JAMA Network Open

Original Investigation | Gastroenterology and Hepatology

Analysis of a Simulation Model to Estimate Long-term Outcomes in Patients with Nonalcoholic Fatty Liver Disease

Jagpreet Chhatwal, PhD; Ozden O. Dalgic, PhD; Wanyi Chen, PhD; Sumeyye Samur, PhD; Emily D. Bethea, MD; Jade Xiao, BE; Chin Hur, MD, MPH; Kathleen E. Corey, MD, MPH, MMSc; Rohit Loomba, MD, MHSc

Abstract

IMPORTANCE Quantitative assessment of disease progression in patients with nonalcoholic fatty liver disease (NAFLD) has not been systematically examined using competing liver-related and non–liver-related mortality.

OBJECTIVE To estimate long-term outcomes in NAFLD, accounting for competing liver-related and non–liver-related mortality associated with the different fibrosis stages of NAFLD using a simulated patient population.

DESIGN, SETTING, AND PARTICIPANTS This decision analytical modeling study used individual-level state-transition simulation analysis and was conducted from September 1, 2017, to September 1, 2021. A publicly available interactive tool, dubbed *NAFLD Simulator*, was developed that simulates the natural history of NAFLD by age and fibrosis stage at the time of (hypothetical) diagnosis defined by liver biopsy. Model health states were defined by fibrosis states F0 to F4, decompensated cirrhosis, hepatocellular carcinoma (HCC), and liver transplant. Simulated patients could experience nonalcoholic steatohepatitis resolution, and their fibrosis stage could progress or regress. Transition probabilities between states were estimated from the literature as well as calibration, and the model reproduced the outcomes of a large observational study.

EXPOSURE Simulated natural history of NAFLD.

MAIN OUTCOMES AND MEASURES Main outcomes were life expectancy; all cause, liver-related, and non–liver-related mortality; and cumulative incidence of decompensated cirrhosis and/or HCC.

RESULTS The model included 1 000 000 simulated patients with a mean (range) age of 49 (18-75) years at baseline, including 66% women. The life expectancy of patients aged 49 years was 25.3 (95% CI, 20.1-29.8) years for those with F0, 25.1 (95% CI, 20.1-29.4) years for those with F1, 23.6 (95% CI, 18.3-28.2) years for those with F2, 21.1 (95% CI, 15.6-26.3) years for those with F3, and 13.8 (95% CI, 10.3-17.6) years for those with F4 at the time of diagnosis. The estimated 10-year liver-related mortality was 0.1% (95% uncertainty interval [UI], <0.1%-0.2%) in F0, 0.2% (95% UI, 0.1%-0.4%) in F1, 1.0% (95% UI, 0.6%-1.7%) in F2, 4.0% (95% UI, 2.5%-5.9%) in F3, and 29.3% (95% UI, 21.8%-35.9%) in F4. The corresponding 10-year non–liver-related mortality was 1.8% (95% UI, 0.6%-5.0%) in F0, 2.4% (95% UI, 0.8%-6.3%) in F1, 5.2% (95% UI, 2.0%-11.9%) in F2, 9.7% (95% UI, 4.3%-18.1%) in F3, and 15.6% (95% UI, 10.1%-21.7%) in F4. Among patients aged 65 years, estimated 10-year non–liver-related mortality was higher than liver-related mortality in all fibrosis stages (eg, F2: 16.7% vs 0.8%; F3: 28.8% vs 3.0%; F4: 40.8% vs 21.9%).

CONCLUSIONS AND RELEVANCE This decision analytic model study simulated stage-specific long-term outcomes, including liver- and non–liver-related mortality in patients with NAFLD. Depending

(continued)

Key Points

Question What are the long-term outcomes associated with nonalcoholic fatty liver disease (NAFLD) by age and stage of fibrosis?

Findings This decision-analytic modeling study that simulated the life course of 1 000 000 patients with NAFLD estimated 10- and 20-year competing liver- and non–liver-related mortality and cumulative incidence of decompensated cirrhosis and hepatocellular carcinoma by patient age and fibrosis stage at diagnosis. The simulation tool, dubbed the *NAFLD Simulator,* is publicly available and could serve as an educational tool for health care practitioners and their patients and increase public awareness of NAFLD.

Meaning The findings of this study provide important data to patients and clinicians for understanding the associations between surrogate end points and long-term adverse outcomes of NAFLD.

+ Invited Commentary

+ Supplemental content

Author affiliations and article information are listed at the end of this article.

Abstract (continued)

on age and fibrosis stage, non–liver-related mortality was higher than liver-related mortality in patients with NAFLD. By translating surrogate markers into clinical outcomes, the NAFLD Simulator could be used as an educational tool among patients and clinicians to increase awareness of the health consequences of NAFLD.

JAMA Network Open. 2022;5(9):e2230426. doi:10.1001/jamanetworkopen.2022.30426

Introduction

Nonalcoholic fatty liver disease (NAFLD) is the most common cause of chronic liver disease worldwide, with an estimated prevalence ranging from 25% to 40%.[1-3] In parallel with the burgeoning prevalence of obesity, the prevalence of NAFLD has continued to increase in the US. Nonalcoholic steatohepatitis (NASH), an aggressive form of NAFLD, can progress to decompensated cirrhosis and hepatocellular carcinoma (HCC). NAFLD is currently the second most common indication for liver transplantation in the US. Among candidates for liver transplant, NAFLD is the fastest increasing cause of HCC.[4] NAFLD is associated with a substantial economic burden, incurring $103 billion in direct medical costs each year in the US.[5]

Effective treatments for NAFLD and NASH are lacking. Current options include lifestyle interventions (eg, diet, exercise), control of metabolic syndrome, and limited off-label pharmacotherapy.[6] Weight loss can be highly effective in treating NASH,[7] but very few patients succeed in maintaining a healthy weight in the long term.[8] Bariatric surgical treatment has been associated with improved or completely resolved steatohepatitis and fibrosis,[1] and improved clinical outcomes[9]; however, it is not widely used as an intervention for NASH. Several pharmacological treatments for NASH are under development, but none has yet been approved for use.[10]

Because NAFLD is a slowly progressive disease, ongoing clinical trials use surrogate markers as primary end points. Therefore, it is important that patients and clinicians understand the associations between surrogate end points and long-term adverse outcomes. For instance, what is the risk of HCC or mortality from competing liver- and non–liver-related causes associated with each NAFLD fibrosis stage? How would a patient's prognosis change if their NAFLD fibrosis score was reduced by 1 stage? Answering these questions using clinical trials or observational studies could be prohibitively expensive and take decades to complete. While earlier studies provide data on all-cause and/or liver-related mortality,[11-17] to our knowledge, quantitative assessment of disease progression in patients with NAFLD has not been systematically examined using competing risk models incorporating both liver-related and non–liver-related mortality.

The primary objective of this study was to develop a mathematical model of long-term outcomes in NAFLD, including competing liver-related and non–liver-related mortality, associated with the different fibrosis stages of NAFLD. We further developed an interactive online tool, the NAFLD Simulator, to make these results available for educational use.

Methods

The study was exempt from institutional review board review because it used only publicly available data and was not human participants research. Informed consent was not necessary because simulated individuals were used. We followed the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) reporting guideline.

Model Overview

We developed a microsimulation model that replicates the natural history of NAFLD for each patient. The patient can transition between different health states, including NAFL (ie, simple steatosis),

NAFLD-related fibrosis states F0 to F4, decompensated cirrhosis, HCC, and liver transplant (**Figure 1**). Stages F1 to F3 are further stratified into NASH and non-NASH states. We incorporate 3 causes of mortality: liver-related mortality, non–liver-related mortality (from cardiovascular events), and background mortality. The model reproduced the outcomes of a large observational study by Hagstrom et al.[13] The analysis was conducted from September 1, 2017, to September 1, 2021.

Baseline Population

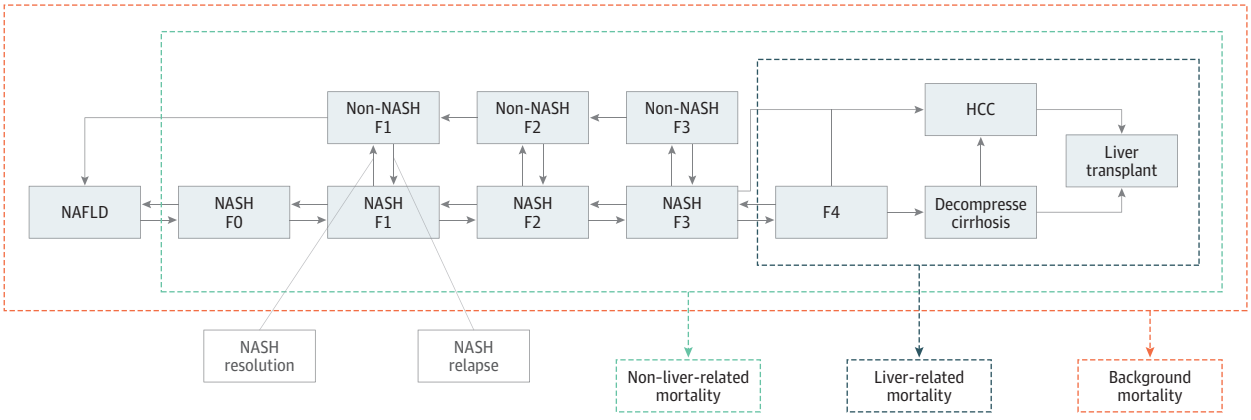
We simulated 1 million patients with characteristics similar to those in the NASH Clinical Research Network study.[18] At baseline (ie, at the time of hypothetical diagnosis), patients in the F1 to F3 stages could have NASH resolution, based on published studies.[19] The simulated patient population included 1 000 000 patients with a mean (range) age of 49 (18-75) years, including 66% women.

NAFLD Natural History

The natural history of NAFLD was defined using the following health states: NAFL, NAFLD-related fibrosis stages F0 to F4, decompensated cirrhosis, HCC, and liver transplant (Figure 1). Owing to the slow progression of NAFLD, we chose 1 year as the cycle length. Patients' disease in NAFLD fibrosis stages could progress or regress; these progression and regression rates were informed by either published studies or calibration.[20-26] Patients could also experience NASH resolution, and those with NASH resolution could relapse; NASH resolution and relapse rates were extracted from clinical trial data.[27] Patients with F3, F4, and decompensated cirrhosis could develop HCC. Patients with decompensated cirrhosis and HCC were classified as eligible for liver transplantation, with transplantation rates extracted from published studies using United Network for Organ Sharing data.[28-31]

We accounted for 3 types of mortalities: liver-related mortality, non–liver-related mortality (including cardiovascular events or extrahepatic malignant neoplasm), and background mortality. Patients in stages F4 and above have a higher risk of liver-related mortality in the model. Additionally, all NAFLD-associated health states (ie, excluding NAFL) were subject to non–liver-related mortality, dependent on a patient's disease stage, sex, and age. We estimated liver- and non–liver-related mortality rates from published studies,[24,32-34] and extracted background mortality from the US Life Tables.[35]

Figure 1. Model Schematic of the Natural History of Nonalcoholic Fatty Liver Disease (NAFLD)



Each box represents a patient health state. Arrows indicate possible transitions between states. The patient can transition between different health states, including NAFL (ie, simple steatosis), NAFLD-related fibrosis states F0 to F4, decompensated cirrhosis, hepatocellular carcinoma (HCC), and liver transplant. Stages F1 to F3 are further stratified into nonalcoholic steatohepatitis (NASH) and non-NASH states. The model incorporates 3 causes of mortality: liver-related mortality, non–liver-related mortality, and background mortality. Patients' disease in NAFLD fibrosis stages could progress or regress; these progression and regression rates were informed by either published studies or calibration.

Some progression and regression rates (liver-related mortality for F4; non–liver-related mortality for F0-F4) were not directly available from published studies. These rates were estimated by calibrating our model-estimated patient survival (ie, 20-year survival by fibrosis stage at diagnosis) to reported values from a large observational study by Hagstrom et al.[13] We used the simulated annealing algorithm to search for sets of parameter values that minimize total error between the model outcomes and reported survival.[36] We repeated this process 1000 times, each time starting from a different initial value to generate 1000 sets of calibrated parameter values and corresponding outcomes. These sets were used to characterize the uncertainty in our estimations. Details of the calibration procedure and validation of model-estimated survival with the reported outcomes by Hagstrom et al[13] are presented in the eAppendix in the Supplement. The full list of extracted and calibrated model parameters are presented in eTable 1 in the Supplement.

Statistical Analysis

Our model estimated the 10- and 20-year cumulative incidence of advanced sequalae of NAFLD, as well as background, liver-related, and non–liver-related mortality by age and fibrosis stages at diagnosis using liver biopsy. For each health state, we further estimated overall survival up to 20 years, life expectancy, and survival time. We generated 95% uncertainty intervals (UIs) for the outcomes to account for uncertainty from calibration (eAppendix in the Supplement).

We developed a publicly available, interactive tool, NAFLD Simulator,[37] using the Shiny package in R statistical software version 3.5 (R Project for Statistical Computing). The tool allows users to specify a patient profile defined by age, sex, and NAFLD fibrosis score, then provides model-estimated long-term outcomes in a graphic format. Outcomes include the cause of death (liver related, non–liver related, or background), overall survival, cumulative risks of developing decompensated cirrhosis and HCC, and probability of receiving a liver transplant.

Results

Using the decision-analytic model, we generated outcomes for different hypothetical patients defined by their age and fibrosis stage at diagnosis. We validated the model estimated outcomes with data from an observational study.

Model Validation

Using our model, we simulated the population reported by Hagstrom et al[13] and generated 20-year patient survival by fibrosis stage at diagnosis. Our model-estimated overall survival closely matched the reported outcomes in the study by Hagstrom et al[13] (**Figure 2**). The overlapping curves show that the model accurately estimated stage-specific Kaplan-Meier survival curves for patients with F0 through F4 for up to 20 years.[13] We independently validated estimated all-cause mortality for patients with cirrhosis using data from a study by Simon et al.[16]

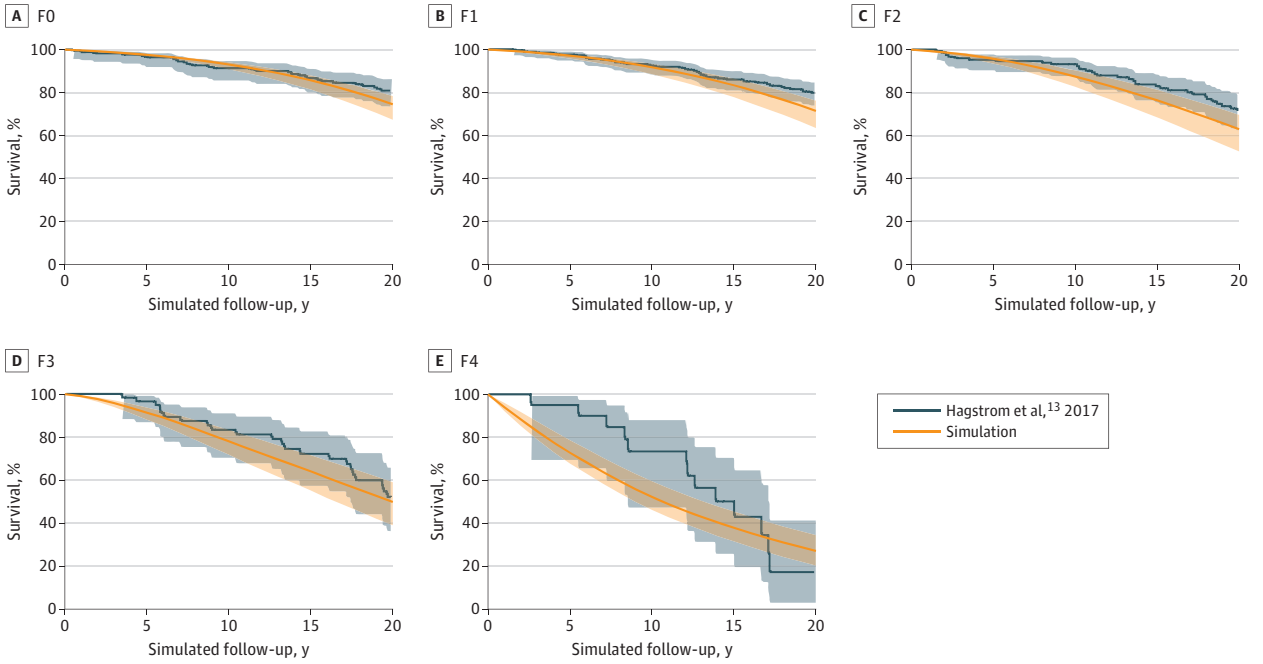
Survival

For a patient aged 49 years (the mean age), the model-estimated 10-year survival was 92.9% (95% UI, 89.8%-94.1%) for stage F0, 92.2% (95% UI, 88.4%-93.9%) for stage F1, 88.7% (95% UI, 82.3%-91.9%) for stage F2, 81.4% (95% UI, 72.9%-86.9%) for stage F3, and 51.3% (95% UI, 44.2%-59.4%) for stage F4 (**Figure 3**). Of note, the largest drop in survival (30.1 percentage points) was observed between stages F3 and F4. The life expectancy of patients aged 49 years was 25.3 (95% CI, 20.1-29.8) years for those with F0, 25.1 (95% CI, 20.1-29.4) years for those with F1, 23.6 (95% CI, 18.3-28.2) years for those with F2, 21.1 (95% CI, 15.6-26.3) years for those with F3, and 13.8 (95% CI, 10.3-17.6) years for those with stage F4 at baseline (ie, at the time of diagnosis). The decrease in life expectancy was 7.3 years between stages F3 and F4.

Liver and Non–liver-related Mortality

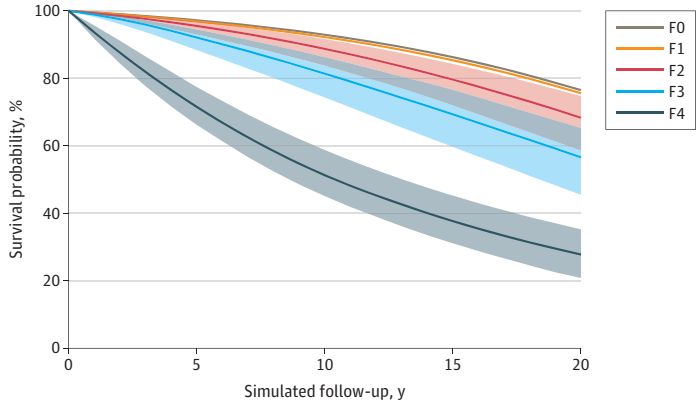
Figure 4 shows liver-related, non–liver-related, and background mortality by fibrosis stage in patients aged 49 years. The estimated 10-year liver-related mortality was 0.1% (95% UI, <0.1%-0.2%) in stage F0, 0.2% (95% UI, 0.1%-0.4%) in F1, 1.0% (95% UI, 0.6%-1.7%) in stage F2, 4.0% (95% UI, 2.5%-5.9%) in stage F3, and 29.3% (95% UI, 21.8%-35.9%) in stage F4 patients (Figure 4; eTable 2 in the Supplement). The higher the fibrosis stage, the higher the odds of death from liver disease. Compared with stage F0, 10-year liver-related mortality was larger by a factor of 2 in stage F1, by a factor of 10 in stage F2, by a factor of 40 in stage F3, and by a factor of 293 in stage F4. Of note, 10-year liver-related mortality in stage F4 was 7.3-fold higher than in stage F3. eTable 2 in the Supplement presents 20-year outcomes for NAFLD patients by disease stage.

Figure 2. Model Validation by Comparison With Published Outcomes



We compared our model-estimated long-term survival results outcomes from a simulated population cohort stratified by fibrosis states with those from Hagstrom et al.[13]

Figure 3. Survival in Patients Aged 49 Years With Nonalcoholic Fatty Liver Disease–Related Fibrosis Stage



Shaded regions represent the 95% uncertainty intervals generated from probabilistic sensitivity analysis.

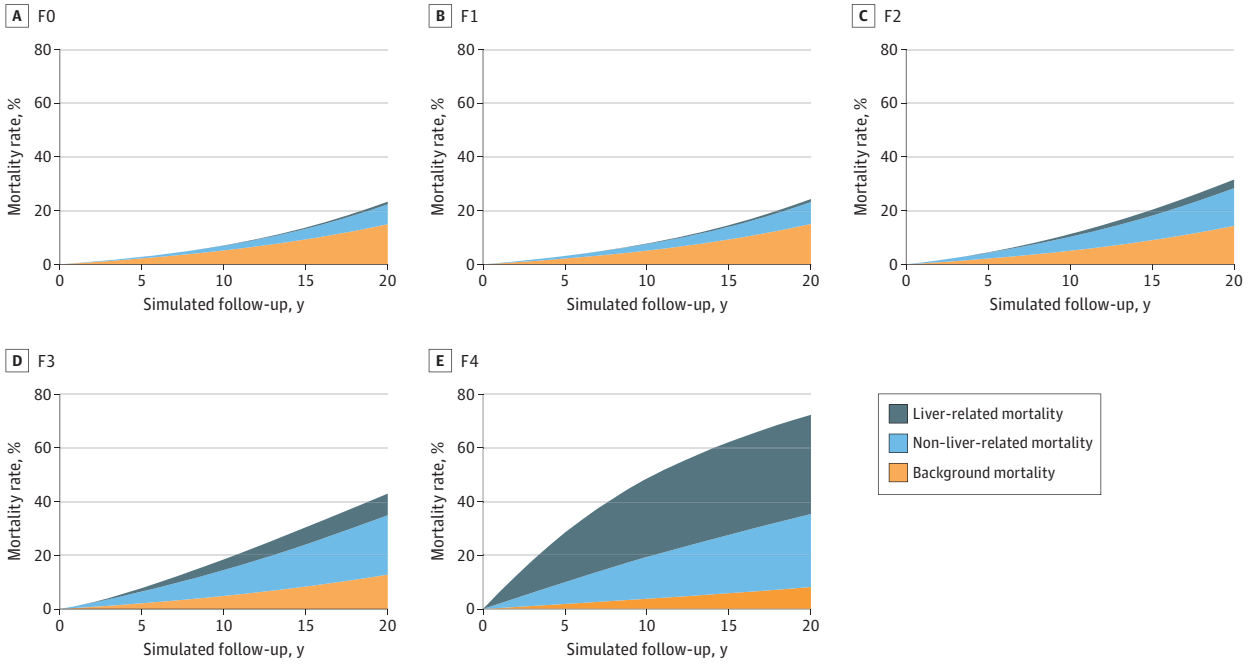
The estimated 10-year non–liver-related mortality was 1.8% (95% UI, 0.6%-5.0%) in stage F0, 2.4% (95% UI, 0.8%-6.3%) in stage F1, 5.2% (95% UI, 2.0%-11.9%) in stage F2, 9.7% (95% UI, 4.3%-18.1%) in stage F3, and 15.6% (95% UI, 10.1%-21.7%) in stage F4 patients (eTable 2 in the Supplement). The higher the fibrosis stage, the higher the odds of non–liver-related mortality. Compared with stage F0, 10-year non–liver-related mortality was greater by a factor of 1.3 in stage F1, by a factor of 2.9 in stage F2, by a factor of 5.4 in stage F3, and by a factor of 8.7 in stage F4. Additionally, 10-year non–liver-related mortality in stage F4 was 1.6-fold higher than in stage F3.

In stages F0 to F3, 10-year non–liver-related mortality was higher than liver-related mortality; whereas in stage F4, 10-year liver-related mortality was substantially higher than non–liver-related mortality. The largest increase in mortality (both liver and non–liver) was observed when patients progressed from stage F3 to stage F4, indicating an imperative need for effective treatments and interventions to halt progression at stage F3 and aid regression from stage F4.

Advanced Sequelae

The cumulative incidences of decompensated cirrhosis and HCC by baseline fibrosis stage in patients aged 49 years are presented in the eFigure in the Supplement. The estimated 10-year cumulative incidence of decompensated cirrhosis was 0.08% (95% UI, 0.05%-0.1%) in stage F0, 0.15% (95% UI, 0.1%-0.25%) in stage F1, 0.7% (95% UI, 0.5%-1.0%) in stage F2, 2.7% (95% UI, 2.1%-3.4%) in stage F3, and 17.2% (95% UI, 15.9%-18.6%) in stage F4 (eFigure and eTable 2 in the Supplement). Compared with stage F3, the cumulative incidence of decompensated cirrhosis in the F4 stage was 6.4 times larger. The 10-year cumulative incidence of HCC was 0.03% (95% UI, 0.02%-0.05%) in stage F0, 0.06% (95% UI, 0.03%-0.09%) in stage F1, 0.29% (95% UI, 0.19%-0.40%) in stage F2, 1.12% (95% UI, 0.88%-1.37%) in stage F3, and 7.88% (95% UI, 7.41%-8.67%) in stage F4. Compared with stage F3, the cumulative incidence of HCC in the F4 stage was 7.2-fold larger.

Figure 4. Mortality in Patients Aged 49 Years With Nonalcoholic Fatty Liver Disease–Related Fibrosis Stages F1 to F4



As fibrosis stage increased, the odds of dying from liver disease increased.

Competing Liver-Related and Non–liver-related Mortality

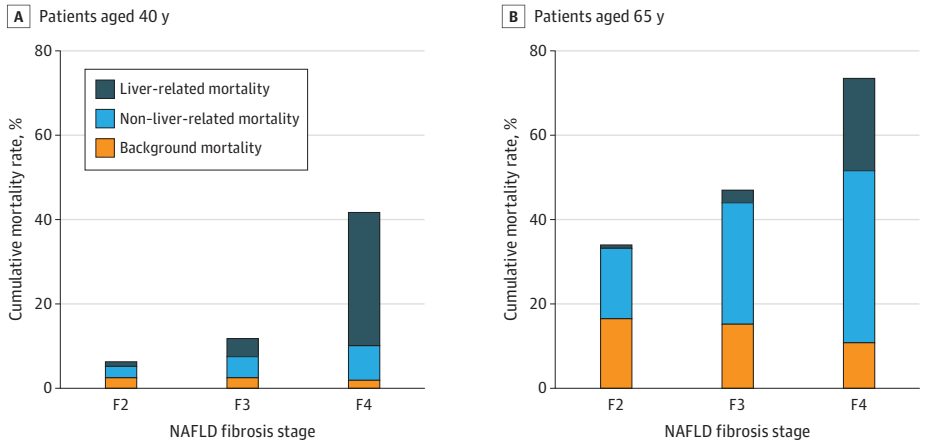
The estimated 10-year mortality (liver, non–liver, and background) in patients aged 40 years or 65 years are presented in **Figure 5** and eTable 3 in the Supplement. Among patients aged 40 years, non–liver-related mortality was higher than liver-related mortality in those with stage F2 (2.7% vs 1.1%) or F3 (5.0% vs 4.3%); however, this trend was reversed in those with stage F4 (8.2% vs 31.6%) because of a higher competing liver-related mortality associated with stage F4. Among patients aged 65 years, non–liver-related mortality was higher than liver-related mortality in all stages because of higher competing cardiovascular risk in older age (F0: 6.0% vs 0.08%; F1: 8.1% vs 0.2%, F2: 16.7% vs 0.8%; F3: 28.8% vs 3.0%; F4: 40.8% vs 21.9%). Compared with patients aged 40 years, 10-year liver-related mortality was lower in those aged 65 years across all fibrosis stages; however, 10-year non–liver-related mortality was higher in patients aged 65 years, primarily because of the aforementioned higher cardiovascular risk.

Discussion

In this decision analytic modeling study that simulated the life course of NAFLD natural history, we found a nonlinear a nonlinear increase in adverse clinical outcomes with increasing fibrosis stage. Specifically, in patients without cirrhosis, 10-year non–liver-related mortality was higher than liver-related mortality; in contrast, in patients with cirrhosis, 10-year liver-related mortality was substantially higher than non–liver-related mortality. The largest increase in mortality—both liver- and non–liver-related—was observed when patients who progressed from stage F3 to stage F4, indicating an imperative need for early recognition, effective treatments, and interventions to halt progression at the precirrhosis stage.

NAFLD represents a substantial disease burden, and our study provides several new insights into the natural history of NAFLD. While earlier studies estimated overall mortality and liver-related mortality,[12-17] none have reported non–liver-related mortality associated with the different NAFLD stages, to our knowledge. We provide stage-specific non–liver-related mortality estimates while accounting for competing risk between liver and non–liver events. As noted in some of the earlier studies, we also found a nonlinear increase in adverse clinical outcomes with increasing fibrosis stage.[16] In particular, when a patient progressed from stage F3 to stage F4, there was a 25% decrease in 10-year survival. Cumulative incidence of decompensated cirrhosis and HCC from the F4 stage was 7-fold higher than from the F3 stage. Therefore, preventing the progression from stage F3 to stage F4 may substantially reduce adverse outcomes, prevent the need for liver transplant in patients with NAFLD, and save health care resources.

Figure 5. Competing Liver-Related and Non–liver-related Mortality in Patients Aged 40 Years or 65 Years With Nonalcoholic Fatty Liver Disease (NAFLD) by Fibrosis Stage



We have also developed an interactive online tool, NAFLD Simulator, that displays our model-estimated outcomes in a graphic format. By translating surrogate marker outcomes into clinical outcome estimates in a form that can be easily understood by patients and clinicians, the NAFLD Simulator could be used as an educational tool to increase awareness of the health consequences of NAFLD among patients and health care practitioners. Users can also download simulated patient data, plots, and an executive report for a given patient profile.

The NAFLD Simulator is an accessible, easy-to-use simulation tool that could serve as an educational tool for health care practitioners and their patients and simultaneously increase public awareness of NAFLD. In future, the NAFLD Simulator could incorporate the long-term outcomes associated with new therapies. Further extensions could evaluate long-term outcomes associated with noninvasive testing methods, such as imaging and serum-based biomarkers. Our framework will be constantly updated to incorporate new evidence as it arises, thereby maintaining its relevance to the NAFLD community.

Limitations

The findings of our study should be understood in the context of its limitations. First, our study does not account for differences in outcomes when the patient has comorbidities, such as diabetes and obesity, while it is known that long-term outcomes in different comorbidity subgroups can vary substantially. Second, our model may be limited in its applicability to the wider population because it requires patients to know their biopsy-confirmed fibrosis stage. As more data become available, our model could be extended to evaluate long-term outcomes associated with noninvasive tests, including emerging imaging and serum-based biomarkers.[38] Third, we assumed that patients' long-term outcomes were dependent on their current NAFLD fibrosis stage only and not on any prior change in the fibrosis score. For instance, it is possible that patients who regressed from stage F4 to stage F3 may have different outcomes than patients with stage F3 who never progressed to stage F4.

Conclusions

In this decision analytical model study, we developed an online, interactive tool, the NAFLD Simulator, that simulates long-term outcomes in patients with NAFLD. Depending on the age and fibrosis stage at diagnosis, non–liver-related mortality can be higher than liver-related mortality in NAFLD patients. By translating surrogate marker outcomes into clinical outcomes easily understood by patients and clinicians, the NAFLD Simulator could be used as an educational tool to increase awareness of the health consequences of NAFLD among patients and health care practitioners.

ARTICLE INFORMATION

Accepted for Publication: July 15, 2022.

Published: September 13, 2022. doi:10.1001/jamanetworkopen.2022.30426

Corresponding Author: Jagpreet Chhatwal, PhD, Institute for Technology Assessment, Massachusetts General Hospital, 101 Merrimac St, 10th Floor, Boston, MA 02114 (JagChhatwal@mgh.harvard.edu).

Author Affiliations: Institute for Technology Assessment, Massachusetts General Hospital, Boston (Chhatwal, Dalgic, Chen, Samur, Bethea, Xiao); Harvard Medical School, Boston, Massachusetts (Chhatwal, Dalgic, Chen, Samur, Bethea, Corey); Department of Gastroenterology, Massachusetts General Hospital, Boston (Chhatwal, Bethea, Corey); Georgia Institute of Technology, Atlanta (Xiao); Columbia University, New York, New York (Hur); NAFLD Research Center, University of California, San Diego, La Jolla (Loomba).

Author Contributions: Dr Chhatwal had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Concept and design: Chhatwal, Dalgic, Bethea, Hur, Corey, Loomba.

Acquisition, analysis, or interpretation of data: Chhatwal, Dalgic, Chen, Samur, Xiao, Corey, Loomba.

Drafting of the manuscript: Chhatwal, Dalgic, Chen, Loomba.

Critical revision of the manuscript for important intellectual content: Dalgic, Chen, Samur, Bethea, Xiao, Hur, Corey, Loomba.

Statistical analysis: Dalgic, Chen, Samur.

Obtained funding: Chhatwal, Loomba.

Administrative, technical, or material support: Samur.

Supervision: Chhatwal, Bethea, Corey, Loomba.

Conflict of Interest Disclosures: Dr Chhatwal reported personal fees from Value Analytics Labs, Novo Nordisk, and Flatiron Health outside the submitted work. Dr Loomba reported personal fees from Aardvark Therapeutics, Altimmune, Anylam/Regeneron, Amgen, Arrowhead Pharmaceuticals, AstraZeneca, Bristol-Myer Squibb, CohBar, Eli Lilly, Galmed, Gilead, Glympse Bio, Hightide, Inipharma, Intercept, Inventiva, Ionis, Janssen Inc, Madrigal, Metacrine, NGM Biopharmaceuticals, Novartis, Novo Nordisk, Merck, Pfizer, Sagimet, Theratechnologies, 89 Bio, Terns Pharmaceuticals, and Viking Therapeutics; grants from Arrowhead Pharmaceuticals, AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, Eli Lilly, Galectin Therapeutics, Galmed Pharmaceuticals, Gilead, Hanmi, Intercept, Inventiva, Ionis, Janssen, Madrigal Pharmaceuticals, Merck, NGM Biopharmaceuticals, Novo Nordisk, Pfizer, Sonic Incytes, and Terns Pharmaceuticals; and serving as a cofounder of LipoNexus. No other disclosures were reported.

Funding/Support: This study was supported by the American Association for the Study of Liver Disease (AASLD) Innovation Award Innovation Fund, and the American Cancer Society Research Scholar (grant No. RSG-17-022-01-CPPB). Dr Loomba receives funding support from the National Institute of Environmental Health Sciences (grant No. 5P42ES010337), National Center for Advancing Translational Sciences (grant No. 5UL1TR001442), Department of Defense Peer Reviewed Cancer Research Program (grant No. W81XWH-18-2-0026), National Institute of Diabetes and Digestive and Kidney Diseases (grants No. U01DK061734, R01DK106419, R01DK121378, R01DK124318, and P30DK120515), National Heart, Lung, and Blood Institute (grant No. P01HL147835), and National Institute on Alcohol Abuse and Alcoholism (grant No. U01AA029019).

Role of the Funder/Sponsor: The funders had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

REFERENCES

1. Chalasani N, Younossi Z, Lavine JE, et al. The diagnosis and management of non-alcoholic fatty liver disease: practice guideline by the American Association for the Study of Liver Diseases, American College of Gastroenterology, and the American Gastroenterological Association. *Hepatology*. 2012;55(6):2005-2023. doi:10.1002/hep.25762

2. Loomba R, Sanyal AJ. The global NAFLD epidemic. *Nat Rev Gastroenterol Hepatol*. 2013;10(11):686-690. doi:10.1038/nrgastro.2013.171

3. Younossi ZM, Golabi P, de Avila L, et al. The global epidemiology of NAFLD and NASH in patients with type 2 diabetes: a systematic review and meta-analysis. *J Hepatol*. 2019;71(4):793-801. doi:10.1016/j.jhep.2019.06.021

4. Younossi ZM, Stepanova M, Ong J, et al. Nonalcoholic steatohepatitis is the most rapidly increasing indication for liver transplantation in the United States. *Clin Gastroenterol Hepatol*. 2021;19(3):580-589.e5. doi:10.1016/j.cgh.2020.05.064

5. Younossi ZM, Blissett D, Blissett R, et al. The economic and clinical burden of nonalcoholic fatty liver disease in the United States and Europe. *Hepatology*. 2016;64(5):1577-1586. doi:10.1002/hep.28785

6. McPherson S, Hardy T, Henderson E, Burt AD, Day CP, Anstee QM. Evidence of NAFLD progression from steatosis to fibrosing-steatohepatitis using paired biopsies: implications for prognosis and clinical management. *J Hepatol*. 2015;62(5):1148-1155. doi:10.1016/j.jhep.2014.11.034

7. Vilar-Gomez E, Martinez-Perez Y, Calzadilla-Bertot L, et al. Weight loss through lifestyle modification significantly reduces features of nonalcoholic steatohepatitis. *Gastroenterology*. 2015;149(2):367-78.e5. doi:10.1053/j.gastro.2015.04.005

8. Wadden TA, Sternberg JA, Letizia KA, Stunkard AJ, Foster GD. Treatment of obesity by very low calorie diet, behavior therapy, and their combination: a five-year perspective. *Int J Obes*. 1989;13(suppl 2):39-46.

9. Aminian A, Al-Kurd A, Wilson R, et al. Association of bariatric surgery with major adverse liver and cardiovascular outcomes in patients with biopsy-proven nonalcoholic steatohepatitis. *JAMA*. 2021;326(20):2031-2042. doi:10.1001/jama.2021.19569

10. Neuschwander-Tetri BA. Therapeutic landscape for NAFLD in 2020. *Gastroenterology*. 2020;158(7):1984-1998.e3. doi:10.1053/j.gastro.2020.01.051

11. Taylor RS, Taylor RJ, Bayliss S, et al. Association between fibrosis stage and outcomes of patients with nonalcoholic fatty liver disease: a systematic review and meta-analysis. *Gastroenterology*. 2020;158(6):1611-1625.e12. doi:10.1053/j.gastro.2020.01.043

12. Vilar-Gomez E, Calzadilla-Bertot L, Wai-Sun Wong V, et al. Fibrosis severity as a determinant of cause-specific mortality in patients with advanced nonalcoholic fatty liver disease: a multi-national cohort study. *Gastroenterology*. 2018;155(2):443-457.e17. doi:10.1053/j.gastro.2018.04.034

13. Hagström H, Nasr P, Ekstedt M, et al. Fibrosis stage but not NASH predicts mortality and time to development of severe liver disease in biopsy-proven NAFLD. *J Hepatol*. 2017;67(6):1265-1273. doi:10.1016/j.jhep.2017.07.027

14. Dulai PS, Singh S, Patel J, et al. Increased risk of mortality by fibrosis stage in nonalcoholic fatty liver disease: systematic review and meta-analysis. *Hepatology*. 2017;65(5):1557-1565. doi:10.1002/hep.29085

15. Ekstedt M, Franzén LE, Mathiesen UL, et al. Long-term follow-up of patients with NAFLD and elevated liver enzymes. *Hepatology*. 2006;44(4):865-873. doi:10.1002/hep.21327

16. Simon TG, Roelstraete B, Khalili H, Hagström H, Ludvigsson JF. Mortality in biopsy-confirmed nonalcoholic fatty liver disease: results from a nationwide cohort. *Gut*. 2021;70(7):1375-1382. doi:10.1136/gutjnl-2020-322786

17. Sanyal AJ, Van Natta ML, Clark J, et al; NASH Clinical Research Network (CRN). Prospective study of outcomes in adults with nonalcoholic fatty liver disease. *N Engl J Med*. 2021;385(17):1559-1569. doi:10.1056/NEJMoa2029349

18. Brunt EM, Kleiner DE, Wilson LA, Belt P, Neuschwander-Tetri BA; NASH Clinical Research Network (CRN). Nonalcoholic fatty liver disease (NAFLD) activity score and the histopathologic diagnosis in NAFLD: distinct clinicopathologic meanings. *Hepatology*. 2011;53(3):810-820. doi:10.1002/hep.24127

19. Angulo P, Kleiner DE, Dam-Larsen S, et al. Liver fibrosis, but no other histologic features, is associated with long-term outcomes of patients with nonalcoholic fatty liver disease. *Gastroenterology*. 2015;149(2):389-97.e10. doi:10.1053/j.gastro.2015.04.043

20. Perumpail BJ, Khan MA, Yoo ER, Cholankeril G, Kim D, Ahmed A. Clinical epidemiology and disease burden of nonalcoholic fatty liver disease. *World J Gastroenterol*. 2017;23(47):8263-8276. doi:10.3748/wjg.v23.i47.8263

21. Younossi ZM, Ratziu V, Loomba R, et al; REGENERATE Study Investigators. Obeticholic acid for the treatment of non-alcoholic steatohepatitis: interim analysis from a multicentre, randomised, placebo-controlled phase 3 trial. *Lancet*. 2019;394(10215):2184-2196. doi:10.1016/S0140-6736(19)33041-7

22. Kanwal F, Kramer JR, Mapakshi S, et al. Risk of hepatocellular cancer in patients with non-alcoholic fatty liver disease. *Gastroenterology*. 2018;155(6):1828-1837.e2. doi:10.1053/j.gastro.2018.08.024

23. Gilead Announces Topline Data From Phase 3 STELLAR-4 Study of Selonsertib in Compensated Cirrhosis (F4) Due to Nonalcoholic Steatohepatitis (NASH). News release. Gilead. February 11, 2019. Accessed August 8, 2022. https://www.gilead.com/news-and-press/press-room/press-releases/2019/2/gilead-announces-topline-data-from-phase-3-stellar4-study-of-selonsertib-in-compensated-cirrhosis-f4-due-to-nonalcoholic-steatohepatitis-nash

24. Sanyal AJ, Banas C, Sargeant C, et al. Similarities and differences in outcomes of cirrhosis due to nonalcoholic steatohepatitis and hepatitis C. *Hepatology*. 2006;43(4):682-689. doi:10.1002/hep.21103

25. Fattovich G, Giustina G, Degos F, et al. Morbidity and mortality in compensated cirrhosis type C: a retrospective follow-up study of 384 patients. *Gastroenterology*. 1997;112(2):463-472. doi:10.1053/gast.1997.v112.pm9024300

26. Planas R, Ballesté B, Alvarez MA, et al. Natural history of decompensated hepatitis C virus-related cirrhosis: a study of 200 patients. *J Hepatol*. 2004;40(5):823-830. doi:10.1016/j.jhep.2004.01.005

27. Neuschwander-Tetri BA, Loomba R, Sanyal AJ, et al; NASH Clinical Research Network. Farnesoid X nuclear receptor ligand obeticholic acid for non-cirrhotic, non-alcoholic steatohepatitis (FLINT): a multicentre, randomised, placebo-controlled trial. *Lancet*. 2015;385(9972):956-965. doi:10.1016/S0140-6736(14)61933-4

28. Thuluvath PJ, Guidinger MK, Fung JJ, Johnson LB, Rayhill SC, Pelletier SJ. Liver transplantation in the United States, 1999-2008. *Am J Transplant*. 2010;10(4 Pt 2):1003-1019. doi:10.1111/j.1600-6143.2010.03037.x

29. Lang K, Danchenko N, Gondek K, Shah S, Thompson D. The burden of illness associated with hepatocellular carcinoma in the United States. *J Hepatol*. 2009;50(1):89-99. doi:10.1016/j.jhep.2008.07.029

30. Davis GL, Alter MJ, El-Serag H, Poynard T, Jennings LW. Aging of hepatitis C virus (HCV)–infected persons in the United States: a multiple cohort model of HCV prevalence and disease progression. *Gastroenterology*. 2010;138(2):513-521, 521.e1-521.e6. doi:10.1053/j.gastro.2009.09.067

31. Saab S, Hunt DR, Stone MA, McClune A, Tong MJ. Timing of hepatitis C antiviral therapy in patients with advanced liver disease: a decision analysis model. *Liver Transpl*. 2010;16(6):748-759. doi:10.1002/lt.22072

32. Younossi Z, Stepanova M, Ong JP, et al; Global Nonalcoholic Steatohepatitis Council. Nonalcoholic steatohepatitis is the fastest growing cause of hepatocellular carcinoma in liver transplant candidates. *Clin Gastroenterol Hepatol*. 2019;17(4):748-755.e3. doi:10.1016/j.cgh.2018.05.057

33. Younossi ZM, Otgonsuren M, Henry L, et al. Association of nonalcoholic fatty liver disease (NAFLD) with hepatocellular carcinoma (HCC) in the United States from 2004 to 2009. *Hepatology*. 2015;62(6):1723-1730. doi:10.1002/hep.28123

34. Cholankeril G, Wong RJ, Hu M, et al. Liver transplantation for nonalcoholic steatohepatitis in the US: temporal trends and outcomes. *Dig Dis Sci*. 2017;62(10):2915-2922. doi:10.1007/s10620-017-4684-x

35. Arias E, Heron M, Xu J. United States life tables, 2013. *Natl Vital Stat Rep*. 2017;66(3):1-64.

36. Aarts EHL, Korst JHM. *Simulated Annealing and Boltzmann Machines: A Stochastic Approach to Combinatorial Optimization and Neural Computing*. Wiley; 1989.

37. Chhatwal J, Loomba R, Bethea E, et al. NAFLD Simulator. Accessed August 8, 2022. https://www.nafldsimulator.org/

38. Loomba R. Role of imaging-based biomarkers in NAFLD: Recent advances in clinical application and future research directions. *J Hepatol*. 2018;68(2):296-304. doi:10.1016/j.jhep.2017.11.028

SUPPLEMENT.

eAppendix. Model Parameters, Assumptions, and Calibration
eTable 1. Input Parameters Used to Simulate the Natural History of NAFLD in the NAFLD Simulator
eFigure. Cumulative Incidence of NAFLD-Associated Advanced Sequelae in Patients Aged 49 Years With NAFLD-Related Fibrosis Stages F0 to F4
eTable 2. Mortality and Clinical Outcomes in Patients with NAFLD by NAFLD Fibrosis Stage
eTable 3. 10-Year Mortality and Clinical Outcomes in Patients With NAFLD Aged 40 Years or 65 Years by NAFLD Fibrosis Stage
eReferences.