ORIGINAL RESEARCH

# Clinical course of nonalcoholic fatty liver disease: an assessment of severity, progression, and outcomes

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**Purpose:** To identify the characteristics and initial disease severity of patients with nonalcoholic fatty liver disease (NAFLD) and assess incidence and risk factors for disease progression in a retrospective study.

**Methods:** Patients ≥18 years of age without alcoholism or other liver diseases (eg, hepatitis B/C) were selected from Geisinger Health System electronic medical record data from 2004 to 2015. Initial disease stage was stratified into uncomplicated NAFLD, advanced fibrosis, cirrhosis, hepatocellular carcinoma (HCC), and liver transplant using clinical biomarkers, diagnosis, and procedure codes. Disease progression was defined as stage progression or death and analyzed via Kaplan–Meier plots and multistate models.

**Results:** In the NAFLD cohort (N=18,754), 61.5% were women, 39.0% had type 2 diabetes mellitus (T2DM), and the mean body mass index was $38.2\pm10.2$ kg/m$^2$. At index, 69.9% had uncomplicated NAFLD, 11.7% had advanced fibrosis, and 17.8% had cirrhosis. Of 18,718 patients assessed for progression, 17.3% progressed (11.0% had stage progression, 6.3% died without evidence of stage progression) during follow-up (median=842 days). Among subgroups, 12.3% of those without diabetes mellitus progressed vs 24.7% of those with T2DM. One-year mortality increased from 0.5% in uncomplicated NAFLD to 22.7% in HCC. After liver transplant, mortality decreased to 5.6% per year.

**Conclusions:** In 2.3 years of follow-up, approximately 17% of patients progressed or died without evidence of stage progression. T2DM was associated with approximately twice the risk of disease progression, and mortality risk increased with disease stage. Early diagnosis and monitoring of disease progression, especially in patients with T2DM, is warranted.

**Keywords:** NAFLD, clinical course, disease progression, multistate model, retrospective study, type 2 diabetes

## Introduction

Nonalcoholic fatty liver disease (NAFLD) is the most common chronic liver disease in the United States.[1] Epidemiological surveys estimate that 6%–35% of the global general population has NAFLD[2] and that 2%–5% have nonalcoholic steatohepatitis (NASH).[2,3] By definition, NAFLD refers to the accumulation of fat, primarily triglycerides, in greater than 5%–10% of hepatocytes.[3] The histological features of NAFLD are similar to those seen with liver disease due to excessive alcohol intake. As a result, diagnosis of NAFLD is clinicopathological, and excessive alcohol intake precludes an NAFLD diagnosis.

NAFLD comprises a spectrum of liver pathology including simple steatosis, NASH (hepatocyte ballooning and lobular inflammation), fibrosis, and cirrhosis (scarring).

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In early stages, NAFLD patients are often asymptomatic; thus, the condition is underdiagnosed. Although simple steatosis is a precursor to NASH, the two stages are not easily differentiated in practice. A diagnosis of NASH requires histological evidence through liver biopsy; however, biopsy is an invasive procedure generally reserved for more severe cases. For this reason, the International Classification of Diseases, Ninth Edition, Clinical Modification (ICD-9-CM) classified both simple steatosis and NASH into one category (571.8: Other chronic nonalcoholic liver disease). As the severity of NAFLD increases, so does morbidity and mortality. Advanced fibrosis is a risk factor for progression to liver failure as identified by both fibrosis scoring approaches[4–6] and by biopsy.[7,8]

The frequency and time course of disease progression are not well characterized in either clinical trials or observational data, due to limitations on sample size (particularly in studies relying on biopsy data), and the length of follow-up required to identify disease progression. Evidence on the clinical course of NAFLD and the patient characteristics associated with disease progression is limited. Recognized risk factors for NAFLD include insulin resistance[9] and obesity, particularly central adiposity.[10] NAFLD is associated with the development of type 2 diabetes mellitus (T2DM) and vice versa.[11–13]

The present study assessed the clinical course of NAFLD, including the subset of patients with diabetes mellitus (DM), in a real-world cohort of patients. Specifically, the objectives were to identify and characterize a large cohort of patients with a diagnosis of NAFLD, to describe the disease stage/severity at diagnosis, and to assess disease progression over time.

## Methods

This was a retrospective cohort study of electronic medical record (EMR) data from the Geisinger Health System from January 2004 to April 2015. Geisinger is an integrated health system in Northern and Central Pennsylvania that includes a 1,200+ multispecialty physician group practice, nine hospitals, 83 ambulatory clinics, a clinical reference lab, a nonexclusive 467,000-member health plan, and two dedicated research centers. Data reflect both inpatient and outpatient settings, including primary through specialty care, detailed lab results, vital signs, medication orders, procedures, and diagnoses. Mortality was captured in the EMR data, but cause of death was not available. Patient informed consent was neither required nor possible. As data were de-identified,

this retrospective study is considered a category of exempt human subjects research under Code of Federal Regulations: 45 CFR 46.101(b)(4).

The primary study population was comprised of patients who were diagnosed with NAFLD during the study period. Subgroup analyses were performed among those patients also diagnosed with DM. At least one inpatient or outpatient diagnosis of NAFLD from January 1, 2005 to December 31, 2014 (ICD-9-CM codes 571.5 or 571.8) was required for study inclusion. The first recorded diagnosis of NAFLD during the study period was designated as the index date. Activity in the Geisinger Health System in the 12 months preceding and 90 days following the index date was also required. Patients aged <18 years and patients with at least one diagnosis of alcoholism, alpha-1 antitrypsin deficiency, hemochromatosis, hepatitis B, hepatitis C, or Wilson's disease were excluded from the study sample.

A subgroup of patients with evidence of T2DM at any time prior to the index date or up to 90 days after the index date was identified from those with DM in the overall NAFLD cohort; this required distinguishing T2DM from type 1 diabetes mellitus (T1DM) and gestational diabetes. Patients were first considered to have DM if they had a diagnosis of DM (ICD-9 code 250.xx) on two different days over a two-year period, one hospitalization with a discharge diagnosis of DM, or an outpatient prescription for a glucose-lowering medication. Patients were identified as having T1DM if they had at least as many diagnosis codes indicating T1DM (250.x1 or 250.x3) as T2DM codes (250.x0 or 250.x2), and had an outpatient prescription for insulin within six months of their first DM diagnosis and no other outpatient glucose-lowering medications other than insulin or pramlintide at any point during the study period. All other DM patients were classified as having T2DM. Although patients with T1DM and gestational diabetes are included in the overall study cohort, they are excluded from the T2DM and non-DM subcohorts.

## Study measures

Characteristics of interest were identified, including demographic characteristics (i.e., age and gender) and clinical characteristics, such as body mass index (BMI), comorbidities, medication use, lab results, and procedures of interest. Comorbidities and medications were assessed during the baseline period, defined as the 12 months prior to the index date. For patients with more than one result of a given lab test during the baseline period, the result closest to the index date was used. Lab values within a 15-day time period were

combined to calculate liver function scores, including the aspartate aminotransferase (AST) to Platelet Ratio Index (APRI),[14] fibrosis-4 (FIB-4),[15] NAFLD Fibrosis Score (NFS),[4] and Model for End-stage Liver Disease (MELD).[16]

## Disease stages and progression outcomes

The disease stage at index diagnosis was identified from diagnoses and procedures, as well as values of liver function scores, contained in the EMR data. Uncomplicated NAFLD was defined as the presence of an NAFLD diagnosis, with no evidence of disease progression within 90 days. Advanced fibrosis was defined as an FIB-4 score[15] of 3.25[5]–3.6 or an NFS >0.676,[4] or an APRI score >1.5 and <2.0.[6] Cirrhosis was defined as the presence of a diagnosis of cirrhosis (ICD-9 code 571.5), or an APRI score ≥2.0,[6,14] or an FIB-4 >3.6.[17] Hepatocellular carcinoma (HCC) was defined as the presence of a diagnosis for HCC (ICD-9 code 155.0). Liver transplantation was identified using procedure codes, and patients with evidence of a liver transplant at the index date were not eligible for progression analyses. Death was identified from mortality records as a progression outcome.

Any transition to a more advanced disease stage or death from any cause was considered progression of NAFLD. Progression could occur sequentially (eg, uncomplicated NAFLD to advanced fibrosis) or nonsequentially (eg, advanced fibrosis to HCC). Records indicating multiple disease states during a 90-day period were considered evidence of diagnostic evaluation for one disease state rather than evidence of rapid disease progression, and the most advanced diagnosis within a 90-day period was used to classify the stage of disease at index and during follow-up. For instance, if diagnosis codes for cirrhosis and HCC were observed within 90 days of the index date, the patient was classified as having HCC at index. Similar methods were used to characterize disease progression during follow-up.

## Statistical analysis

Baseline characteristics, including demographics, comorbidities, and lab values, were summarized for the NAFLD cohort overall and separately for patients with T2DM, and without DM. NAFLD severity information was analyzed from the time of first diagnosis of NAFLD through the end of available data for each patient. The frequency of liver disease progression was calculated within the full study cohort, as well as by DM status, over the study period. Kaplan–Meier curves were used to present the time to disease progression in the overall study cohort and subgroups of interest.

A multistate model (MSM) was fitted to the study data to assess disease progression. MSM is a generalization of traditional survival analysis that examines multiple transitions simultaneously.[18,19,20] In traditional survival analysis, time-to-event data are used to fit a model describing the rate at which patients move between two states (eg, from one disease stage to another). In MSM, the researcher specifies multiple states/disease stages and the allowed transitions between those stages; in the present model assessing NAFLD disease progression, transitions to other disease states were assumed to be unobserved (as is often the case in clinical practice), with the exception of transitions to the death state. The time-to-event data and times and observations of patient states are then used to fit a model describing the transition rates. In this way, transition rates between NAFLD disease stages in a one-year time period starting from the index date were calculated for the study sample.

Data management, descriptive analyses, and time-to-event analyses were conducted using SAS version 9.4 or higher (SAS Institute Inc., Cary, NC, USA). The MSM was conducted using Multi-State Models for Panel Data: The msm Package for R.[21]

## Results

A total of 30,440 patients with an NAFLD diagnosis were originally identified in the study data (Table S1); of those, 18,754 patients met all criteria for study inclusion. The most common reason for study exclusion (25.8% of starting total) was the requirement of activity in the health care system at least 12 months before the index date and >90 days after the index date. Also of note, 6.3% of the NAFLD-diagnosed cohort was excluded due to a diagnosis of alcoholism.

From the overall NAFLD study cohort, 39.0% had a diagnosis of T2DM (Table 1).

Patients without DM were younger than those with T2DM; of those without DM, 35.8% were aged 18–44 compared to 23.9% of those with T2DM. In the overall cohort, 61.5% were female. Of those with BMI data (90.3%), the mean BMI in the overall cohort was 38.2±10.2, and was higher among those with T2DM (40.6±10.5). In the overall NAFLD cohort, more than half of the patients had hyperlipidemia (51.9%) and hypertension (52.8%). In general, the prevalence of the comorbidities assessed in the study was lowest among those without DM and highest among patients with T2DM. An analysis of baseline medication

**Table 1** Baseline characteristics of the overall NAFLD cohort and by diabetes status

| Baseline patient characteristics[a] | Overall NAFLD cohort (N=18,754), n (%)[b] | No diabetes (N=11,097), n (%) | Type 2 diabetes (N=7,311), n (%) |
|---|---|---|---|
| **Age category, years** | | | |
| 18–44 | 5,999 (32.0) | 3,970 (35.8) | 1,750 (23.9) |
| 45–54 | 4,562 (24.3) | 2,753 (24.8) | 1,774 (24.3) |
| 55–64 | 4,199 (22.4) | 2,321 (20.9) | 1,859 (25.4) |
| 65–74 | 2,732 (14.6) | 1,396 (12.6) | 1,331 (18.2) |
| 75–84 | 1,039 (5.5) | 531 (4.8) | 502 (6.9) |
| 85+ | 223 (1.2) | 126 (1.1) | 95 (1.3) |
| **Gender** | | | |
| Male | 7,211 (38.5) | 4,499 (40.5) | 2,689 (36.8) |
| Female | 11,543 (61.5) | 6,598 (59.5) | 4,622 (63.2) |
| **BMI category[c]** | | | |
| Underweight (<18.5 kg/m²) | 58 (0.3) | 45 (0.4) | 13 (0.2) |
| Normal (18.5–24.9 kg/m²) | 997 (5.3) | 770 (6.9) | 217 (3.0) |
| Overweight (25–29.9 kg/m²) | 2,594 (13.8) | 1,809 (16.3) | 755 (10.3) |
| Obese (≥30 kg/m²) | 13,283 (70.8) | 7,057 (63.6) | 5,936 (81.2) |
| Unknown/missing | 1,822 (9.7) | 1,416 (12.8) | 390 (5.3) |
| **Baseline comorbidities[d]** | | | |
| Atherosclerosis | 2,714 (14.5) | 1,133 (10.2) | 1,566 (21.4) |
| Atrial fibrillation | 1,007 (5.4) | 471 (4.2) | 529 (7.2) |
| Coronary heart disease | 3,118 (16.6) | 1,348 (12.1) | 1,751 (24.0) |
| Heart failure | 1,223 (6.5) | 425 (3.8) | 789 (10.8) |
| Hyperlipidemia | 9,734 (51.9) | 4,820 (43.4) | 4,769 (65.2) |
| Hypertension | 9,897 (52.8) | 4,699 (42.3) | 5,066 (69.3) |
| Diabetes | 7,364 (39.3) | 0 (0) | 7,311 (100.0) |
| **Baseline medication use[e]** | | | |
| Biguanides | 4,323 (23.1) | 0 (0) | 4,170 (57.0) |
| Sulfonylureas/meglitinides | 2,070 (11.0) | 0 (0) | 2,030 (27.8) |
| Thiazolidinediones | 813 (4.3) | 0 (0) | 803 (11.0) |
| GLP-1 receptor agonists | 232 (1.2) | 0 (0) | 226 (3.1) |
| DPP-4 inhibitors | 578 (3.1) | 0 (0) | 571 (7.8) |
| Insulin | 2,013 (10.7) | 0 (0) | 1,928 (26.4) |
| Other glucose-lowering treatments | 336 (1.8) | 0 (0) | 328 (4.5) |
| Lipid-lowering drugs | 7,273 (38.8) | 3,058 (27.6) | 4,124 (56.4) |
| ARBs and ACE inhibitors | 5,518 (29.4) | 2,083 (18.8) | 3,369 (46.1) |

**Notes:** [a]Baseline characteristics are measured from the year prior to and including the index date. [b]Patients with gestational and type 1 diabetes are included in the overall NAFLD cohort, but excluded from the no diabetes and type 2 diabetes subgroups. [c]If multiple observations during the baseline period are available, BMI is calculated from the height and weight recorded closest to the index date. [d]Comorbidities were identified by the presence of at least one diagnosis code during the baseline period. [e]Excludes medication prescribed on the index date.
**Abbreviations:** ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blockers; BMI, body mass index; DPP-4, dipeptidyl peptidase-4; GLP-1, glucagon-like peptide-1; NAFLD, nonalcoholic fatty liver disease.

use (excluding the index date) indicated that the most frequent medications taken by the overall NAFLD cohort were lipid-lowering medications (38.8%), angiotensin-converting enzyme inhibitors and angiotensin receptor blockers (29.4%), and biguanides (23.1%); use of all medications of interest was more common in the T2DM subgroup.

The liver function scores of the overall NAFLD cohort and DM subgroups at the date closest to or on the index date are presented for patients with available data (Table 2); higher values of all scores indicate more advanced disease. Over 71% of patients in the overall cohort had an APRI score ≤0.5, with a similar percentage noted in all subgroups. Over half of

the patients had an FIB-4 score <1.30, while approximately one-fourth to one-third of patients had a score of 1.30–<3.25. In the overall NAFLD cohort, 33.3% of patients had an NFS <−1.455, and 23.8% had a score >0.676. When compared to the overall cohort, a greater percentage of patients in the T2DM subgroup (42.8%) had an NFS >0.676. Few patients (11.7%) had the necessary data for calculating the MELD score.

In the overall cohort, 69.9% of patients were classified in the uncomplicated NAFLD disease stage within 90 days of the index date, while 78.1% of the non-DM subgroup and 57.0% of patients in the T2DM subgroup were classified in the same category (Table 3). Among those without DM,

4.7% were classified with advanced fibrosis, compared to 22.4% of those with T2DM. Nearly 18% of patients in the overall cohort were classified with cirrhosis, compared to 19.8% among the subgroup with T2DM. Few patients were classified with HCC or liver transplant at the index date in the overall study cohort and subgroups.

Figure 1 indicates a lower probability of disease progression during all follow-up time among those without DM compared to those with T2DM (*P*<0.0001). In the overall study cohort, the median follow-up time was 842 days (~2.3 years; range: 1–3,845 days). The median length of follow-up was ~100 days shorter for all patients without DM (801 days) when compared to all patients with T2DM (905 days), but similar among those who progressed in those subgroups (731 days among those without DM vs 714

days among those with T2DM). Nearly one-fifth (17.3%) of patients progressed during the study period; 11.0% progressed to a more advanced disease stage, while 6.3% died without evidence of stage progression. The median time to progression among those who progressed was 725 days (range: 1–3,845). Among subgroups, 12.3% of those without DM progressed compared to 24.7% of those with T2DM.

In the overall study cohort, a clear increase in the rate of all-cause mortality within one year was noted as a patient progressed from uncomplicated NAFLD to HCC (0.5%–22.7%, Figure 2). After receiving a liver transplant, the rate of mortality decreased to 5.6% a year, which is approximately equivalent to the rate of mortality among patients with cirrhosis in the same time period (5.7%).

**Table 2** Baseline liver function scores of the overall NAFLD cohort and by diabetes status

| Liver function severity scores[a] | Overall NAFLD cohort (N=18,754), n (%) | No diabetes (N=11,097), n (%) | Type 2 diabetes (N=7,311), n (%) |
|---|---|---|---|
| **AST to Platelet Ratio Index** | | | |
| Number with data available | 12,038 | 7,062 | 4,746 |
| ≤0.5 | 8,649 (71.8) | 5,171 (73.2) | 3,297 (69.5) |
| >0.5 to 1.5 | 2,721 (22.6) | 1,513 (21.4) | 1,164 (24.5) |
| >1.5 (advanced fibrosis/cirrhosis)[6,14] | 668 (5.5) | 378 (5.4) | 285 (6.0) |
| **Fibrosis-4** | | | |
| Number with data available | 11,988 | 7,032 | 4,726 |
| <1.30 | 7,006 (58.4) | 4,299 (61.1) | 2,507 (53.0) |
| 1.30 to <3.25 | 3,713 (31.0) | 2,122 (30.2) | 1,565 (33.1) |
| ≥3.25 (advanced fibrosis/cirrhosis)[5,17] | 1,269 (10.6) | 611 (8.7) | 654 (13.8) |
| **NAFLD Fibrosis Score** | | | |
| Number with data available | 10,550 | 6,000 | 4,334 |
| <−1.455 | 3,512 (33.3) | 2,888 (48.1) | 548 (12.6) |
| −1.455 to 0.676 | 4,522 (42.9) | 2,480 (41.3) | 1,933 (44.6) |
| >0.676 (advanced fibrosis/cirrhosis)[4] | 2,516 (23.8) | 632 (10.5) | 1,853 (42.8) |
| **Model for End-stage Liver Disease** | | | |
| Number with data available | 2,203 | 1,213 | 961 |
| <10: least severe: | 1,461 (66.3) | 873 (72.0) | 565 (58.8) |
| 10 to <20 | 583 (26.5) | 280 (23.1) | 299 (31.1) |
| 20 to <30 | 152 (6.9) | 59 (4.9) | 91 (9.5) |
| ≥30: most severe: | 7 (0.3) | 1 (0.1) | 6 (0.6) |

**Notes:** [a]For patients with multiple laboratory values during the baseline period, the value selected was closest to or on the index date. Advanced fibrosis/cirrhosis thresholds were identified using references 6, 14, 5, 17, and 4, as indicated in the table.
**Abbreviations:** AST, aspartate aminotransferase; NAFLD, nonalcoholic fatty liver disease.

**Table 3** Disease severity of overall NAFLD cohort and by diabetes status at the index date[a]

| Disease stage within 90 days of index date | All NAFLD cohort (N=18,754), n (%) | No diabetes (N=11,097), n (%) | Type 2 diabetes (N=7,311), n (%) |
|---|---|---|---|
| Uncomplicated NAFLD | 13,109 (69.9) | 8,672 (78.1) | 4,165 (57.0) |
| Advanced fibrosis | 2,198 (11.7) | 519 (4.7) | 1,635 (22.4) |
| Cirrhosis | 3,337 (17.8) | 1,862 (16.8) | 1,448 (19.8) |
| Hepatocellular carcinoma | 74 (0.4) | 25 (0.2) | 47 (0.6) |
| Liver transplant | 36 (0.2) | 19 (0.2) | 16 (0.2) |

**Note:** [a]Time frame for severity indicators was within 90 days of the first qualifying NAFLD diagnosis date.
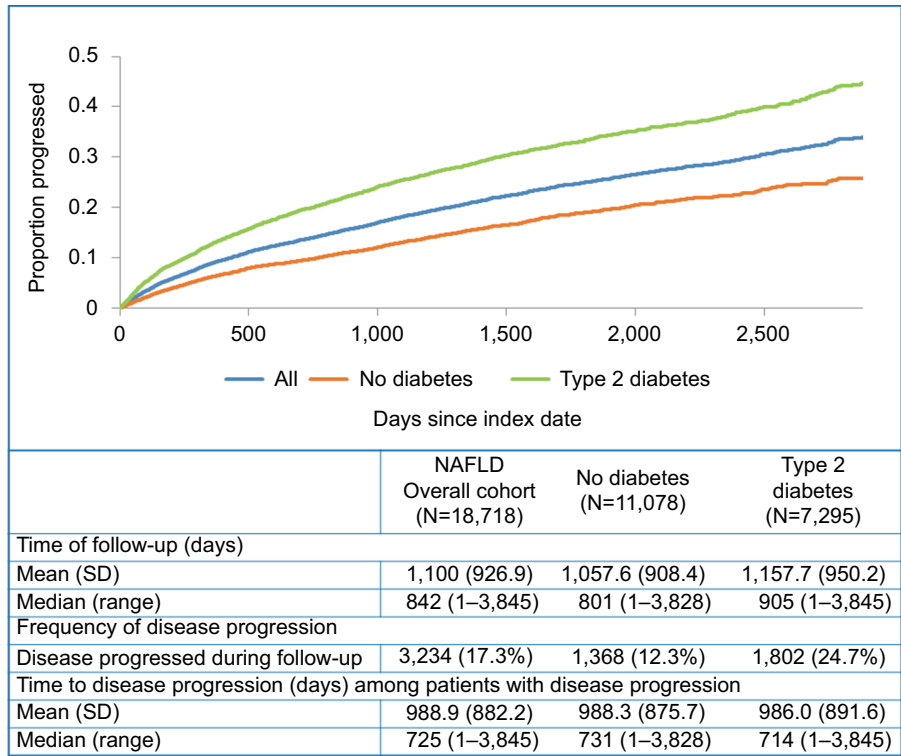**Abbreviation:** NAFLD, nonalcoholic fatty liver disease.

**Figure 1** Time to disease progression among patients,[a] stratified by diabetes status.
**Notes:** [a]Includes patients with index stage of uncomplicated NAFLD, advanced fibrosis, cirrhosis, or hepatocellular carcinoma; patients with an index stage of liver transplant were excluded from progression analyses.
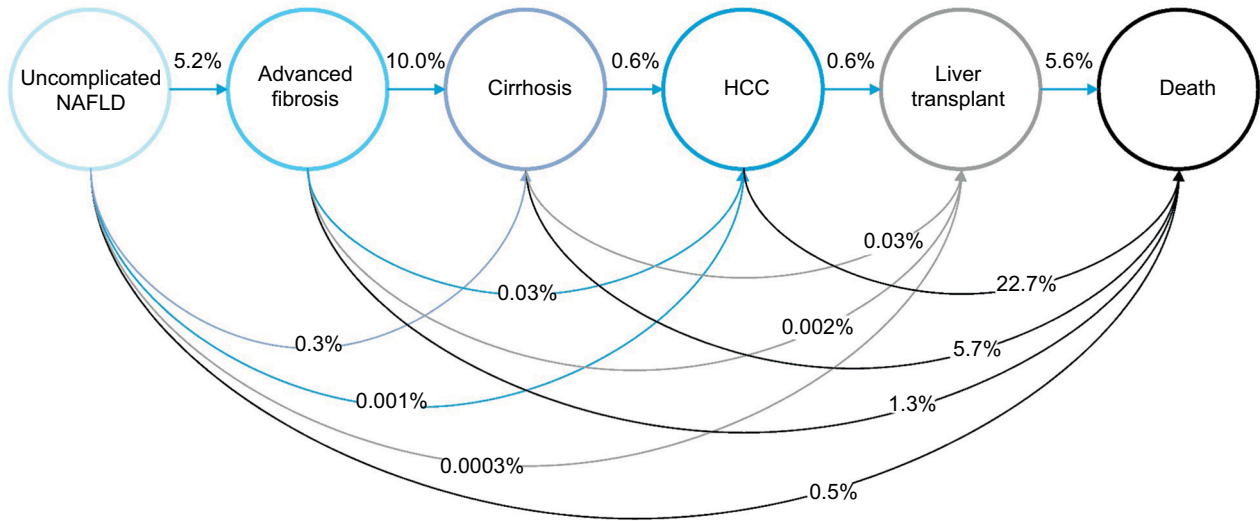**Abbreviations:** NAFLD, nonalcoholic fatty liver disease; SD, standard deviation.



**Figure 2** Transition rates of disease progression within one year, derived from multistate model.
**Notes:** Arrows indicate progression from one disease stage to another. Colored circles indicate different disease stages over the NAFLD disease course, and colored arrows indicate progression to the corresponding disease stage.
**Abbreviations:** HCC, hepatocellular carcinoma; NAFLD, nonalcoholic fatty liver disease.

Patients with uncomplicated NAFLD were most likely to remain at that disease stage over time, with a rate of only 5.9% progressing per year in the overall cohort. The rate of progression from advanced fibrosis to cirrhosis within one year was 10.0%.

## Discussion

The present study indicates that the rate of progression within one year for those with uncomplicated NAFLD was relatively slow (5.9%), but that the probability of mortality increases markedly as the disease progresses. Among patients

with NAFLD who progressed, the median time to disease progression was approximately two years, and those with T2DM had approximately twice the risk of disease progression when compared to those without DM. Patients with T2DM were also older and more likely than those without DM to have other clinical characteristics associated with poor health outcomes, including a higher BMI and a greater comorbidity burden.

The average time to NAFLD disease progression was reported in a meta-analysis of paired-biopsy studies by Singh et al.[22] In that analysis of 11 cohort studies including 411 patients, the pooled time to disease progression was 14.3 years for patients with NAFLD (95% confidence interval [CI], 9.1–50.0 years) and 7.1 years for patients with NASH (95% CI, 4.8–14.3 years). Those findings are not directly comparable with our study; among other differences, the median time to progression in the current study was calculated among only patients who progressed. The meta-analysis required biopsy samples at least a year apart, compared to the 90-day minimum time period for the assessment of disease progression in the present study. While repeat biopsies are rarely performed, the use of biomarker measurements, diagnosis codes, and procedure codes likely provided more opportunity for the classification of disease progression, due to the increased frequency of medical visits in which these measures are recorded. The current data do, however, provide evidence of progression based on readily available clinical characteristics.

Our finding of an increased risk of mortality with advancing disease stage is supported by other published literature.[8,23,24] For instance, Ekstedt et al reported on 229 biopsy-proven patients with NAFLD over a mean follow-up period of 26.4 years and found that those with fibrosis stage 3–4 (bridging fibrosis or cirrhosis) had over a threefold greater risk of mortality (hazard ratio [HR]: 3.3, 95% CI: 2.27–4.76) when compared to the general population, but no such difference was seen for those with lower fibrosis stages.[8] Another study of 619 patients from the United States, Europe, and Thailand by Angulo et al found that increasing fibrosis stage was associated with outcomes of death or liver transplant, from fibrosis stage 1 (HR: 1.88; 95% CI: 1.28–2.77) to stage 4 (HR: 10.9; 95% CI: 6.06–19.62), when compared with stage 0.[24]

In the current study, nearly 40% of NAFLD patients had a concomitant diagnosis of DM, and patients with T2DM had twice the risk of NAFLD disease progression compared to those without DM. This observation has clinical implications for the management of both diseases. The American

Diabetes Association supports the importance of lifestyle modification, as well as pharmaceutical intervention when necessary, among patients with T2DM.[25] The relationship between NAFLD and T2DM underscores the importance of DM disease management to reduce the risk of liver-related mortality and adverse outcomes.

The strengths of the present study include the use of a large observational dataset with longitudinal follow-up in the usual care setting, with a sample size permitting the assessment of patient subgroups, including T2DM and no DM. The Geisinger Health System captures EMR-level information on patients, including phenotypic and clinical biomarkers, from inpatient and outpatient treatment settings. The clinical practice guidelines for the management of NAFLD published in 2016 by the European Association for the Study of the Liver (EASL), European Association for the Study of Diabetes (EASD), and European Association for the Study of Obesity (EASO) state that "Whenever imaging tools are not available or feasible (eg, large epidemiological studies), serum biomarkers and scores are an acceptable alternative for the diagnosis of steatosis".[26] Mortality data are also captured, which is not typical of all US-based observational datasets. Therefore, this study provides new information on the clinical course of NAFLD in this large patient cohort.

Limitations include the following: disease stage was identified using algorithms derived from liver severity scores based on clinical biomarkers, diagnosis codes, and procedure codes, rather than results from biopsies, although multiple liver biopsies are infrequently performed on the same patient in clinical practice. Patients with diabetes may have had more opportunities to be classified as having disease progression than patients without diabetes due to increased monitoring by health care providers; however, the present study was intended to characterize the clinical course of NAFLD in a real-world cohort of patients. As diagnosis codes for NAFLD were used to identify patients in the study sample, all included patients should be considered as having clinically significant nonalcoholic liver disease. Published algorithms that reliably identify mild fibrosis from liver disease severity scores were not found in the literature, so this disease stage could not be included in the progression model. Cause of death information was not available; some deaths observed in the data were likely unrelated to progression of NAFLD.

Other limitations are consistent with those of retrospective observational studies. Diagnosis codes may represent justifications for billing and may not be accurate. Medication prescriptions may not have been filled or used. Care received outside the health system does not appear in the study data,

so indicators of disease progression may be missing from medical records. Lastly, the characteristics of the study sample may be unique to the source population and may not be generalizable to other populations; for example, populations with a lower prevalence of morbid obesity and diabetes may experience lower rates of disease progression and death.

## Conclusion

In this large real-world cohort, 17.3% of patients with NAFLD progressed in 2.3 years of follow-up, including 11.0% who advanced to a more severe disease stage and 6.3% who died without evidence of stage progression. Those with T2DM had approximately twice the risk of disease progression compared to patients without DM. Increasing disease severity prior to receipt of a liver transplant was also associated with mortality. Especially among patients with DM, health care providers should seek to diagnose NAFLD early in the disease course and monitor carefully for disease progression.

## Acknowledgments

## Disclosure

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# Supplementary material

**Table S1** Study sample attrition

| Criterion | Number of patients remaining | N (%) excluded[a] |
|---|---|---|
| With diagnosis of NAFLD | 30,440 | N/A |
| Earliest activity date in system at least 12 months before index date[b] and latest activity date >90 days after index | 22,577 | 7,863 (25.8) |
| Age ≥18 years at index date | 22,203 | 374 (1.2) |
| Exclude diagnosis of alcoholism | 20,286 | 1,917 (6.3) |
| Exclude other diagnoses of interest[c] | 18,754 | 1,532 (5) |

**Notes:** [a]Percentage excluded from the starting total. [b]The index date may not be the first NAFLD diagnosis date. [c]Patients may have had more than one of the diagnoses listed: Alpha-1 antitrypsin deficiency, hemochromatosis, hepatitis B, hepatitis C, Wilson's disease.
**Abbreviations:** N/A, not applicable; NAFLD, nonalcoholic fatty liver disease.