



Obesity and NAFLD activity score increase rate of fibrosis progression in a continuous-time Markov model based on long-term follow-up biopsies in NAFLD patients



UPPSALA
UNIVERSITET

Ibrahim Khalil E^{1,2}, Knöchel J³, Kechagias S^{4,5}, Ekstedt M^{4,5}, Bergenholm L²

¹Department of Pharmaceutical Biosciences, Uppsala University, Sweden, ²Drug Metabolism and Pharmacokinetics, Early Cardiovascular, Renal and Metabolism, Biopharmaceuticals R&D, AstraZeneca, Gothenburg, Sweden, ³Clinical Pharmacology, ADME, and AI, Clinical Pharmacology & Safety Sciences, Biopharmaceuticals R&D, AstraZeneca, Gothenburg, Sweden, ⁴Department of Gastroenterology and Hepatology & ⁵Department of Medical and Health Sciences, Linköping University, Linköping, Sweden.

LINKÖPINGS
UNIVERSITET

Introduction

Non-alcoholic fatty liver disease (NAFLD) is now one of the most common causes of liver-related morbidity and mortality [1]. To this day there does not exist an approved drug therapy for NAFLD and life style advice to achieve weight loss is considered the standard of care. Furthermore, there is a great urge to better understand NAFLD disease with a high focus to understand fibrosis progression in associated with disease, as it is the best predictor of disease morbidity and mortality [1].

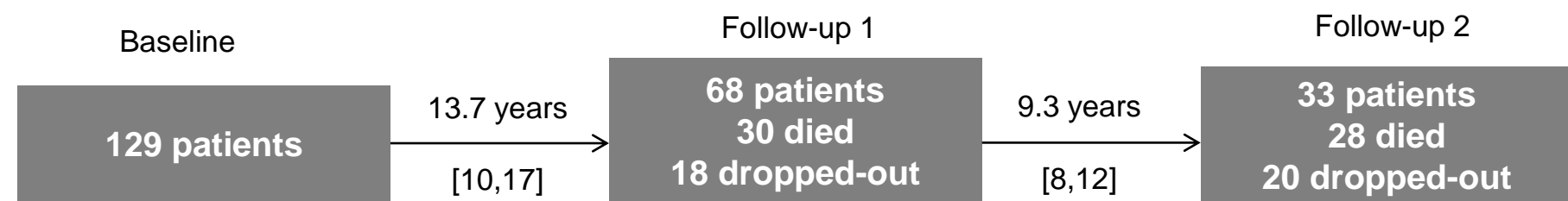
Objectives

- To develop a Markov model that describes fibrosis progression, cardiovascular and liver related mortality, all-cause mortality and drop-out based on a longitudinal clinical cohort of long-term follow-up biopsy in NAFLD patients.
- To investigate a number of measured covariates on disease progression.

Methods

Dataset

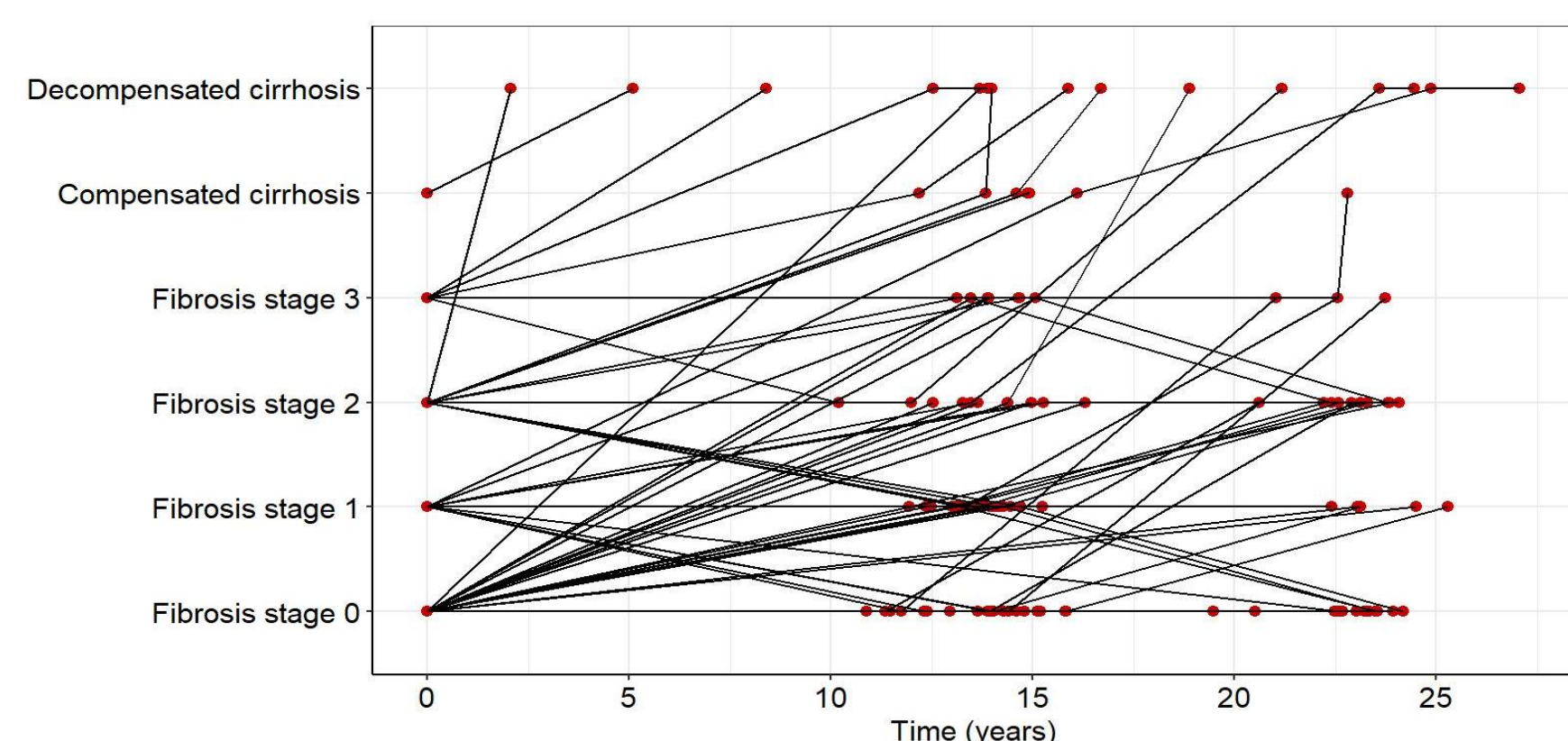
- Unique clinical cohort with liver biopsy proven NAFLD patients over multiple decades [2]



Fibrosis stage	Fibrosis location
1A	Zone 3, perisinusoidal, delicate
1B	Zone 3, perisinusoidal, dense
1C	Portal, periportal only
2	Zone 3, perisinusoidal + portal, periportal only
3	Bridging fibrosis
4	Cirrhosis (compensated cirrhosis (CC) and decompensated cirrhosis (DC))

- Liver biopsy is used as surrogate for clinical outcome
- It is used to evaluate fibrosis stage (range from 0 to 4)

Figure 1 Individual fibrosis stage over time given for each patient during the longitudinal cohort study [2]:



Red dots illustrate observations of fibrosis stage at the different study visits, black lines link the different observations for each individual.

Model / covariate selection

A continuous-time Markov model (CTMM) with first order markovian features was used to describe the forward and backward transition rates between different fibrosis stages in addition to transition rates to death and drop-out.

For the covariates, a manual covariate modelling approach was performed using forward inclusion ($\alpha=0.05$) and backward elimination ($\alpha=0.01$). The choice of the final model was based on:

- statistical significance
- uncertainty of the parameter estimates
- diagnostic plots
- clinical relevance

Results

CTMM structural model

The fibrosis stage, death and drop-out states were described by a nine compartment model (cf. Figure 2). Backwards transition rates shared the same parameter estimate. Death transition rates from $F_0/F_1/F_2$ were similar and increase exponentially from F_3 and above. Drop-out transition rates were assumed to be the same from each stage.

Covariate model

The covariates were included as a proportional relation on the rate parameters. The forward transition rates and the transition rates to death increase exponentially with age. The forward transition rates from F_0 to F_3 increase exponentially with BMI for non-obese and NAS. The transition rate to drop-out increases linearly with time.

$$\begin{aligned} & \text{EXP}(COV_{AGE} * (AGE - \text{median})) \\ & \text{EXP}(COV_{BMI \text{ for non-obese}} * (BMI - 30)) \\ & \text{EXP}(COV_{NAS} * (NAS - \text{median})) \\ & (1 + (COV_{TIME} * (TIME - \text{median}))) \end{aligned}$$

Figure 2 Schematic representation of the developed continuous-time Markov model:

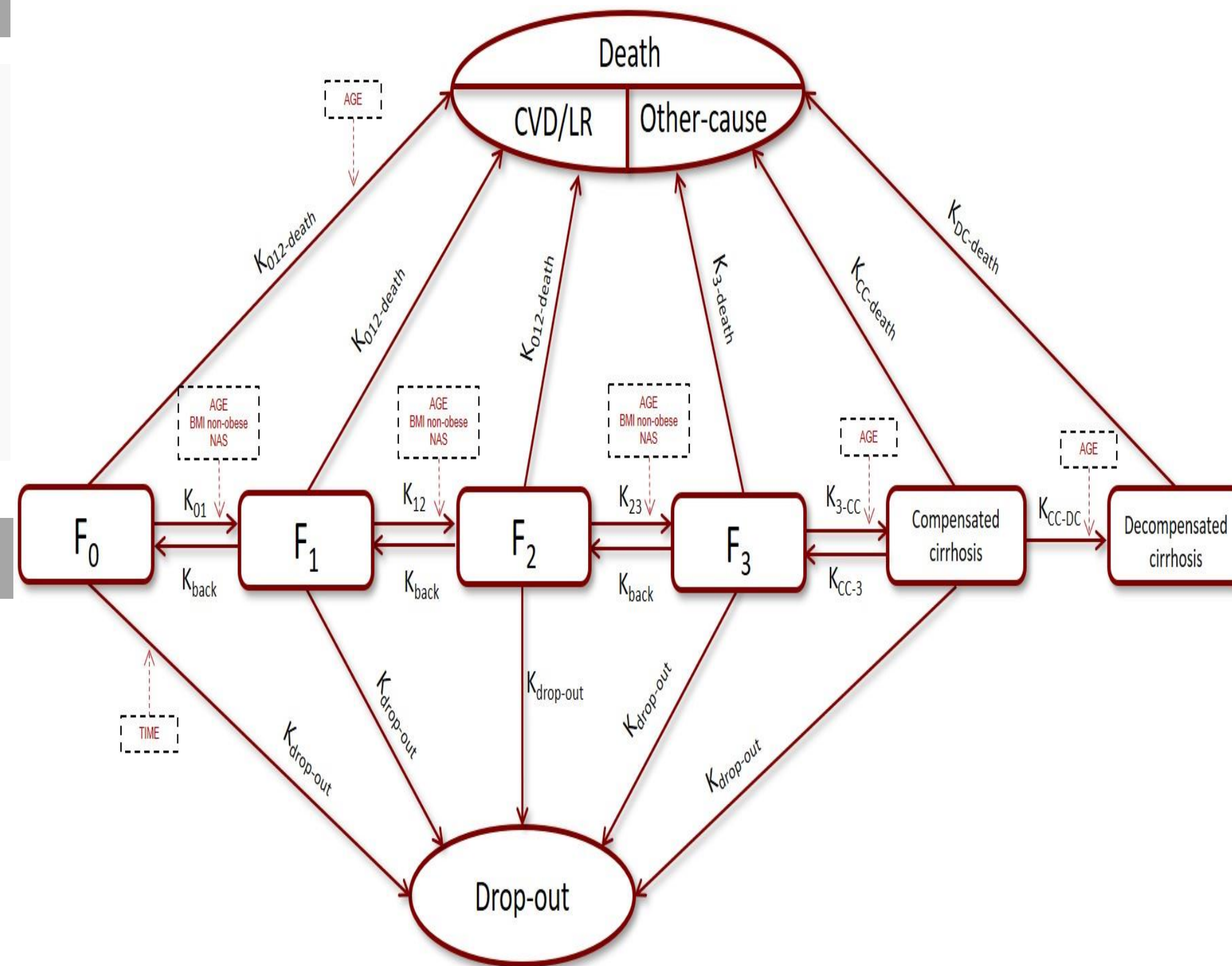


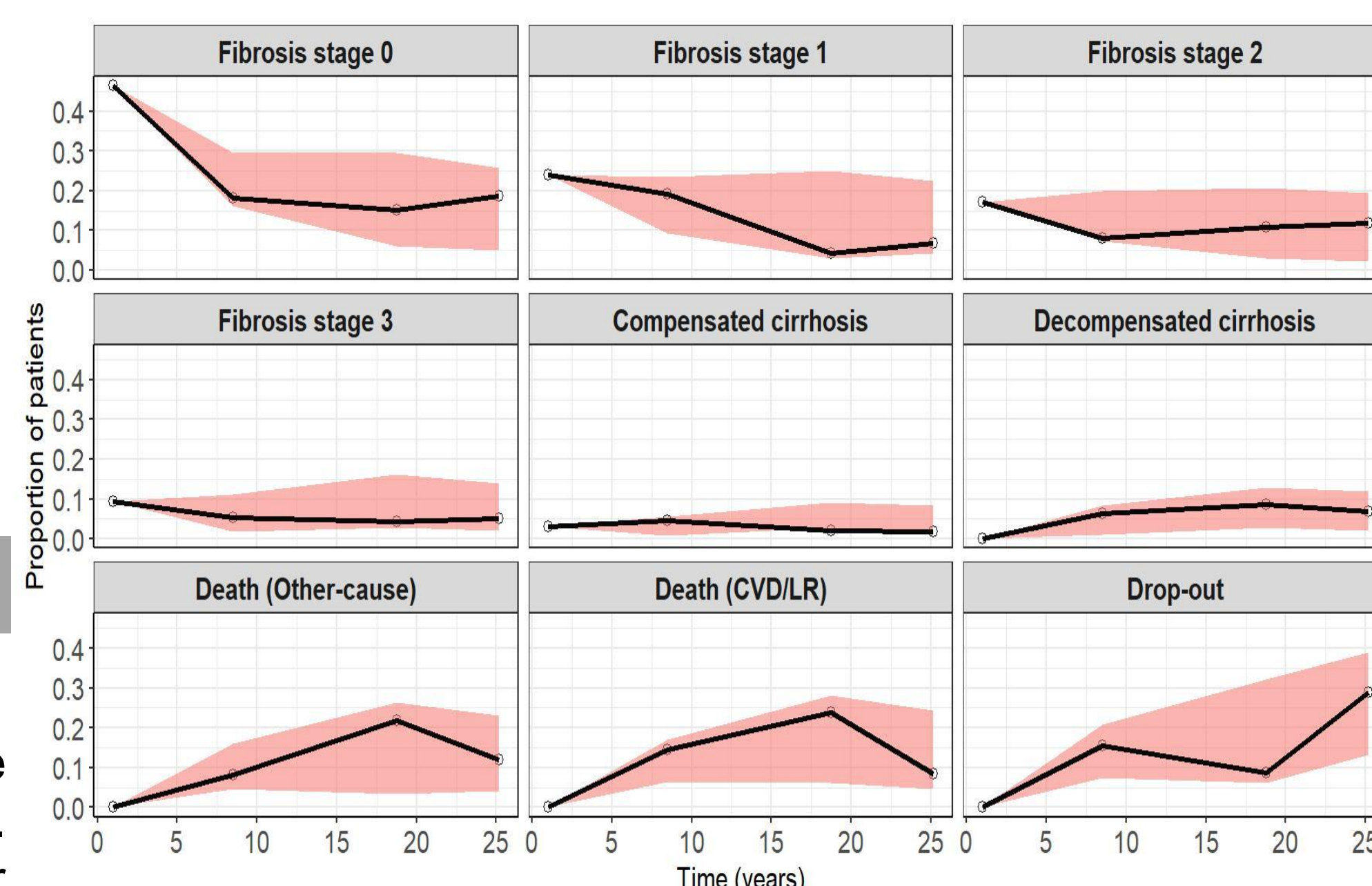
Table 1 Summary of the estimated model parameters:

Parameter	Estimate	95% CI
K_{01} (year ⁻¹)	0.1398	(0.0817 - 0.3193)
K_{12} (year ⁻¹)	0.128	(0.0674 - 0.257)
K_{23} (year ⁻¹)	0.08979	(0.0396 - 0.179)
K_{3-CC} (year ⁻¹)	0.1015	(0.0541 - 0.1746)
K_{CC-DC} (year ⁻¹)	0.2715	(0.1196 - 0.936)
K_{back} (year ⁻¹)	0.08354	(0.0466 - 0.1589)
K_{CC-3} (year ⁻¹)	1E-05 (fixed)	
NAS on $K_{01}/K_{12}/K_{23}$	0.5283	(0.3571 - 0.8522)
BMI on $K_{01}/K_{12}/K_{23}$ For non-obese	0.2088	(0.0874 - 0.3845)
Age on all forward rates	0.04254	(0.0232 - 0.0747)
K_{012} -all-cause-Mortality	0.03517	(0.0142 - 0.0655)
K_{012} -CVD/LR-Mortality	0.05967	(0.0298 - 0.1021)
Age on $K_{all-cause-Mortality}$	0.1049	(0.0552 - 0.1799)
Age on $K_{CVD/LR-Mortality}$	0.1554	(0.1103 - 0.2335)
Exponent of fibrosis stage on both mortality rates	0.7018	(0.4514 - 1.0804)
$K_{drop-out}$	0.02986	(0.0203 - 0.0416)
Time on $K_{drop-out}$	0.06525	(0.0289 - 0.0928)

Baseline forward transition rates (K_{ij}) at the median of included covariates (age = 57.54 years and NAS = 2) and BMI = 30 kg/m², baseline mortality transition rates (K_{012} -cause-mortality) at median age = 78.22 years

Model evaluation

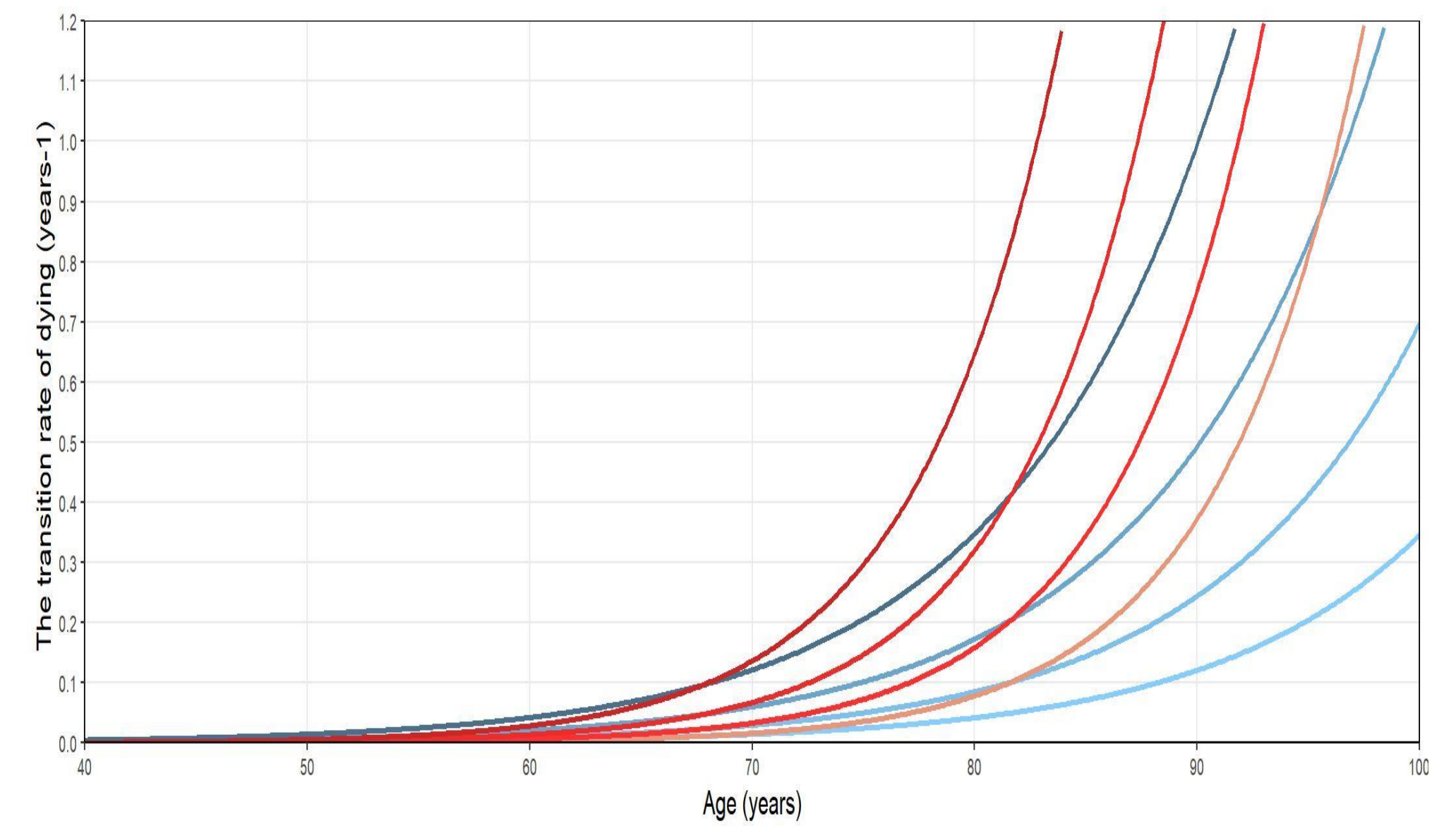
Figure 3 Visual predictive checks showing the proportions of the NAFLD patients at each fibrosis stage, death and drop-out state along the study period. The observed proportions in the Linköping data are illustrated by the black lines and the 95% prediction intervals from 1000 simulations is illustrated by the light pink region:



References

- Fibrosis stage but not NASH predicts mortality and time to development of severe liver disease in biopsy-proven NAFLD, Hannes Hagström et al, J. Hepatol.(2017).
- Natural history of nonalcoholic fatty liver disease: A prospective follow-up study with serial biopsies, Patrik Nasr et al, Hepatol Commun. (2018).
- Fibrosis Progression in Nonalcoholic Fatty Liver vs Nonalcoholic Steatohepatitis: A Systematic Review and Meta-analysis of Paired-Biopsy Studies, Siddharth Singh et al, Clinical Gastroenterology and Hepatology (2015).

Figure 4 Death transition rates over patient age :



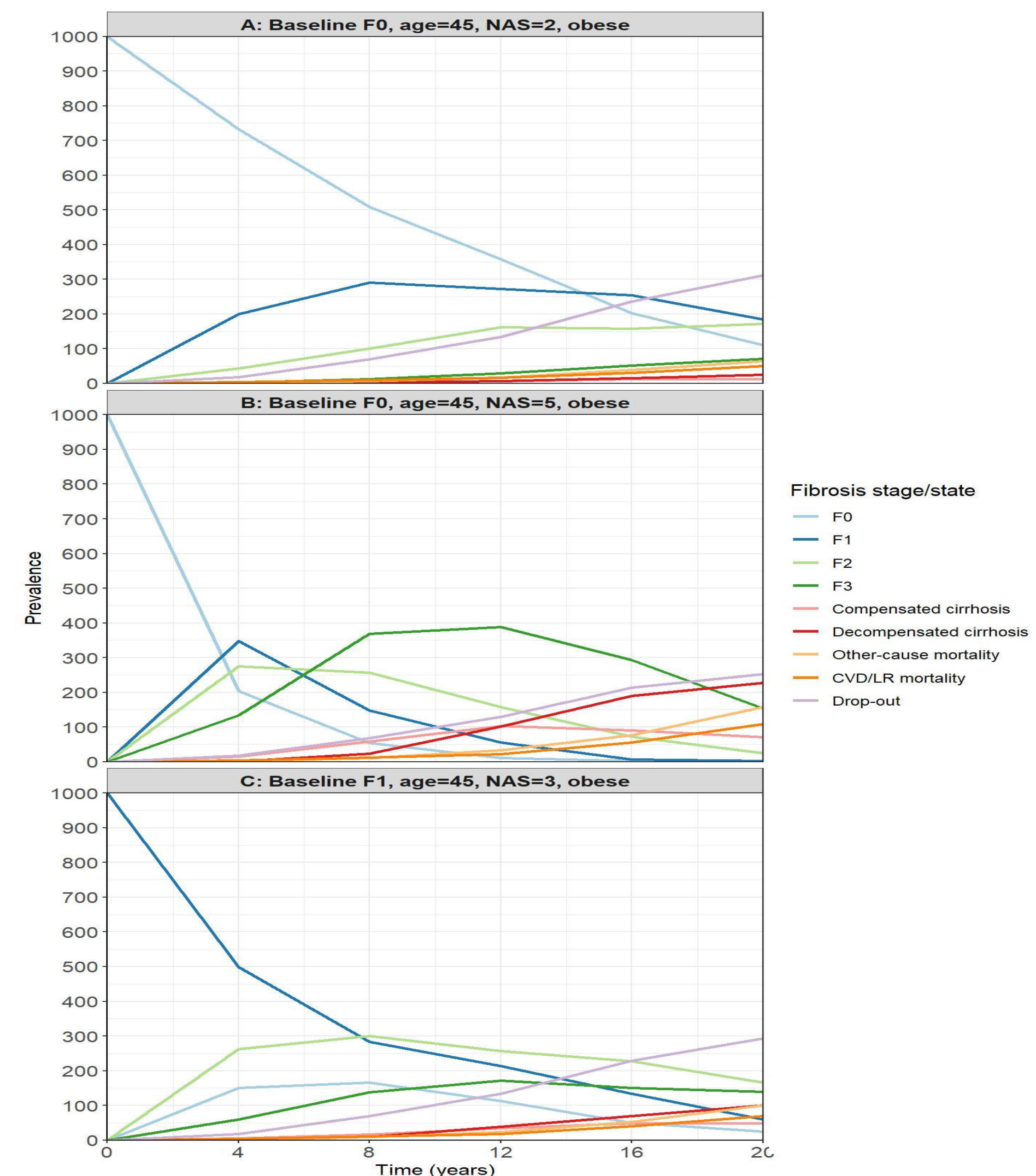
Conclusions

- The developed CTMM Markov model provides a good description of proportions of patients in the respective fibrosis stages over time.
- The rate of fibrosis progression is higher in obese patients than in non-obese patients in the early stages of the disease and increases exponentially with NAS.
- The risk of death from F3, compensated cirrhosis, decompensated cirrhosis is 2, 4 and 8 times higher than that from lower fibrosis stages respectively.

Model validation

- Simulations of various hypothetical cohorts with 1000 patients with baseline fibrosis stage 0 or 1, constant NAS and BMI for 20 years
- The average fibrosis progression rate (FPR) was calculated for each simulation

Figure 5 Results of hypothetical cohorts simulations :



- Resulting average FPR ranges from 0.07 to 0.22 depending on the assumed baseline fibrosis stage, age, NAS and BMI which is in line with previous published results of 0.12 ([0.07,0.16], 95% CI) [3]

Next steps

- Extending the model by adding other covariates like genetic factors and drug exposure as predictors on the transition rates allowing the effect of drug on the fibrosis progression to be quantified in clinical trials