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ORIGINAL ARTICLE

NAFLD fibrosis score: A prognostic predictor for mortality and liver complications among NAFLD patients

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Abstract

AIM: To study whether the severity of liver fibrosis estimated by the nonalcoholic fatty liver disease (NAFLD) fibrosis score can predict all-cause mortality, cardiac complications, and/or liver complications of patients with NAFLD over long-term follow-up.

METHODS: A cohort of well-characterized patients with NAFLD diagnosed during the period of 1980-2000 was identified through the Rochester Epidemiology Project. The NAFLD fibrosis score (NFS) was used to separate NAFLD patients with and without advanced liver fibrosis. We used the NFS score to classify the probability of fibrosis as < -1.5 for low probability, > -1.5 to < 0.67 for intermediate probability, and > 0.67 for high probability. Primary endpoints included all-cause death and cardiovascular- and/or liver-related mortality. From the 479 patients with NAFLD assessed, 302 patients (63%) greater than 18 years old were included. All patients were followed, and medical charts were reviewed until August 31, 2009 or the date when the first primary endpoint occurred. By using a standardized case record form, we recorded a detailed history and physical examination and the use of statins and metformin during the follow-up period.

RESULTS: A total of 302/479 (63%) NAFLD patients (mean age: 47 ± 13 year) were included with a follow-up period of 12.0 ± 3.9 year. A low probability of advanced fibrosis (NFS < -1.5 at baseline) was found in 181 patients (60%), while an intermediate or high probability of advanced fibrosis (NSF > -1.5) was found in 121 patients (40%). At the end of the follow-up period, 55 patients (18%) developed primary endpoints. A total of 39 patients (13%) died during the follow-up. The leading causes of death were non-hepatic malignancy (n = 13/39; 33.3%), coronary heart disease (CHD) (n = 8/39; 20.5%), and liver-related mortality (n = 5/39; 12.8%). Thirty patients had new-onset CHD, whereas 8 of 30 patients (27%) died from CHD-related causes during the follow-up. In a multivariate analysis, a higher NFS at baseline and the presence of new-onset CHD were significantly predictive of death (OR = 2.6 and 9.2, respectively; P < 0.0001). Our study showed a significant, graded relationship between the NFS, as classified into 3 subgroups (low, intermediate and high probability of liver fibrosis), and the occurrence of primary endpoints. The use of metformin or simvastatin for at least 3 mo during the follow-up was associated with fewer deaths in patients with NAFLD (OR = 0.2 and 0.03, respectively; P < 0.05). Additionally, the rate of annual NFS change in patients with an intermediate or high probability of advanced liver fibrosis was significantly lower than those patients with a low probability of advanced liver fibrosis (0.06 *vs* 0.09, P = 0.004). The annual NFS change in patients who died was sig-

nificantly higher than those in patients who survived (0.14 *vs* 0.07, P = 0.03). At the end of the follow-up, we classified the patients into 3 subgroups according to the progression pattern of liver fibrosis by comparing the NFS at baseline to the NFS at the end of the follow-up period. Most patients were in the stable-fibrosis (60%) and progressive-fibrosis (37%) groups, whereas only 3% were in the regressive fibrosis.

CONCLUSION: A higher NAFLD fibrosis score at baseline and a new onset of CHD were significantly predictive of death in patients with NAFLD.

Key words: Nonalcoholic fatty liver disease fibrosis score; Prognostic predictor; Mortality; Liver complications

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INTRODUCTION

Nonalcoholic fatty liver disease (NAFLD) is one of the most common causes of chronic liver disease in Western countries[1]. The prevalence of NAFLD is increasing and varies significantly with ethnicity, ranging from 24% in blacks to 33% in whites and 45% in Hispanics according to a recent study from the United States[2]. The mortality rate of NAFLD patients in the community was found to be higher than that of the general population in both the US and Sweden[3]. During an average 7.6 years of follow-up, 13% of the patients died, mainly from malignancy, coronary heart disease (CHD) and liver-related mortality[4]. Another study revealed that the survival of patients with nonalcoholic steatohepatitis (NASH) was reduced and that these patients died significantly more often from CHD and liver-related causes[3]. Patients with more advanced liver fibrosis tend to have more liver complications than those without liver fibrosis[4]. Liver biopsy is considered the gold standard for the diagnosis and assessment of fibrosis severity but has several limitations, such as sampling variability, invasiveness and expense[5]. Patients with NASH can have a significant progression of fibrosis within a few years[6-8]. Recently, a simple, noninvasive tool used for liver fibrosis assessment has been developed[9]. This new scoring system, the NAFLD fibrosis score (NFS), is a composite score of age, hyperglycemia, body mass index, platelet count, albumin, and aspartate aminotransferase and alanine aminotransferase (AST/ALT) ratio[9] and was found to independently identify NAFLD patients with and without advanced fibrosis at initial NAFLD diagnosis. Another clinical score composed of body mass index (BMI) $\geqslant$ 28 kg/m^2, AST/ALT ratio $\geqslant$ 0.8 and diabetes mellitus (the BARD score) has also been used to predict an increased chance of liver fibrosis[10]. However, the BARD score does not have the capacity to differentiate the severity of liver fibrosis among patients with a higher BMI or a higher ratio of AST/ALT, whereas the NFS takes into consideration the different ranges of BMI or AST/ALT ratios[9]. A study from Japan validated the NFS and found it to have an acceptable sensitivity, specificity, and positive and negative predictive values for advanced liver fibrosis of 100%, 83%, 63%, and 100%, respectively[11]. A longitudinal study of 103 NAFLD patients showed that the fibrosis stage progressed in 37%, remained stable in 34% and regressed in 29% of patients with a mean interval between liver biopsies of approximately 3 years[12]. The rate of fibrosis change ranged from -2.1 to 1.7 stages per year. The prognostic predictors for a higher rate of liver fibrosis were diabetes, a low initial fibrosis stage and a higher body mass index. In the current study, we aimed to determine whether the severity of liver fibrosis estimated by the NFS can predict a higher risk of overall mortality, cardiac complications, and/or liver complications among patients with NAFLD. Additionally, we aimed to determine the annual rate of the NFS change from the baseline to the end of the follow-up among NAFLD patients.

MATERIALS AND METHODS

Study subjects

In this a historical cohort study, patients residing in Olmsted County, Rochester, Minnesota, United States who had been diagnosed with NAFLD-fatty liver (HICDA Code 05710420), fatty liver hypertrophy (HICDA Code 05710421), fatty liver cirrhosis (HICDA Code 05710422), fatty liver steatohepatitis (HICDA Code 05710423) or NASH (HICDA Code 05710431), or fatty liver steatohepatitis (HICDA Code 05710-42-43) or steatosis (HICDA Code 02790-44-1) between January 1, 1980 and January 1, 2000 were drawn from the Rochester Epidemiology Project (REP) master diagnostic index. The REP index is a unique database system of medical diagnoses of the population living in Olmsted County, Minnesota[13]. Although fatty liver was recognized prior to 1980, this liver condition was better characterized in 1980[14]; therefore, we chose to identify patients after this date.

Inclusion criteria

From the 479 patients with NAFLD assessed, 302 patients (63%) greater than 18 years old were included. All of these patients were followed, and their medical charts were reviewed, until August 31, 2009 or the date when the first primary endpoint occurred. By using a standardized case record form, we recorded a detailed history and physical examination and use of statins and metformin during the follow-up period.

Exclusion criteria

We excluded NAFLD patients who lacked the data

needed for the NFS calculation, patients with pre-existing poor outcomes including overt CHD or overt liver complications at the time of NAFLD diagnosis and patients with duration of follow-up of less than 5 years. One hundred seventy-seven NAFLD patients were excluded due to missing the data needed for the NFS calculation (n = 95), overt CHD confirmed at baseline (n = 63), liver cirrhosis with complications confirmed at baseline (n = 11) and duration of follow-up of less than 5 years (n = 8).

Definitions

The diagnosis of NAFLD was based on a liver biopsy showing steatosis in at least 5% of hepatocytes or fatty infiltration of the liver confirmed by imaging study (ultrasound, computed tomography, or magnetic resonance imaging) and the exclusion of liver disease of other etiologies, including alcohol-induced liver disease (history of excessive alcohol consumption greater than 20 gm/d), drug-induced liver disease, autoimmune or viral hepatitis and cholestatic or metabolic/genetic liver disease[1]. Cirrhosis was defined based on the pathological term for the chronic liver diseases[15]. In our study, 85% of patients (n = 256) were diagnosed by liver imaging. Liver biopsy was performed in 46 patients (15% of 302 patients). The staging of fibrosis was divided into fibrosis stage 0 to stage 4 using the Brunt criteria[16]. The NAFLD patients with a histological liver fibrosis stage of 1-2 were classified as "mild liver fibrosis," and those with a histological fibrosis stage of 3-4 were classified as "advanced liver fibrosis"[16].

The primary endpoints were all-cause mortality, cardiac complications, and/or liver complications. Cardiac complications included new-onset CHD events as recorded in the medical records, defined as congestive heart failure, unstable angina, myocardial infarction, flow-limiting stenosis from angiography or angina requiring revascularization during the follow-up period and need for hospitalization[17]. Liver complications were diagnosed by clinical signs and symptoms[18], including the presence of ascites, variceal bleeding, a severe grade of hepatic encephalopathy, liver failure or hepatocellular carcinoma, that occurred during the follow-up and required hospitalization with or without death[19]. All causes of death listed on the death certificates or pathological findings (underlying, intermediate, immediate and other major conditions) were recorded using the 10th revision of the International Classification of Diseases (ICD-10). The presence of metabolic syndrome (MetS) was defined by using the 2001 National Cholesterol Education Program Adult Treatment Panel Ⅲ (NCEP-ATPⅢ) criteria and the new definition, which requires the presence of at least three of the five features[20,21]. The NFS is composed of 6 variables, including age, hyperglycemia, BMI, platelet count, albumin, and AST/ALT ratio as independent indicators of advanced liver fibrosis[9]. NAFLD fibrosis score = -1.675 + 0.037 × age (year) + 0.094 × BMI (kg/m^2) + 1.13 × IFG/diabetes (yes = 1, no = 0) + 0.99 × AST/ALT ratio - 0.013 × platelet count (×10^9/L) - 0.66 × albumin (g/dL)[9].

In this study, the NFS was used to classify advanced liver fibrosis into 2 categories[9]. NAFLD patients with a score less than -1.5 were classified as "low probability of advanced liver fibrosis," and those patients with a score of at least -1.5 were classified as "intermediate or high probability of advanced liver fibrosis"[9]. Because the information required for determination of the NFS was not always available on the same day, the scores were calculated at the time of NAFLD diagnosis using data from the medical records from visits within 3 mo of the "true" NAFLD diagnosis date and the last follow-up date. If more than one assessment for a given variable was available in the medical records during this time period, the value closest to the "true" follow-up date was used for the NFS calculation[9]. According to the 3 subgroups of low, intermediate and high probability of fibrosis, we used parameters of NFS < -1.5 for low, NFS ⩾ -1.5 to NFS < 0.67 for intermediate and NFS ⩾ 0.67 for high probability of fibrosis at baseline.

At the end of the follow-up period, we classified the patients into 3 subgroups according to the progression pattern of the liver fibrosis by comparing the NFS at baseline to the end of follow-up. The first group had stable fibrosis, defined as stability of the NFS during the follow-up. The second group had regression of fibrosis, defined as a reduction of the NFS to a milder stage of fibrosis during the follow-up. Lastly, the third group had fibrosis progression, defined as an increase of the NFS to a more advanced stage during the follow-up.

Sample-size/statistical power considerations

We assumed that the overall mortality rate in NAFLD would be 12%, with liver-related complications being observed in at least 3% and cardiac complications in 11% of patients based on results from a previous study[4]. We anticipated that at least 150 patients, or 50% of the total cohort, would be classified as "low probability of advanced liver fibrosis" using the NFS, and at least 150 would be classified as "intermediate or high probability of advanced liver fibrosis"[12]. However, a portion of patients were expected to develop new CHD events, liver complications and death. We anticipated that 15% of patients would be identified as having experienced a primary endpoint. We assumed that, at most, 10% of patients with a low probability of advanced liver fibrosis would experience events within 5 years and at least 20% of patients with an intermediate or high probability of advanced liver fibrosis would experience events within 5 years to obtain a statistical power of at least 82%.

Statistical analysis

Patients were categorized by the NFS into 2 groups of probability of advanced liver fibrosis. Differences between the primary endpoints of the two groups of low and high NFS were compared by using the χ^2 test. Differences between NAFLD patients with and without primary endpoints were tested by independent t tests for

Table 1 Demographic data of 302 patients by nonalcoholic fatty liver disease fibrosis score at baseline *n* (%) (mean ± SD)

Variable at baseline	Total (*n* = 302)	Patients with a low probability of advanced liver fibrosis (NFS < -1.5) (*n* = 181)	Patients with an intermediate or high probability of advanced liver fibrosis (NFS ⩾ -1.5) (*n* = 121)	*P* value
Age (yr)	47.3 ± 12.9	42.9 ± 11.1	53.8 ± 12.8	< 0.0001
Sex (% male)	132 (44)	92 (51)	40 (33)	0.002
Race, number (% White)	288 (95)	170 (94)	119 (97.5)	0.150
History of diabetes	48 (16)	5 (2.8)	43 (35.5)	< 0.0001
History of hypertension	125 (41)	55 (30.4)	70 (58)	< 0.0001
BMI (kg/m^2)	33.6 ± 6.2	32.0 ± 5.2	36.0 ± 6.9	< 0.0001
Presence of obesity (BMI > 30 kg/m^2)	221 (73)	121 (67)	100 (82.6)	0.002
Systolic blood pressure (mmHg)	136 ± 18	133 ± 17	139 ± 18	0.003
Diastolic blood pressure (mmHg)	83 ± 9	84 ± 8	81 ± 9	0.010
Cholesterol (mg/dL)	214 ± 48	215 ± 46	214 ± 50	0.780
Triglycerides (mg/dL)	221 ± 167	208 ± 123	242 ± 218	0.150
Glucose (mg/dL)	115 ± 41	103 ± 25	132 ± 54	< 0.0001
AST (U/L)	41.4 ± 21.9	40.8 ± 21.8	42.2 ± 28.9	0.620
ALT (U/L)	61.5 ± 43.3	69.7 ± 46	49.4 ± 35.7	< 0.0001
AST/ALT ratio	0.8 ± 0.4	0.7 ± 0.3	1.0 ± 0.6	< 0.0001
GGT (U/L)	131.9 ± 39.8	129.9 ± 32.9	134.2 ± 46.7	0.560
Platelets (× 10^9/L)	240 ± 62	259 ± 60	212 ± 53	< 0.0001
Albumin (g/dL)	4.3 ± 0.4	4.4 ± 0.3	4.1 ± 0.3	< 0.0001
Alkaline phosphatase (U/L)	196 ± 88	186 ± 68	211 ± 111	0.030
Framingham Risk Score	8.4 ± 6.2	6.9 ± 6.4	10.5 ± 5.2	< 0.0001
Calculated CHD risk (%)	16.2 ± 14.6	14.1 ± 13.8	19.3 ± 15.2	0.003
NFS	-1.7 ± 1.4	-2.6 ± 0.8	-0.4 ± 0.9	< 0.0001

NAFLD: Nonalcoholic fatty liver disease; BMI: Body mass index; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; GGT: Glutamyltransferase; CHD: Coronary heart disease; NFS: NAFLD fibrosis score.

continuous variables and were tested by the χ^2 test for proportions. Continuous outcomes were presented as the mean ± SD, and categorical data were presented as numbers (percentage). Logistic regression analysis was used to identify the factors significantly associated with death among NAFLD patients. Only those variables with a *P* value < 0.1 by univariate analysis were included in multivariate analysis. To avoid overestimation of the model, we excluded those variables used as a part of the NFS calculation. We estimated receiver operating characteristics of related variables for the predicting of death to maximize the area under the curve (AUC). Two-sided *P* values < 0.05 were considered statistically significance. The rate of NFS change in each patient was calculated by the difference of NFS at the end of follow-up and at baseline divided by the duration of the follow-up time (Δ NFS/Δ time). Both phases of the study used the SPSS statistical software package (SPSS Version 15.0.1.1, Windows VISTA, July 3, 2007) for analysis. The study was approved by the Institutional Review Board (IRB) of the Mayo Clinic, Rochester, MN, United States, and all participants provided permission for their medical information to be used for research.

RESULTS

Baseline characteristic data of 302 patients with NAFLD

This study included three hundred two NAFLD patients aged 47 ± 13 year (range 21-86 year), of which 95% were white, and 44% were male. Obesity was present in 73%, and a history of diabetes mellitus type Ⅱ and hypertension was observed in 16% and 41%, respectively. Eighty-five percent of patients (*n* = 256) were diagnosed by liver imaging. Liver biopsy was performed in 46 patients (15%). Mild liver fibrosis (stage F 0-2) was found in 34 patients (74%), while advanced fibrosis (stage F 3-4) was found in 12 patients (26%). NAFLD patients who underwent a liver biopsy had a significantly lower diastolic blood pressure, a lower BMI and a higher AST level than those without a liver biopsy (*P* < 0.05). The characteristics of the 302 patients based on the degree of advanced liver fibrosis estimated by the NFS at baseline are shown in Table 1. A low probability of advanced liver fibrosis (NFS < -1.5) was found in 60% of patients, while an intermediate or high probability of advanced liver fibrosis (NFS ⩾ -1.5) was found in 40%. The mean ± SD value of NFS in patients with a low probability of advanced liver fibrosis was -2.6 ± 0.8 and was lower than in patients with an intermediate or high probability of advanced liver fibrosis (-0.4 ± 0.9, *P* < 0.0001). Patients with a low probability of advanced liver fibrosis had a lower CHD risk at baseline, as estimated by the Framingham risk score (FRS) calculation, compared to patients with an intermediate or high probability of advanced liver fibrosis (14% *vs* 19%, *P* = 0.003).

Clinical outcomes of long-term follow-up

The mean follow-up of the total cohort was 11.9 ± 3.9 years for a total of 3594 person-years. Approximately 47% of patients with a low probability of advanced liver fibrosis at baseline progressed to an intermediate or high probability of advanced liver fibrosis at the end of follow-up, while 94% of patients with an intermediate

Table 2 Clinical parameters, laboratory features and clinical outcomes at the end of follow-up by nonalcoholic fatty liver disease fibrosis score at baseline *n* (%) (mean ± SD)

Variable at the end of follow-up	Patients with a low probability of advanced liver fibrosis (NFS < -1.5) (*n* = 181)	Patients with an intermediate or high probability of advanced liver fibrosis (NFS > -1.5) (*n* = 121)	*P* value
Clinical findings			
BMI (kg/m^2)	32.9 ± 6.6	34.9 ± 7.6	0.02
Obesity (BMI > 30 kg/m^2)	119 (65.8)	91 (75.2)	0.08
NFS	-1.4 ± 1.3	0.4 ± 1.4	< 0.0001
NFS of intermediate or high probability of advanced liver fibrosis	85 (47)	114 (94)	< 0.0001
History of diabetes	54 (29.8)	83 (68.6)	< 0.0001
Use of metformin	32 (17.7)	48 (39.7)	< 0.0001
Use of glitazones	10 (5.5)	19 (15.7)	0.003
Use of aspirin	84 (46)	83 (69)	0.0001
History of hypothyroidism	19 (10.5)	31 (25.6)	0.0005
History of cholecystectomy	27 (15)	33 (27.3)	0.008
History of obstructive sleep apnea	33 (18.2)	34 (28.1)	0.04
Laboratory findings			
AST (U/L)	38.9 ± 30.6	33.2 ± 17.8	0.04
ALT (U/L)	53.9 ± 49.7	38.9 ± 21	0.0004
AST/ALT ratio	0.8 ± 0.5	1.0 ± 0.8	0.03
Hematocrit (%)	40.4 ± 4.4	38.6 ± 5.3	0.003
Platelets (× 10^9/L)	259 ± 67	217 ± 74	< 0.0001
Albumin (g/dL)	4.1 ± 0.4	3.9 ± 0.6	< 0.0001
Cholesterol (mg/dL)	193 ± 40	178 ± 43	0.005
LDL-cholesterol (mg/dL)	109 ± 34	92 ± 30	< 0.0001
Glucose (mg/dL)	119 ± 42	131 ± 42	0.02
Clinical outcomes at the end of follow-up			
Lost to follow up	27 (15)	8 (7)	
Alive with continued follow-up	131 (72)	81 (67)	
Presence of primary endpoints	23 (13)	32 (26)	0.002
All-cause death	12 (6.6)	27 (22.3)	< 0.0001
New events of coronary heart disease	15 (8.3)	15 (12.4)	0.24
Liver complications	1 (0.6)	5 (4.1)	0.03

NAFLD: Nonalcoholic fatty liver disease; BMI: Body mass index; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; NFS: NAFLD fibrosis score; LDL: Low-density lipoprotein.

or high probability of advanced liver fibrosis remained in the same group. At the end of the follow-up, patients with an intermediate or high probability of advanced liver fibrosis had a significantly higher BMI, more frequent diabetes, and more frequent histories of hypothyroidism, cholecystectomy and obstructive sleep apnea. Furthermore, the patients with an intermediate or high probability of advanced liver fibrosis were more likely to use metformin, glitazones and aspirin compared to those with a low probability of advanced liver fibrosis ($P < 0.05$).

A history of diabetes at baseline was found in 16%, while the proportion of patients with NAFLD who developed impaired fasting glycemia or diabetes during the follow-up was 89 patients (29%) with an average interval of 6.3 ± 4.2 year (range 0.2-17.2) from the diagnosis of NAFLD. Patients who developed impaired fasting glycemia or diabetes during the follow-up were more frequent male, had less hypertension, and had a lower NAFLD Fibrosis Score at baseline compared to those with diabetes at baseline ($P < 0.05$). The primary endpoints of both groups were not significantly different.

Patients with an intermediate or high probability of advanced liver fibrosis had a significantly higher glucose and a higher AST/ALT ratio at the end of follow-up compared to those with a low probability of advanced liver fibrosis. Hematocrit, platelet count, AST, ALT, albumin, cholesterol and low-density lipoprotein (LDL)-cholesterol level were significantly lower in patients with an intermediate or high probability of advanced liver fibrosis compared to those with a low probability of advanced liver fibrosis (Table 2). At the end of follow-up, 55 patients developed primary endpoints, including death or the presence of CHD or liver complications. Thirty of these patients had new-onset CHD, whereas 8 of 30 patients (27%) died from CHD-related complications during the follow-up period (Table 2). Patients with new CHD events ($n = 30$) were significantly older and had a higher systolic blood pressure (SBP), FRS at baseline, calculated % CHD risk at baseline, and NFS at the end of follow-up and exhibited a lower ALT than those patients without new CHD events ($n = 272$) ($P < 0.05$). In addition, the NFS at baseline was similar in patients with and without new CHD events (-1.2 ± 1.6 *vs* -1.8 ± 1.4, $P = 0.07$). Liver complications occurred in 6 patients, 5 of whom (83%) died during the follow-up. The liver complications included massive ascites requiring abdomi-

Table 3 Causes of mortality in 39 patients with nonalcoholic fatty liver disease

Causes of death	All causes mortality *n* (% of death)	All causes mortality (% of 302 patients)
Non-liver cancer	13 (33.3)	4.3%
Coronary heart disease	8 (20.5)	2.6%
Liver-related mortality (including hepatocellular carcinoma)	5 (12.8)	1.7%
Infection (including sepsis)	4 (10.3)	1.3%
Stroke	3 (7.7)	1.0%
Cardiac arrhythmia	2 (5.1)	0.7%
COPD and/or respiratory failure	2 (5.1)	0.7%
Other causes of death (GI bleeding, renal failure)	2 (5.1)	0.7%
Total	39 (100)	12.9%

COPD: Chronic obstructive lung disease; GI: Gastrointestinal.

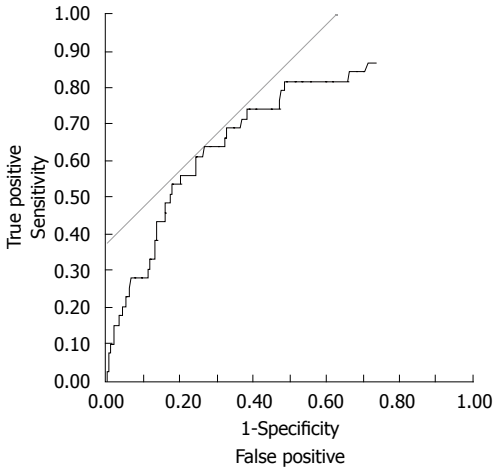

Figure 1 Presence of death estimated by the nonalcoholic fatty liver disease fibrosis score at baseline. Using the receiver operating characteristics curve, the nonalcoholic fatty liver disease fibrosis score at baseline of -0.9 was the best cutoff value for predicting death based on a sensitivity of 62%, specificity of 76%, positive predictive value of 28%, negative predictive value of 93% and area under the curve of 0.7.

nal paracentesis (n = 3), hepatopulmonary syndrome and hepatocellular carcinoma (n = 1 each).

A total of 39/302 (13%) patients died during the follow-up period. The leading causes of death were non-hepatic malignancy (n = 13/39; 33.3%), CHD (n = 8/39; 20.5%), and liver related mortality (n = 5/39; 12.8%). The other 13 patients (33.3%) died from various causes (Table 3). The primary types of cancers were gastric cancer (n = 2), colon cancer (n = 2), pancreatic cancer (n = 2), breast cancer (n = 2), leiomyosarcoma of uterus (n = 1), diffuse B cell lymphoma (n = 1), endometrial cancer (n = 1), lung cancer (n = 1) and unknown primary cancer with liver metastasis (n = 1). Additionally, our study showed a significant, graded relationship between the NAFLD fibrosis score, classified into 3 subgroups (low, intermediate and high probability of liver fibrosis), and the occurrence of primary endpoints, as shown in Table 4.

Predicting mortality

Patients who died (n = 39) were significantly older with more frequent diabetes and had a higher SBP, NFS at baseline, FRS, glucose, and a lower diastolic blood pressure, ALT and albumin (Table 5). Moreover, they had greater NFS changes per year than those who survived (n = 263, P <0.05). Three models of multivariate analysis were used to identify the best fit model for predictors of death and are illustrated in Table 6. In model 1, we added 9 variables, including gender, systolic blood pressure, diastolic blood pressure, NFS at baseline, use of metformin, use of simvastatin, use of aspirin, presence of new-onset CHD and new-onset liver complications, without interaction among these variables. Model 2 included 10 variables, gender, systolic blood pressure, diastolic blood pressure, NFS at baseline, NFS changes per year, use of metformin, use of simvastatin, use of aspirin, presence of new-onset of CHD and new-onset of liver complications without interaction among these variables. Finally, model 3 added the interaction between NFS at baseline and NAFLD NFS changes per year with the use of aspirin, metformin, and simvastatin into model 2. We did not add the FRS into these models due to the repetition of several variables in the NFS and the FRS. Model 3 was the best fit model, which found that a higher NFS at baseline and more frequent new-onset CHD were significantly predictive of death (OR = 2.6 and 9.2, respectively; P < 0.0001). The use of metformin or simvastatin for at least 3 mo during the follow-up were associated with fewer deaths in patients with NAFLD (OR = 0.2 and 0.03, respectively; P < 0.05).

Table 7 showed the results of the comparison of NAFLD patients with and without death after excluding those with established type 2 diabetes at baseline (n = 254). After excluding patients with established type 2 diabetes at baseline, we found that a higher NFS at baseline and higher alkaline phosphatase remained significantly predictive of death (OR = 1.9 and 1.006; P <0.0001 and 0.012, respectively) as shown in Table 8. Additionally, Table 9 showed that non-diabetic patients with intermediate or high probability of liver fibrosis had a significantly higher rate of primary end point and all-cause death than those patients with low probability of liver fibrosis.

Using the ROC curves to predict death, we found that a baseline NFS of -0.9 was the best cutoff value with a sensitivity of 62%, specificity of 76%, positive predictive value of 28%, negative predictive value of 93% and AUC of 0.7 (Figure 1).

The median rate of annual NFS change for all patients was 0.1 (IQR of 0.02, 0.13). The rate of annual NFS change in patients with an intermediate or high probability of advanced liver fibrosis was significantly lower than in patients with a low probability of advanced liver fibrosis (0.06 *vs* 0.09, P = 0.004). The annual NFS change in patients who died was significantly higher than those in patients who survived (0.14 *vs* 0.07, P = 0.03). At the end of the follow-up, we classified the patients into 3 subgroups according to the progression pattern of the

Table 4 Association between the primary endpoint and the grading of the nonalcoholic fatty liver disease fibrosis score, classified into 3 subgroups (*n* = 302) *n* (%)

Grading of the NAFLD fibrosis score (*n* = 302)	Low prob. of advanced liver fibrosis (*n* = 181)	Intermediate prob. of advanced liver fibrosis (*n* = 108)	High prob. of advanced liver fibrosis (*n* = 13)	*P* value
Presence of primary endpoint (*n* = 55, 18.2%)	23/181 (12.7)	24/108 (22.2)	8/13 (61.5)	< 0.0001
All-cause death (*n* = 39, 12.9%)	12/181 (6.6)	21/108 (19.4)	6/13 (46.2)	< 0.0001

NAFLD: Nonalcoholic fatty liver disease.

Table 5 Comparison of nonalcoholic fatty liver disease patients alive *vs* deceased *n* (%) (mean ± SD)

Variables	NAFLD patients alive (*n* = 263)	NAFLD patients deceased (*n* = 39)	*P* value
At baseline			
Age (yr)	45.2 ± 11.5	61.1 ± 13.8	< 0.0001
Sex (% male)	120 (45.6)	12 (30.8)	0.08
History of diabetes	37 (14.1)	11 (28.2)	0.02
Systolic blood pressure (mmHg)	134 ± 17	143 ± 21	0.02
Diastolic blood pressure (mmHg)	83 ± 8	79 ± 10	0.03
Glucose (mg/dL)	112 ± 38.6	132.7 ± 54.3	0.03
AST (U/L)	42.2 ± 25.5	35.5 ± 20.0	0.06
ALT (U/L)	64.2 ± 44.6	43.6 ± 27.4	0.000
AST/ALT ratio	0.8 ± 0.4	1.0 ± 0.7	0.06
Albumin (g/dL)	4.3 ± 0.3	4.0 ± 0.4	< 0.0001
FRS	7.9 ± 6.2	11.4 ± 5.2	0.000
Calculated CHD risk (%)	15.3 ± 14.0	22.2 ± 17.1	0.02
NFS	-1.9 ± 1.3	-0.8 ± 1.7	0.0004
NFS of intermediate or high probability of advanced liver fibrosis (%)	94 (35.7)	27 (69.2)	< 0.0001
Presence of histologically advanced liver fibrosis	7/35 (20.0)	5/11 (45.5)	0.09
During the follow-up period	77 (29.3)	3 (7.7)	0.004
Use of metformin			
Use of aspirin	151 (57.4)	16 (41.0)	0.05
Use of simvastatin	107 (40.7)	3 (7.9)	< 0.0001
New events of coronary heart disease	16 (6.1)	14 (35.9)	< 0.0001
Liver complications	1 (0.4)	5 (12.8)	< 0.0001
At the end of follow-up			
BMI (kg/m^2)	33.9 ± 6.9	31.8 ± 8.2	0.1
Hematocrit (%)	40.4 ± 4.1	34.5 ± 6.3	< 0.0001
Glucose (mg/dL)	122.0 ± 38.6	139.0 ± 62.3	0.12
AST/ALT ratio	0.9 ± 0.5	1.3 ± 1.0	0.01
Albumin (g/dL)	4.1 ± 0.3	3.3 ± 0.7	< 0.0001
Creatinine (mg/dL)	1.0 ± 0.5	1.7 ± 1.3	0.004
NFS	-0.9 ± 1.4	0.7 ± 2.3	< 0.0001
NFS change per year (Median; IQR)	0.07 (0.02, 0.12)	0.14 (0.01, 0.31)	0.03
NFS of intermediate to high probability of advanced liver fibrosis (%)	168 (63.9)	31 (79.5)	0.05

To avoid overestimation of the model, we excluded those variables used as a part of NAFLD fibrosis score calculation (age, history of diabetes, aspartate aminotransferase/alanine aminotransferase ratio, platelet count, albumin, body mass index and Framingham risk score). NAFLD: Nonalcoholic fatty liver disease; BMI: Body mass index; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; FRS: Framingham risk score; CHD: Coronary heart disease; NFS: NAFLD fibrosis score.

liver fibrosis by comparing the NFS at baseline to that at the end of follow-up. Most patients were in the stable-fibrosis (60%) and progressive-fibrosis (37%) groups, whereas only 3% were in the regressive-fibrosis group. The annual NFS change in the progressive-fibrosis group and the stable-disease group was 0.20 ± 0.02 and 0.05 ± 0.08, respectively (*P* = not significant).

DISCUSSION

In the current study, we found that a higher NFS at baseline and the presence of new-onset CHD were significantly predictive of death. The use of noninvasive methods to predict poor clinical outcomes in NAFLD patients during follow-up is urgently needed. Studies of noninvasive markers used to identify steatohepatitis patients from NAFLD patients require validation before being widely used, as previously suggested[22]. Although liver biopsy is the currently recommended practice for identifying liver fibrosis, in NAFLD patients with risk factors that include older age, diabetes, severe obesity and metabolic syndrome, serial liver biopsies are invasive and are not applicable in clinical practice. Recently, Rafiq *et al*[22] showed that at least 3 risk factors, including type

Table 6 Multivariate logistic regression model showing OR (95%CI) for predictors for death in 302 patients with non-alcoholic fatty liver disease

Multivariate analysis	*P* value	OR	95%CI
Model 1			
Presence of new-onset CHD	< 0.0001	9.0	2.9-28.4
NFS at baseline	< 0.0001	1.9	1.4-2.6
Use of metformin	0.02	0.2	0.04-0.8
Use of simvastatin	0.001	0.05	0.01-0.3
Model 2			
NFS changes per year	0.04	14.9	1.1-206.4
Presence of new onset of CHD	0.001	8.0	2.4-26.1
NFS at baseline	< 0.0001	2.1	1.5-2.9
Use of metformin	0.02	0.2	0.04-0.7
Use of simvastatin	0.001	0.06	0.01-0.3
Model 3			
Presence of new onset of CHD	< 0.0001	9.2	2.6-32.2
NFS at baseline	< 0.0001	2.6	1.7-3.9
Use of metformin	0.03	0.2	0.04-0.8
Use of simvastatin	0.001	0.03	0.003-0.2
Interaction between NFS at baseline and NFS change per year	0.004	0.06	0.008-0.4
NFS changes per year	0.6	2.2	0.07-67.8

Model 1 without interaction among 9 included variables: gender, systolic blood pressure, diastolic blood pressure, nonalcoholic fatty liver disease (NAFLD) fibrosis score at baseline, use of metformin, use of simvastatin, use of aspirin, presence of new-onset of coronary heart disease (CHD) and new onset of liver complications; Model 2 without interaction among 10 included variables: gender, systolic blood pressure, diastolic blood pressure, NAFLD fibrosis score (NFS) at baseline, NFS changes per year, use of metformin, use of simvastatin, use of aspirin, presence of new-onset coronary heart disease (CHD) and new onset of liver complications; Model 3 added variables of interaction between NFS at baseline and NFS changes per year, interaction among use of aspirin, metformin, aspirin and simvastatin into model 2.

2 diabetes, older age and low albumin level, were predictors of mortality and liver-related mortality. Most of these risk factors are components of the NFS[9]. Thus, a benefit of the current study is an extension of the clinical use of the NFS system for predicting death in patients with NAFLD.

Our results show that the annual NFS change in patients who died was two times higher than in survivors during the follow-up. Thus, it would be valuable to calculate NFS in newly diagnosed patients.

The annual rate of NFS change in the progressive-fibrosis group was approximately 4 times higher than that in the stable-disease group. Therefore, the median value of the annual rate of NFS change might be used as a surrogate marker for progression of liver fibrosis, but this measure requires further study to validate its benefit.

The long-term outcomes of patients with NAFLD are not uniform across the spectrum of the disease[3,22,23]. Poor outcomes are more frequent in patients with NASH, which was confirmed by our results, which showed patients with an intermediate or high probability of advanced liver fibrosis had an increased frequency of primary endpoints, all-cause deaths, and liver complications compared to those with a low probability of advanced liver fibrosis.

Several previous studies have demonstrated a higher mortality rate (30%-45%) than observed in the current study (13%). This difference may be at least partly explained by a difference in patient selection. For instance, the prevalence of diabetes or impaired glucose tolerance, a well-known risk factor for increased mortality, was three times higher in a Swedish study than in the current study (53% *vs* 16%)[3]. In addition, previous studies did not exclude patients with known CHD or known liver complications at baseline[3,22,23].

The use of metformin or simvastatin was found to be a protective factor against death in the present study. This finding is in line with a study by Ekstedt *et al*[24], who showed a significant reduction in liver steatosis in NAFLD patients on statins *vs* those not on statins. A recent study found diabetes mellitus to be one of the important predictors for developing moderate to severe liver fibrosis[25], and treatment with metformin improved liver histology and ALT levels in one-third of patients with NASH[26]. Two other studies suggested that metformin improved only the insulin sensitivity but did not improve liver histology in NASH patients[26,27]. Limited data exist concerning the efficacy of metformin in patients with NAFLD, and the result of the current study does not necessarily imply causality. Our results show that the use of simvastatin seems to improve the prognosis in patients with NAFLD. This improvement may relate to the effect on prevention of new-onset CHD, which accounted for 20% of deaths in our study. Recent data showed that the statins are safe and well-tolerated in patients with NAFLD[28-32]. Moreover, the use of statins was associated with a reduction of hepatic steatosis in NAFLD patients[24,32,33]. No study has assessed the efficacy of statins to reduce CHD mortality in NAFLD patients, although the benefits are well-recognized for both the primary and secondary prevention of CHD and the reduction of overall mortality in the general population[34,35]. Thus, the benefit of statins for CHD prevention in NAFLD patients with dyslipidemia and/or a high calculated risk of coronary heart disease by the FRS should be considered[36,37].

The main strengths of our study are the inclusion of NAFLD patients from the community along with the long-term follow-up. All patients had complete data for calculation of the NFS at the time of NAFLD diagnosis and at the end of the follow-up. The exclusion of known CHD or liver cirrhosis with complications at baseline is important to reduce the overestimation of the incidence of primary endpoints or mortality rate during the follow-up period.

Our study has several limitations. First, only 6.6% of the patients with a low probability of advanced liver fibrosis died, which was less than expected (10%) by a sample size calculation and may affect the power of the study. Second, most of our patients in Olmsted County are white, and recent data showed that non-Caucasian

Table 7 Comparison of nonalcoholic fatty liver disease patients with and without death after excluding those with established type 2 diabetes at baseline (n = 254) n (%) (mean ± SD)

Variables	NAFLD patients without death (n = 226)	NAFLD patients with death (n = 28)	P value
Age (yr)	44.5 ± 11.5	59.2 ± 14.3	< 0.0001
Sex (% male)	113 (50)	10 (35.7)	0.11
History of hypercholesterolemia	56 (24.8)	9 (32.1)	< 0.0001
Obesity	164 (72.6)	22 (78.6)	0.34
BMI (kg/m^2)	33.5 ± 6.2	35.0 ± 6.6	0.25
Platelet count (× 10^9/mm^3)	241 ± 58	242 ± 87	0.98
Glucose (mg/dL)	215.7 ± 46.6	215.7 ± 46.6	
Cholesterol (mg/dL)	215 ± 48	219 ± 56	0.72
HDL-cholesterol (mg/dL)	42 ± 12	43 ± 20	0.76
AST (U/L)	42.0 ± 23.0	39.7 ± 21.0	0.62
ALT (U/L)	65.7 ± 45.0	50 ± 29	0.02
AST/ALT ratio	0.76 ± 0.38	0.93 ± 0.57	0.14
ALP(U/L)	184 ± 66	246 ± 179	0.09
GGT (U/L)	132 ± 41	142 ± 36	0.32
Albumin (g/dL)	4.3 ± 0.3	4.2 ± 0.4	< 0.0001
FRS	7.6 ± 6.2	10.5 ± 5.6	0.02
Calculated CHD risk (%)	15.3 ± 14.4	22.0 ± 18.8	0.076
NFS	-2.11 ± 1.15	-1.09 ± 1.61	0.003
NFS of intermediate or high probability of advanced liver fibrosis (%)	59 (26.1)	19 (67.9)	< 0.0001
B. During the follow-up periods			
Use of metformin	52 (23.0)	1 (3.6)	0.009
Use of aspirin	119 (52.7)	9 (32.1)	0.03
Use of simvastatin	90 (39.8)	3 (10.7)	< 0.0001
NFS change per year (median; IQR)	0.08 ± 0.08	0.12 ± 0.36	0.61

In order to avoid overestimation of the model, we excluded those variables used as a part of nonalcoholic fatty liver disease fibrosis score calculation (age, history of diabetes, aspartate aminotransferase/alanine aminotransferase ratio, platelet counts, albumin, body mass index and Framingham risk score). NAFLD: Nonalcoholic fatty liver disease; BMI: Body mass index; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; FRS: Framingham risk score; CHD: Coronary heart disease; NFS: NAFLD fibrosis score; ALP: Alkaline phosphatase; GGT: Glutamyltransferase; HDL: High-density lipoprotein.

Table 8 Multivariate logistic regression model showing OR (95%CI) of predictors for death in 254 patients with nonalcoholic fatty liver disease after excluding those with established type 2 diabetes at baseline

Multivariate analysis	P value	OR	95%CI
NAFLD fibrosis score at baseline	< 0.0001	1.92	1.4-2.7
Alkaline phosphatase	0.012	1.006	1.001-1.010

Model without interaction among 8 included variables; gender, nonalcoholic fatty liver disease fibrosis score at baseline, use of metformin, use of simvastatin, use of aspirin, history of hypercholesterolemia, alanine aminotransferase and alkaline phosphatase. NAFLD: Nonalcoholic fatty liver disease.

race was an important predictor of decreased survival[22]. With the relatively small sample size and the represented local population in the United States, our results are not necessarily applicable in other ethnic groups.

The current study is important because we extended the clinical use of the NFS system for predicting death or liver complications in NAFLD patients. A higher NFS at baseline and the presence of new-onset CHD can be used as prognostic predictors for mortality and liver complications among NAFLD patients. Further research is needed to validate the benefit of the NFS for predicting death or liver complications in NAFLD patients with other ethnic groups. The NFS is simpler and less invasive than liver biopsy for the initial evaluation of the degree of liver fibrosis in patients with NAFLD. The NFS should be calculated for all patients with NAFLD at initial consultation to estimate the probability of advanced liver fibrosis.

COMMENTS

Background

Nonalcoholic fatty liver disease (NAFLD) is one of the most common causes of chronic liver disease in Western countries. During an average 7.6 years of follow-up, 13% of the patients died, mainly from malignancy, coronary heart disease (CHD) and liver-related mortality.

Research frontiers

Another study revealed that the survival of patients with nonalcoholic steatohepatitis was reduced and that these patients died significantly more often from CHD and liver-related causes. Patients with more advanced liver fibrosis tend to have more liver complications than those without liver fibrosis.

Innovations and breakthroughs

A study from Japan validated the NAFLD Fibrosis Score and found it to have an acceptable sensitivity, specificity, and positive and negative predictive values for advanced liver fibrosis of 100%, 83%, 63%, and 100%, respectively.

Peer review

In this manuscript, the authors intend to evaluate whether the NAFLD fibrosis score could act as a prognostic predictor for mortality and liver complications among NAFLD patients. It is suggested that the NAFLD fibrosis score is a simple, non-invasive method for predicting prognosis in patients with NAFLD. In general, this paper is significant and of clinical importance.

Table 9 The association between the primary end point and the grading of the nonalcoholic fatty liver disease fibrosis score, classified into 2 subgroups, after excluding those with established type 2 diabetes at baseline *n* (%)

Grading of the NAFLD fibrosis score (*n* = 254)	Low prob. of advanced liver fibrosis (*n* = 176)	Intermediate prob. or High prob. of advanced liver fibrosis (*n* = 78)	*P* value
Presence of primary end point (*n* = 43; 17%)	20/176 (11.4)	23/78 (29.5)	< 0.0001
All-cause death (*n* = 28; 11%)	9/176 (5.1)	19/78 (24.4)	< 0.0001

NAFLD: Nonalcoholic fatty liver disease.

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