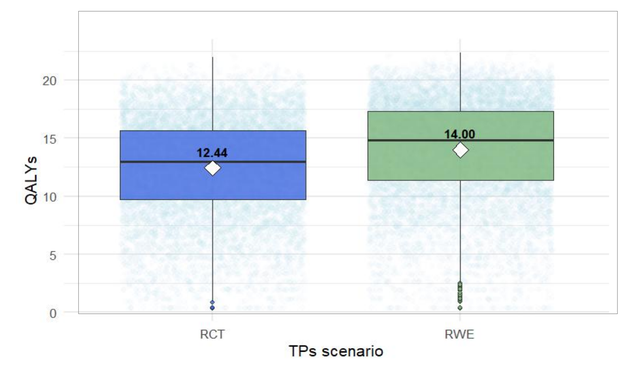


Figure 4. Simulated QALYs under RCT vs RWE-derived transition probabilities.



DISCUSSION

Regardless of the limitations of Le et al. (2023), —which were not the focus of this analysis— the source of transition probabilities (RCT vs. RWE) significantly affected modelled MASLD outcomes, with RWE inputs showing slower progression and higher QALYs—reflecting differences in diagnostic methods and population characteristics.

The differences observed are likely driven by **variation in diagnostic methods**:

- **RCT-derived TPs** are largely based on liver biopsy, providing higher diagnostic accuracy but often reflecting **more advanced or selected populations**.
- In contrast, **RWE-derived TPs** come from **broader populations** using a mix of biopsy and non-invasive tests, as well as not regular diagnostic assessment, potentially introducing measurement variability and underestimating progression risk, especially in earlier stages.

CONCLUSION

Our findings underscore a critical challenge in health economic modelling of MASLD. The result is a meaningful divergence in estimated QALYs and disease trajectories, even under the same model structure and assumptions. These findings raise a fundamental question for HTA and modelling communities:

Can either of these data sources—RCT or RWE—be considered appropriate for modelling the natural history of MASLD, given the considerable heterogeneity among patients with metabolic dysfunction?

As new therapies approach market entry, reliance on historical data—without accounting for population diversity, diagnostic variability, and evolving clinical definitions—may compromise the validity of economic evaluations. There is a growing need for fit-for-purpose, population-specific natural history data, or risk biasing value assessments that guide pricing and access decisions.

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References

1- Le P, Payne JY, Zhang L, Deshpande A, Rothberg MB, Alkhouri N, Herman W, Hernandez AV, Schleicher M, Ye W, Dasarathy S. Disease State Transition Probabilities Across the Spectrum of NAFLD: A Systematic Review and Meta-Analysis of Paired Biopsy or Imaging Studies. Clin Gastroenterol Hepatol. 2023 May;21(5):1154-1168. doi: 10.1016/j.cgh.2022.07.033.

2- Angulo P, Kleiner DE, Dam-Larsen S, Adams LA, Bjornsson ES, Charatcharoenwitthaya P, Mills PR, Keach JC, Lafferty HD, Stahler A, Haflidadottir S, Bendtsen F. Liver Fibrosis, but No Other Histologic Features, Is Associated With Long-term Outcomes of Patients With Nonalcoholic Fatty Liver Disease. Gastroenterology. 2015 Aug;149(2):389-97.e10. doi: 10.1053/j.gastro.2015.04.043.