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Prospective Study of Outcomes in Adults with Nonalcoholic Fatty Liver Disease

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Abstract

BACKGROUND—The prognoses with respect to mortality and hepatic and nonhepatic outcomes across the histologic spectrum of nonalcoholic fatty liver disease (NAFLD) are not well defined.

METHODS—We prospectively followed a multicenter patient population that included the full histologic spectrum of NAFLD. The incidences of death and other outcomes were compared across baseline histologic characteristics.

RESULTS—A total of 1773 adults with NAFLD were followed for a median of 4 years. All-cause mortality increased with increasing fibrosis stages (0.32 deaths per 100 person-years for stage F0 to F2 [no, mild, or moderate fibrosis], 0.89 deaths per 100 persons-years for stage F3 [bridging fibrosis], and 1.76 deaths per 100 person-years for stage F4 [cirrhosis]). The incidence of liver-related complications per 100 person-years increased with fibrosis stage (F0 to F2 vs. F3 vs. F4) as follows: variceal hemorrhage (0.00 vs. 0.06 vs. 0.70), ascites (0.04 vs. 0.52 vs. 1.20), encephalopathy (0.02 vs. 0.75 vs. 2.39), and hepatocellular cancer (0.04 vs. 0.34 vs. 0.14). As compared with patients with stage F0 to F2 fibrosis, patients with stage F4 fibrosis also had a higher incidence of type 2 diabetes (7.53 vs. 4.45 events per 100 person-years) and a decrease of more than 40% in the estimated glomerular filtration rate (2.98 vs. 0.97 events per 100 person-years). The incidence of cardiac events and nonhepatic cancers were similar across fibrosis stages. After adjustment for age, sex, race, diabetes status, and baseline histologic severity, the

*A full list of the investigators in the NASH CRN is provided in the Supplementary Appendix, available at NEJM.org.

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incidence of any hepatic decompensation event (variceal hemorrhage, ascites, or encephalopathy) was associated with increased all-cause mortality (adjusted hazard ratio, 6.8; 95% confidence interval, 2.2 to 21.3).

CONCLUSIONS—In this prospective study involving patients with NAFLD, fibrosis stages F3 and F4 were associated with increased risks of liver-related complications and death. (Funded by the National Institute of Diabetes and Digestive and Kidney Diseases and others; NAFLD DB2 ClinicalTrials.gov number, NCT01030484.)

NONALCOHOLIC FATTY LIVER DISEASE (NAFLD) affects more than one quarter of the adult population globally and is closely linked to underlying obesity, type 2 diabetes, and related disorders.[1] Its clinical and histologic spectrum ranges from nonalcoholic fatty liver to nonalcoholic steatohepatitis (NASH). NAFLD is a growing contributor to the burden of end-stage liver disease and the need for liver transplantation.[2]

The current knowledge of NAFLD-related prognoses is based largely on retrospective post hoc analyses of existing data sets and is limited by that data.[3–8] Whereas population-based studies are limited by the absence of histologic information, studies with histologic data are limited by their small sample size, spectrum bias, varied case definitions, and assessments of disease status and outcomes. Whether the incidence of hepatic outcomes increases in parallel with the incidence of nonhepatic outcomes is also unclear. Furthermore, previous studies have not accounted for the competing risk of death for nonfatal outcomes or included adjustment for age, sex, race, and presence of type 2 diabetes. The true rates and types of clinical outcomes among persons with nonalcoholic fatty liver or NASH with varying grades of disease activity and fibrosis stages thus remain largely unknown. This knowledge is needed in order to counsel patients, design clinical trials, and inform allocation of health care resources for research funding, clinical care, and disease surveillance.

The NASH Clinical Research Network (CRN) is an ongoing research network funded by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK). It established a longitudinal cohort study to generate prospective, protocol-driven assessments of outcomes in a large population of patients with NAFLD and to serve as a platform for translational studies. Here we provide analysis of the principal clinical outcomes involving these adult patients.

METHODS

STUDY DESIGN AND OVERSIGHT

The NAFLD Database Study Phase 2 (NAFLD DB2) is a prospective, noninterventional registry of the NASH CRN. The institutional review board at each clinical center, the data coordinating center, and a central NIDDK-appointed data and safety monitoring board approved the protocol, available with the full text of this article at NEJM.org. All the participants provided written informed consent. The investigators conceived of and implemented the study, analyzed the data, and wrote the manuscript. The authors vouch for the completeness and accuracy of the data and for the fidelity of the study to the protocol. The results reported here follow the Strengthening the Reporting of Observational Studies in Epidemiology guidelines for cohort studies.[9]

PATIENT POPULATION

The study included adults who had liver biopsies that could be evaluated and that revealed NAFLD and who had at least one follow-up visit after 48 weeks. An Alcohol Use Disorders Identification Test questionnaire was used to establish mean consumption of less than 20 g of alcohol daily for women and less than 30 g for men.[10] Patients who had liver disease other than NAFLD, had received a liver transplant, or had hepatocellular cancer before enrollment were excluded from this analysis. All patients received local standard care informed by a NASH CRN standard-of-care document.

HISTOLOGIC ASSESSMENT

Histologic assessment of NAFLD is the reference standard for the assessment of disease phenotype and progression.[11] The histologic characteristics of the liver were assigned fibrosis stages by members of the pathology committee; clinical, laboratory, and outcomes data were masked to the committee members, as described previously.[12,13] The presence of NAFLD, presence of fatty liver as compared with steatohepatitis, NAFLD activity score, and fibrosis stage were assessed with the use of the previously published NASH CRN scoring system.[12]

CLINICAL, LABORATORY, AND OUTCOMES DATA

Clinical and laboratory data were obtained at enrollment (baseline) and then at 48-week intervals in a prospective, protocol-mandated approach and at the time of any liver biopsies performed as local standard care. Clinical outcomes were recorded during these visits and when reported by patients or their families. The overall clinical narrative and source data were verified at the clinical centers. These data were used to fill specific case-record forms, and outcomes were adjudicated centrally with the use of an outcomes document with case definitions as a guide (details of case definitions are provided in the Supplementary Appendix, available at NEJM.org).

The principal outcomes included death from any cause, hepatic decompensation (clinically apparent ascites, overt encephalopathy, or variceal hemorrhage), a Model for End-stage Liver Disease (MELD) score of 15 or higher (scores range from 6 to 40, with higher scores indicating a higher risk of death at 3 months), hepatocellular cancer, nonhepatic cancer, cardiovascular events (including myocardial infarction, unstable angina, sudden death, revascularization intervention, and hospitalization for heart failure), and cerebrovascular events (including transient ischemic attack and stroke). New onsets of coexisting conditions such as type 2 diabetes, hypertension, and chronic kidney disease were defined by standard criteria and also tracked as outcomes of interest.[14,15] A composite outcome of any hepatic decompensation included new onsets of clinically obvious ascites, overt encephalopathy, or variceal hemorrhage.[16] A MELD score of 15 or higher was included as another key outcome because it represents a threshold for increased risk of death warranting consideration for liver transplantation in persons with cirrhosis.[17,18]

STATISTICAL ANALYSIS

Events that occurred at or before enrollment were included in the patient history. Rates of new-onset events were calculated as the number of events during follow-up divided

by the number of person-years at risk among patients who did not have the condition at enrollment and were reported as events per 100 person-years. Only the first decompensating event was used to calculate the incidence of hepatic decompensation; for individual types of events, the first occurrence of that event was used. Estimates of hazard ratios and 95% confidence intervals were derived from regression models that compared mortality and rates of new-onset clinical-event rates according to histologic features; these regression models were stratified according to three age groups (<40 years, 40 to 59 years, and ≥60 years), race (White or non-White), sex, diabetes status (except in models calculating the incidence of diabetes), and length of biopsy specimen (<15 mm or ≥15 mm). Data for patients with missing covariate values were imputed by fixed replacement: one race characteristic was imputed as nonwhite, four diabetes statuses were imputed as no diabetes, and nine biopsy lengths were imputed as ≥15 mm. Owing to the small amount of missing data, multiple imputation was not used. Standard Cox regression modeling with time-dependent covariates was used to analyze all-cause mortality. Fine–Gray models were used to account for competing risk of other causes of death in analyses of liver-related mortality and to account for deaths in analyses of nonfatal outcomes.[19] The statistical analysis plan did not include a provision for correcting for multiplicity when tests were conducted to evaluate associations, and results are reported as point estimates with 95% confidence intervals. The widths of the confidence intervals have not been adjusted for multiplicity, so the intervals should not be used to infer definitive associations. Analyses were conducted with the use of SAS software, version 9.4 (SAS Institute), and Stata software, version 15.1 (StataCorp).

RESULTS

PATIENTS

A total of 2500 adults were enrolled in the NAFLD DB2 study from December 2009 through April 2019 (Fig. 1), including 162 patients who had completed the Farnesoid X Receptor Ligand Obeticholic Acid in NASH Treatment (FLINT) trial, a 72-week, multicenter, randomized trial of obeticholic acid as compared with placebo.[20] The FLINT trial, which involved adult patients 18 years of age or older who had a biopsy-confirmed diagnosis of NASH, showed that patients who received obeticholic acid had greater improvement in NASH-related biopsy findings from baseline than patients who received placebo. After the exclusion of 727 patients owing to a lack of biopsy results within the prespecified time frame (89 patients), an absence of steatosis (70 patients), or no follow-up data (568 patients, 130 of whom were enrolled <48 weeks before the database lock), 1773 patients were included in the analysis. The median duration of follow-up was 4.0 years (interquartile range, 2.1 to 7.4), and the total follow-up was 8120 person-years. As compared with patients who had follow-up data, patients with no follow-up data were younger at enrollment, more likely to be men, and were taking less anti-hypertensive medication but otherwise were similar to the overall population (Table S1 in the Supplementary Appendix).

BASELINE CHARACTERISTICS

The 1773 patients in the analysis included 1141 women (64%) and 632 men (36%) with a mean age of 52 years (Tables 1 and S2). The majority were White and of European ancestry (85%), and 12% were Hispanic. Most patients had definite steatohepatitis (987 patients

[55%]), whereas borderline steatohepatitis was present in 351 patients (20%), and fatty liver without NASH was diagnosed in 435 patients (25%). A total of 536 patients (30%) had bridging fibrosis (stage F3 [369 patients]) or cirrhosis (stage F4 [167 patients]) according to the NASH CRN staging system.12 The median time from biopsy to enrollment was 2.7 months.

PREVALENCE OF CLINICAL OUTCOMES AT ENROLLMENT

The prevalence at baseline of coexisting conditions associated with NAFLD was similar to that reported in the literature,[21] including hypertension (in 1073 patients [61%]), diabetes (in 742 [42%]), chronic kidney disease (in 99 [6%]), and previous nonhepatic primary cancer (in 181 [10%]) (Table S3). A total of 98 patients (6%) had a history of a cardiac event. Ascites (in 17 patients) and encephalopathy (in 6) were the most common liver-related outcomes reported in patient histories before enrollment. At baseline, the prevalence of liver-related outcomes, hypertension, chronic kidney disease, and cardiac events was greater among patients with stage F4 fibrosis (cirrhosis) than among patients with stage F0 to F2 fibrosis (with stage F0 indicating no fibrosis, F1 indicating sinusoidal fibrosis, and F2 indicating sinusoidal and portal fibrosis). A total of 9 patients with disease at stage F0 to F2 had a MELD score of 15 or greater, but these scores were the result of anticoagulant use (in 5 patients) and chronic kidney disease (in 4).

INCIDENCE OF DEATH AND HEPATIC AND EXTRAHEPATIC OUTCOMES

During follow-up, 47 of the 1773 patients (3%) died, a rate of 0.57 per 100 person-years (Table 2). A total of 37 patients had a new-onset decompensation event. Encephalopathy (in 30 patients) and ascites (in 19) were the most common new decompensation events. Two decompensation events developed simultaneously in seven patients. New-onset hypertension (7.8 events per 100 person-years) was the most common new nonhepatic outcome, followed by type 2 diabetes (4.8 events per 100 person-years), chronic kidney disease (2.5 events per 100 person-years), cardiac events (0.8 events per 100 person-years), nonhepatic cancer (0.8 events per 100 person-years), and cerebrovascular events (0.4 events per 100 person-years). The highest mortality (8.6 deaths per 100 person-years) was among patients with hepatic decompensation before enrollment, with the highest incidence of death (8 patients) occurring among patients with a history of two or more events before enrollment (Fig. S1). There were 9 cases of new-onset hepatocellular carcinoma, with only 1 occurring after hepatic decompensation.

ASSOCIATION OF FIBROSIS STAGE WITH HEPATIC AND EXTRAHEPATIC OUTCOMES

All-cause mortality was associated with fibrosis stage at baseline, increasing from 0.32 deaths per 100 person-years at stage F0 to F2, to 0.89 deaths per 100 person-years at stage F3, to 1.76 deaths per 100 person-years at stage F4 (Table 2 and Fig. 2). Patients with stage F4 disease had higher all-cause mortality (hazard ratio, 3.9; 95% confidence interval [CI], 1.8 to 8.4) and liver-related mortality (hazard ratio, 12.7; 95% CI, 1.8 to 88.6) than patients with stage F0 to F2 fibrosis. The hazard ratio for death from any cause among patients with stage F2 fibrosis as compared with patients with stage F0 or F1 was 2.3 (95% CI, 0.8 to 7.0); for stage F3 fibrosis as compared with stage F0 to F2, the hazard ratio was 1.9 (95% CI, 0.9 to 3.7) (Table 2 and Fig. S2). New-onset hepatic decompensation was rare (0.05 per

100 person-years) among patients with stage F0 to F2 fibrosis at baseline, but the incidence increased at stage 3 to 0.99 per 100 person-years (hazard ratio, 18.7; 95% CI, 4.8 to 73.1) and at stage 4 to 2.69 per 100 person-years (hazard ratio, 36.1; 95% CI, 8.9 to 146.3). The incidence of all hepatic decompensation events was greater among patients with stage F4 disease than among patients with fibrosis at lower stages. Hepatocellular carcinoma was rare in stages F0 to F2 (0.04 events per 100 person-years) and the incidence was numerically higher in stage F3 than stage F4 (0.34 events per 100 person-years vs. 0.14 events per 100 person-years) (Fig. 2). The incidence of type 2 diabetes, hypertension, and a decrease in estimated glomerular filtration rate (eGFR) was higher in stage F4 than in stage F0 to F2 (Table 2). However, the incidence of cardiac events and nonhepatic cancers was similar across fibrosis stages (Table 2 and Fig. 2).

ASSOCIATION OF DISEASE ACTIVITY WITH HEPATIC AND EXTRAHEPATIC OUTCOMES

Virtually all patients with stage F4 fibrosis (93%) or stage F3 fibrosis (97%) had histologic evidence of definite or borderline NASH (Table 1). The incidence of liver-related events was also higher among patients with NASH and stage F3 or F4 fibrosis than among patients with nonalcoholic fatty liver and stage F0 to F2 fibrosis (Table S4). Patients with NASH had a higher incidence of type 2 diabetes and hypertension than patients with NAFLD. Among the entire population, patients with a high NAFLD activity score (≥4 on a range of 0 to 8, with higher scores indicating greater steatosis, hepatocellular injury, and inflammation) had a higher incidence of type 2 diabetes. Presence of NASH was not associated with cardiac events or nonhepatic cancer.

ASSOCIATION OF HEPATIC AND NONHEPATIC OUTCOMES WITH MORTALITY

The main causes of death among all patients were liver and cardiovascular complications, cancer, and sepsis (Table S5). In a multivariable model that was adjusted for age, sex, and race, and for the presence of type 2 diabetes, NASH or nonalcoholic fatty liver, and fibrosis stage at baseline, the occurrence of any new hepatic decompensation event was associated with death from any cause (hazard ratio, 6.8; 95% CI, 2.2 to 21.3) (Table S6). In separate models that examined the association between a nonhepatic new event and all-cause mortality, the hazard ratio for cardiac events was 2.2 (95% CI, 0.8 to 6.4), for decline of more than 40% in the eGFR was 1.9 (95% CI, 0.7 to 5.2), and for nonhepatic cancer was 1.7 (95% CI, 0.4 to 7.6). The hazard ratio for death from any cause among patients with NASH and stage F3 or F4 fibrosis after decompensation, as compared with patients with NAFLD without NASH and with stage F0 to F2 fibrosis, was 17.2 (95% CI, 5.2 to 56.6) (Table S4). A competing risk model that was used to compare liver-related deaths with non–liver-related deaths, with adjustment for age, sex, race, presence of type 2 diabetes, and NASH or nonalcoholic fatty liver, yielded a hazard ratio of 5.8 (95% CI, 0.9 to 38.4) for stage F3 fibrosis as compared with stages F0 to F2 and 12.7 (95% CI, 1.8 to 88.6) for stage F4 as compared with stages F0 to F2 (Table 2). In addition, the incidence of ascites, encephalopathy, and variceal hemorrhage had similar associations with mortality (Fig. S1).

DISCUSSION

In this prospective cohort study involving patients with NAFLD, all-cause mortality in the study population (0.57 deaths per 100 person-years) was higher than the expected background age-related rates (0.4 deaths per 100 person-years).[22] Mortality increased with increasing fibrosis stages, from 0.32 per 100 person-years for stage F0 to F2 to 0.89 per 100 person-years for stage F3 and to 1.76 deaths per 100 person-years for stage F4. Adjusted models showed that the incidence of any hepatic decompensation event was associated with higher mortality (hazard ratio, 6.8; 95% CI, 2.2 to 21.3). Although the observational nature of this study cannot establish a causal link between fibrosis severity and all-cause mortality, fibrosis is a well-established cause of portal hypertension, which is mechanistically related to hepatic decompensation events.[23,24] Our findings thus provide support for the use of "progression to cirrhosis" as a generally accepted surrogate outcome for regulatory approval of therapeutic agents. Also, the higher rate of hepatic decompensation events (ascites, variceal bleeding, and encephalopathy) and hepatocellular carcinoma among patients with bridging fibrosis (stage 3) than among patients with lower fibrosis stages provides a rationale for ongoing and future trials to test the hypothesis that a one-stage regression of fibrosis from stage F3 to stage F2 may translate to fewer hepatic decompensation events.

In this study, the hazard ratio for death from any cause among patients with stage F2 fibrosis, as compared with those with stage F0 or F1, was 2.3 (95% CI, 0.8 to 7.0); however, given the low event rates and wide confidence intervals, these data cannot be used to infer a higher risk of death. Additional prospective studies are needed to confirm or refute these data; such data will be important to define the benefits of treatment in patients with stage F2 fibrosis and to define whether benefits accrue from lack of progression alone or also from regression of the fibrosis stage.

It is estimated that in the United States, 9.8 million persons are living with NASH and stage F0 to F2 fibrosis, 2 million with NASH and stage F3 fibrosis, and 1.3 million with NASH and stage F4 fibrosis.[25] On the basis of these estimates and the mortality observed in this study (0.89 and 1.76 deaths per 100 person-years for fibrosis stages F3 and F4, respectively), we estimate that the annual number of deaths that can be expected among persons who currently have stage F3 disease is 17,800 and that the number among persons with stage F4 disease is 22,880. We recently found that approximately 14% of patients with stage F0 to F2 fibrosis have progression to stage F3, and 2% have progression to stage F4 over a mean duration of 4.5 years.[26] Integration of these data with the observed outcomes translates to 15,000 additional deaths annually among persons whose disease transitions to stage F3 or F4. Although not all these deaths are attributable to liver disease, these data provide a framework for the design of outcomes trials and assessment of the benefits of fibrosis improvement in shorter trials.

Disease activity is another key facet of NASH and represents the elements driving the fibrogenic remodeling of the liver.[27] Previous attempts to link NAFLD activity scores to mortality have not shown a link independent of fibrosis.[6,7] These studies were, however, confounded by the collinearity between NASH and advanced fibrosis. It is well known, and noted in this study, that fibrosis progression occurs principally in persons with NASH, and

development of steatohepatitis, another indicator of disease activity, is the principal driver of fibrosis progression in persons with nonalcoholic fatty liver.[26] In relatively short-term clinical trials involving patients with mainly early-stage disease, worsening of the NAFLD activity score has been linked to fibrosis progression.[27] These findings support reduction in disease activity (in terms of NASH resolution) or reduction in the NAFLD activity score by 2 points or more without worsening of fibrosis as relevant short-term end points for clinical trials that target drivers of disease activity.

The generalizability of these data are limited by the ascertainment bias that is inherent in studies conducted at tertiary care centers and with study populations that are predominantly White. The patient population in this study is representative of patient populations treated for NAFLD at the participating clinical centers. Black patients constitute a small proportion of the total NAFLD patient population, as observed in the National Health and Nutrition Examination Survey (NHANES),[28] and were also a small minority of the enrolled population in this study. NAFLD affects many persons of Hispanic ancestry, and this subpopulation was relatively under-represented in this study. Also, the widths of the confidence intervals around the hazard ratios are not adjusted for multiplicity and do not permit statistical inferences regarding the associations. Although this was a carefully selected population with minimal or no alcohol use, in a real-world setting, many patients consume more alcohol than the patients in this study without having liver disease that is entirely attributable to alcohol use. Finally, most deaths occurred in centers outside the study sites, and the quality of the data available to determine the cause of death was mixed. These limitations notwithstanding, the current study provides critically needed prospective data on the rates and types of outcomes among patients with nonalcoholic fatty liver and NASH.

This study showed an association between fibrosis stages F3 and F4 and hepatic decompensation and death in patients with NAFLD. These data may be helpful in the assessment of prognoses and in the use of treatments for NASH.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

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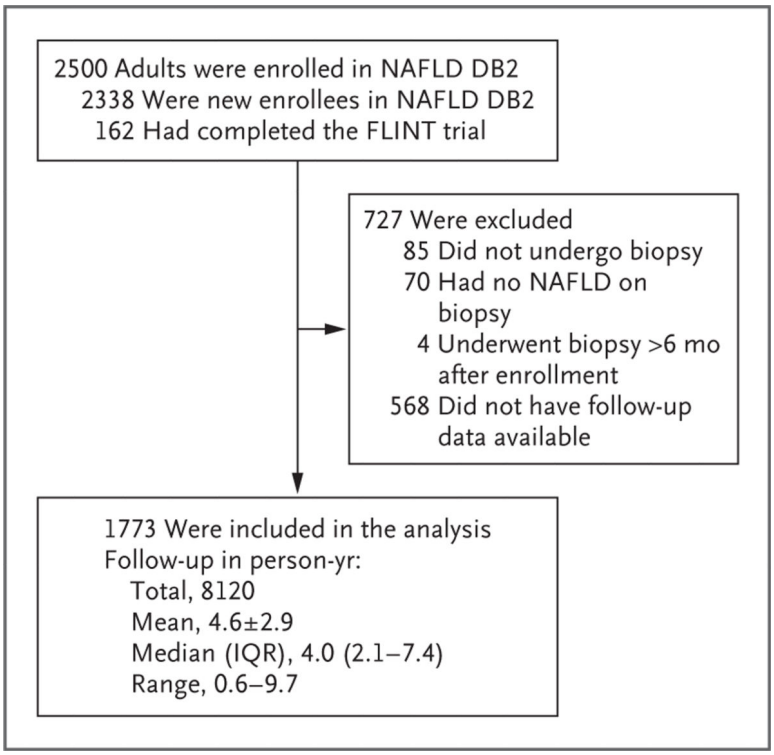

Figure 1. Selection Criteria for Analysis Database.

Patients from the Nonalcoholic Fatty Liver Disease (NAFLD) Database-2 noninterventional registry (DB2) were enrolled along with a subgroup of patients who had previously participated in and completed all study visits for the Farnesoid X Receptor Ligand Obeticholic Acid in Noncirrhotic Nonalcohlic Steatohepatitis (NASH) Treatment (FLINT) trial conducted by the NASH Clinical Research Network. IQR denotes interquartile range.

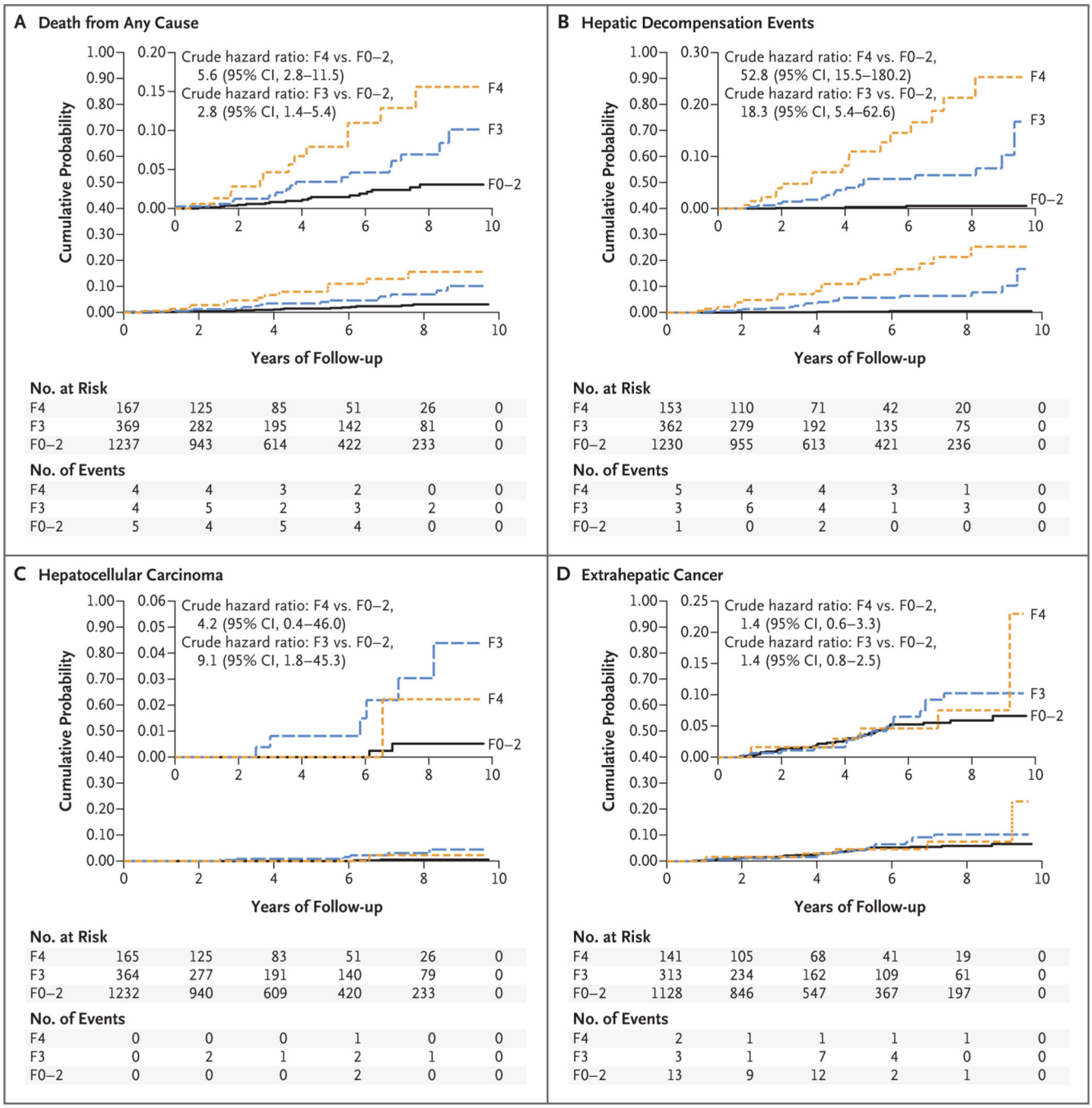

Figure 2. Outcomes in NAFLD.

Shown is a Kaplan–Meier time-to-event analysis for patients with early disease (mild fibrosis stage F0 to F2), bridging fibrosis (stage F3), and cirrhosis (stage F4). Data for stages F0 to F2 are combined owing to very few events in the individual stages within this grouping. Numbers shown in parentheses are the number of events within the interval. The number of censored events is the difference between the number at risk at the beginning and at the end of the interval minus the number of events in the interval. Shown are all-cause mortality (Panel A), new-onset clinical decompensation events (variceal bleed, ascites, or

encephalopathy) (Panel B), hepatocellular carcinoma (Panel C), and extrahepatic cancer (Panel D). Widths of confidence intervals have not been adjusted for multiplicity and should not be used to infer generalizable effects. Insets show the same data on an enlarged y axis.

Table 1.

Baseline Characteristics of Adults with NAFLD, According to Fibrosis Stage at Enrollment.*

Variable	Stage F4, Cirrhosis (N = 167)	Stage F3, Bridging Fibrosis (N = 369)	Stage F0 to F2, No, Mild, or Moderate Fibrosis (N = 1237)	Total (N = 1773)
Demographic characteristics				
Age — yr	57±9	55±12	50±12	52±12
Sex — no. (%)				
Male	44 (26)	116 (31)	472 (38)	632 (36)
Female	123 (74)	252 (69)	765 (62)	1141 (64)
Race — no. (%)†				
White	160 (96)	321 (87)	1028 (83)	1509 (85)
Other or not reported	7 (4)	48 (13)	211 (17)	264 (15)
Hispanic ethnic group†				
Yes	10 (6)	30 (8)	177 (14)	217 (12)
No	157 (94)	339 (92)	1060 (86)	1556 (88)
Body-mass index‡				
Median (IQR)	35 (31 to 40)	34 (31 to 40)	33 (29 to 37)	33 (30 to 38)
Distribution — no. (%)				
<25	5 (3)	17 (5)	55 (4)	77 (4)
25 to <30	27 (16)	61 (17)	325 (26)	413 (23)
30 to <35	52 (31)	121 (33)	403 (33)	576 (33)
≥35	83 (50)	168 (46)	451 (37)	702 (40)
NAFLD history				
Median age at diagnosis (IQR) — yr	53 (47–60)	52 (44–61)	47 (37–56)	49 (39–57)
Median time since diagnosis (IQR) — yr	3.8 (0.5–7.1)	3.1 (0.4–6.4)	2.3 (0.3–5.4)	2.7 (0.4–5.7)
Histologic features				
NAFLD activity score§	4.2±1.3	5.1±1.6	4.0±1.7	4.2±1.7
Steatosis score	1.2±0.8	1.7±0.9	1.8±0.9	1.7±0.9
Lobular inflammation score	1.4±0.7	1.8±0.8	1.4±0.6	1.5±0.7
Ballooning score	1.6±0.7	1.5±0.7	0.8±0.8	1.0±0.9
Fibrosis stage¶	4.0±0.0	3.0±0.0	0.9±0.8	1.6±1.3

Variable	Stage F4, Cirrhosis (N = 167)	Stage F3, Bridging Fibrosis (N = 369)	Stage F0 to F2, No, Mild, or Moderate Fibrosis (N = 1237)	Total (N = 1773)
NASH diagnosis — no. (%)				
Definite or borderline NASH	154 (92)	347 (94)	827 (67)	1338 (75)
NAFLD, not NASH	13 (8)	12 (3)	410 (33)	435 (25)
Median time since biopsy (IQR) — mo	3.4 (1.8–33.2)	2.6 (1.6–7.9)	2.7 (1.5–17.9)	2.7 (1.6–17.5)
Biopsy specimen length — mm	22±12	22±10	20±10	20±10
Liver tests				
Median ALT (IQR) — U/liter	42 (28–60)	59 (37–96)	50 (32–76)	51 (32–79)
Median AST (IQR) — U/liter	44 (31–63)	52 (37–76)	35 (26–52)	38 (28–59)
Median ALP (IQR) — U/liter	88 (72–112)	81 (65–97)	73 (59–88)	75 (61–93)
Total bilirubin — mg/dl	0.8±0.5	0.7±0.4	0.7±0.4	0.7±0.4
INR	1.11±0.25	1.05±0.13	1.01±0.14	1.03±0.15
Laboratory results				
Median serum creatinine (IQR) — mg/dl	0.7 (0.6–0.9)	0.8 (0.7–0.9)	0.8 (0.7–0.9)	0.8 (0.7–0.9)
Median eGFR (IQR) — ml/min/1.73 m^2 //	93 (80–104)	94 (80–104)	96 (82–107)	96 (81–106)
Serum albumin (IQR) — g/dl	4.1 (3.8–4.4)	4.3 (4.0–4.5)	4.3 (4.1–4.6)	4.3 (4.0–4.5)
Platelets per μL (IQR)	154,000 (116,000–207,000)	209,000 (160,000–255,000)	237,000 (197,000–281,000)	227,000 (184,000–270,000)

* Plus–minus values are means ±SD. Percentages may not total 100 because of rounding. Differences seen according to fibrosis stage in this population may not be true for the general population. To convert the values for creatinine to micromoles per liter, multiply by 88.4. Data were missing for the following variables: race (1 patient), body-mass index (5 patients); age at diagnosis and time since diagnosis (199 patients whose data were not captured in the FLINT trial); biopsy length (9 patients); alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), bilirubin, serum creatinine, estimated glomerular filtration rate (eGFR), and platelets (3 patients each); and albumin (4 patients). INR denotes international normalized ratio, IQR interquartile range, NAFLD nonalcoholic fibrotic liver disease, and NASH nonalcoholic steatohepatitis.

† Race and ethic group were reported by the patient.

‡ Body-mass index is the weight in kilograms divided by the square of the height in meters. A body-mass index of less than 25 indicates normal weight, of 25 to less than 30 overweight, of 30 to less than 35 obesity, and of 35 or above morbid obesity.

§ The NAFLD activity score was assessed on a scale of 0 to 8, with higher scores indicating more severe disease; the components of this measure are steatosis (assessed on a scale of 0 to 3), lobular inflammation (assessed on a scale of 0 to 3), and hepatocellular ballooning (assessed on a scale of 0 to 2).

¶ The fibrosis stage was assessed on a scale of 0 to 4, with higher scores indicating more severe fibrosis.

// The eGFR was calculated with the use of the Chronic Kidney Disease Epidemiology Collaboration formula.

Table 2.

Fibrosis Stage, Mortality, and New-Onset Nonfatal Outcomes in Patients with Biopsy-Confirmed NAFLD, According to Fibrosis Stage at Enrollment.*

Variable	Total		Stage F4, Cirrhosis		Stage F3, Bridging Fibrosis		Stage F0 to F2, No, Mild, or Moderate Fibrosis		Hazard Ratio (95% CI)	
									Stage F4 vs. F0–F2	Stage F3 vs. F0–F2
	rate per 100 person-yr	*no. of events/no. at risk*	*rate per 100 person-yr*	*no. of events/no. at risk*	*rate per 100 person-yr*	*no. of events/no. at risk*	*rate per 100 person-yr*	*no. of events/no. at risk*		
Death from any cause	0.57	47/1773	1.76	13/167	0.89	16/369	0.32	18/1237	3.9 (1.8–8.4)	1.9 (0.9–3.7)
Liver-related death	0.15	12/1773	0.68	5/167	0.28	5/369	0.04	2/1237	12.7 (1.8–88.6)	5.8 (0.9–38.4)
Liver-related events										
Variceal bleeding	0.07	6/1757	0.70	5/163	0.06	1/362	0.00	0/1232	NC	NC
Ascites	0.24	19/1747	1.20	8/155	0.52	9/363	0.04	2/1229	29.4 (4.5–190.7)	18.9 (3.2–112.6)
Encephalopathy	0.37	30/1757	2.39	16/161	0.75	13/364	0.02	1/1232	109.1 (18.5–926.0)	40.8 (4.7–350.6)
Any hepatic decompensation event†	0.46	37/1745	2.69	17/153	0.99	17/362	0.05	3/1230	36.1 (8.9–146.3)	18.7 (4.8–73.1)
MELD score≥ 15‡	0.79	63/1744	2.33	16/161	0.87	15/362	0.57	32/1221	3.7 (1.8–7.3)	1.2 (0.6–2.3)
Hepatocellular carcinoma	0.11	9/1761	0.14	1/165	0.34	6/364	0.04	2/1232	4.9 (0.4–63.2)	9.3 (1.4–61.8)
Cardiac and vascular events§										
Cardiovascular disease	0.83	63/1667	0.81	5/144	0.93	15/340	0.80	43/1183	0.7 (0.2–2.0)	0.8 (0.5–1.5)
Cerebrovascular disease	0.40	32/1745	0.99	7/163	0.46	8/363	0.30	17/1219	2.3 (0.9–5.9)	1.0 (0.4–2.6)
Hypertension	7.76	202/695	14.49	18/45	12.17	49/122	6.50	135/528	1.5 (0.9–2.5)	1.4 (1.0–2.1)
Renal function										
eGFR <60 ml/min/1.73 m^2	2.53	185/1660	4.49	27/153	2.97	46/337	2.17	112/1170	1.4 (0.9–2.2)	1.0 (0.7–1.4)
Decrease in eGFR of >40%	1.21	97/1761	2.98	20/164	1.31	23/368	0.97	54/1229	1.9 (1.1–3.4)	0.9 (0.6–1.6)
Other new coexisting events										
Nonhepatic cancer	0.82	58/1582	1.00	6/141	1.03	15/313	0.73	37/1128	1.2 (0.5–2.9)	1.4 (0.8–2.7)
Diabetes	4.84	206/1026	7.53	14/48	6.24	38/155	4.45	154/823	1.7 (1.0–3.0)	1.3 (0.9–2.0)

*Cox regression was used to estimate the hazard ratio and 95% confidence interval (CI) for the outcome of death from any cause; for all nonfatal outcomes, the Fine–Gray extension of Cox regression was used to account for death from any cause as competing risk. The incidence of individual decompensation events is based on patients who did not have that event at or before enrollment. The smaller denominators for nonfatal outcomes reflect patients who had a history of the outcome at or before enrollment. All models were stratified according to age, race, sex, and length of biopsy specimen, and all

models except that for the diabetes outcome were stratified according to diabetes status at enrollment. Since the widths of the confidence intervals have not been adjusted for the multiplicity of outcomes, conclusions that subgroup differences are important should not be inferred simply because a confidence interval does not include a hazard ratio equal to 1. eGFR denotes estimated glomerular filtration rate and NC could not be calculated.

[†]Any clinical hepatic decompensation event includes any of the following: ascites, encephalopathy, or variceal hemorrhage. The first occurrence of any of these events was used to define this outcome. There was one extra patient included in the denominator (1230) of the Stage F0 to F2 analysis who had both variceal bleeding and encephalopathy assessments but was missing the ascites assessment.

[‡]Model for End-stage Liver Disease (MELD) scores range from 6 to 40, with higher scores indicating a higher risk of death at 3 months.

[§]Diagnoses of coronary artery disease and cerebrovascular disease were determined by patient interview and review of medical records.