Supplementary Methods

Subjects and Definitions

First, we identified patients with 2 or more International Classification of Diseases–Ninth Revision–Clinical Modification or International Classification of Diseases–Tenth Revision–Clinical Modification nonalcoholic fatty liver disease (NAFLD) codes at least 30 days apart. The algorithm used at least 2 NAFLD codes to increase the disease specificity because NAFLD codes can include other causes of chronic liver disease, especially when used as an indication for an imaging test. From this initial cohort, we excluded patients with additional International Classification of Diseases–Ninth Revision–Clinical Modification or International Classification of Diseases–Tenth Revision–Clinical Modification codes of chronic diffuse parenchymal liver diseases, such as viral hepatitis, alcohol-related liver disease, cholestatic, autoimmune, congestive liver disease and others (Supplementary Table 1). Because focal diseases can be identified on imaging and region of interest can be drawn around the lesion for liver stiffness measurement (LSM), these diseases were not excluded as long as they were not diffuse. The decision to include/exclude focal and granulomatous diseases were made case by case basis. International Classification of Diseases codes were used solely to gather as much NAFLD patients as possible, not for the purpose of diagnosis or fibrosis quantification. The remaining subjects formed the final study cohort.

Magnetic Resonance Elastography

Each subject underwent magnetic resonance elastography (MRE), as part of the routine clinical evaluation of NAFLD with a 1.5T or 3.0T MR system (various models, GE Medical Systems, Milwaukee, WI). The MRE wave, stiffness, and anatomic images were analyzed by using an in-house, fully automated algorithm for hepatic stiffness measurements described by Dzyubak et al.[1] The mean LSM was automatically calculated for all patients. During chart review of every participant, the automated stiffness was compared to the reported kPa in the clinical radiology report. If the difference was found more than 1.0 kPa, cases were sent to a professional reader with over 12 years of experience in MRE and abdominal imaging (M.Y.) for reanalysis.

Statistical Analysis

Missing values for Model for End-Stage Liver Disease Sodium (30 of 178) were imputed using multivariate imputation by chained equations.[2] Using methods described by Rubin[3] and Lie et al,[4] results of 9 multivariate imputation by chained equations–imputed data sets were used to generate the hazard ratio, 95% confidence interval, and *P* values for the Cox regression model predicting the decompensation or death outcome.

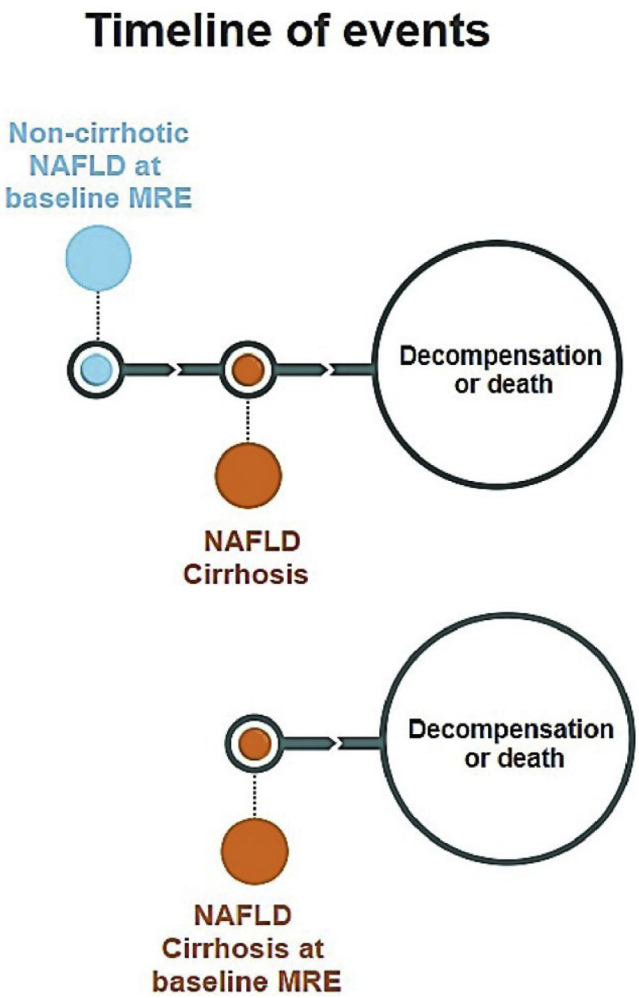
Spearman correlation was used to assess the agreement between LSM by MRE and fibrosis stage for the subset of participants with matched liver biopsy within 6 months of MRE. Increase in LSM per 1-stage increase in fibrosis stage was calculated. The statistical analyses were performed using R (version 3.4.2; R Foundation for Statistical Computing, Vienna, Austria) software package.

Supplementary Discussion

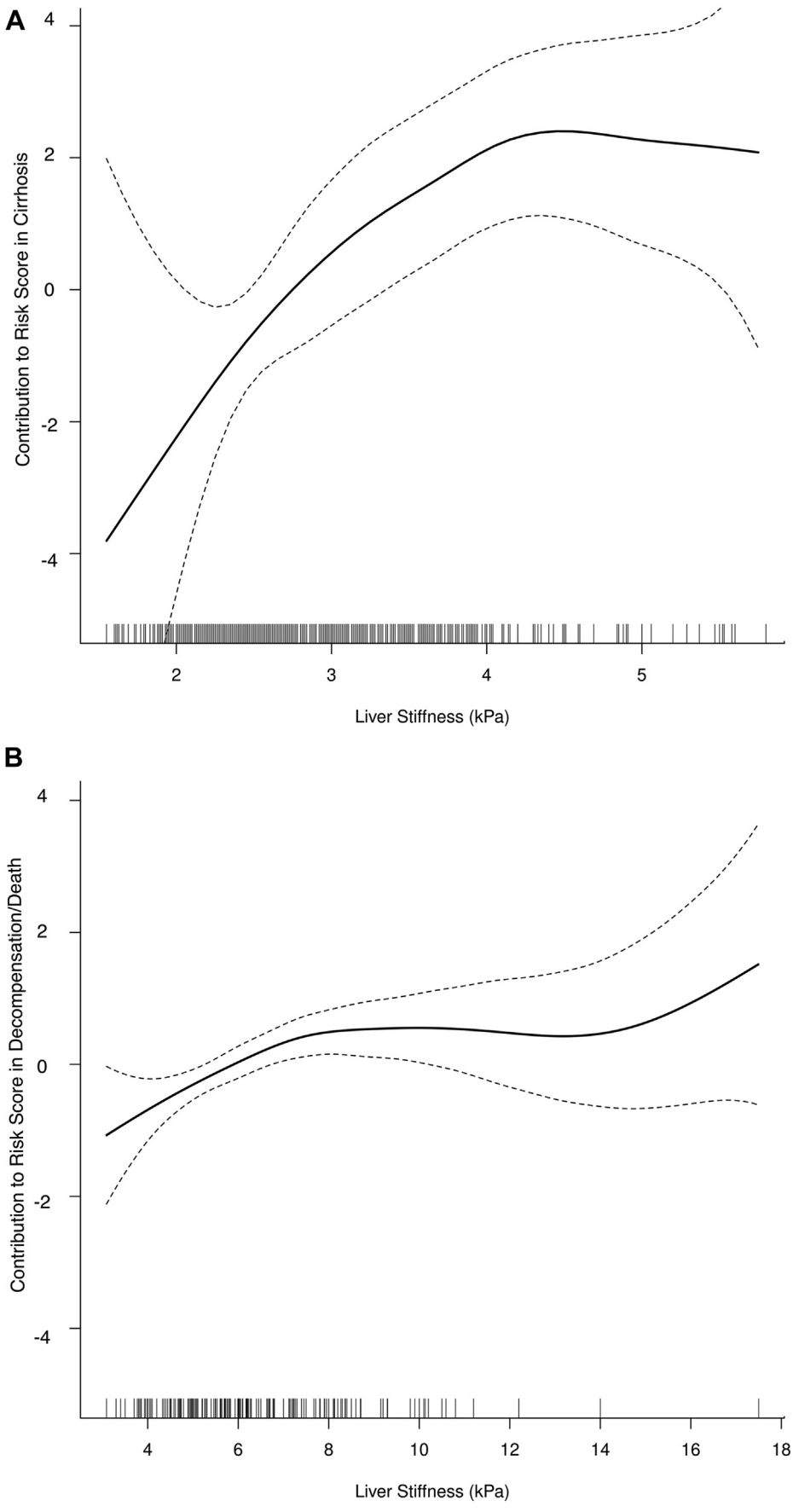
In this patient population of noncirrhotic NAFLD, the number of outcomes (n = 20 developed cirrhosis) allowed the inclusion of only 1 exploratory risk factor in addition to the predictor of interest (LSM). We chose age as the most important covariate, based on previous studies [5] demonstrating its importance as a risk factor for disease progression in NAFLD. Other covariates, such as diabetes mellitus, hypertension, and weight, are important candidates to consider in future larger studies.

Supplementary References

1. Dzyubak B, Glaser K, Yin M, et al. Automated liver stiffness measurements with magnetic resonance elastography. J Magn Reson Imaging 2013;38:371–379.
2. White IR, Royston P, Wood AM. Multiple imputation using chained equations: Issues and guidance for practice. Stat Med 2011;30:377–399.
3. Rubin DB. Multiple Imputation for Nonresponse in Surveys. New York, NY: Wiley, 1987.
4. Li KH, Raghunathan TE, Rubin DB. Large-sample significance levels from multiply imputed data using moment-based statistics and an F reference distribution. J Am Stat Assoc 1991;86:1065–1073.
5. Argo CK, Northup PG, Al-Osaimi AM, et al. Systematic review of risk factors for fibrosis progression in non-alcoholic steatohepatitis. J Hepatol 2009;51:371–379.



Supplementary Figure 1. Timeline of events including cirrhosis development and decompensation or death.



Supplementary Figure 2. P-splines for Liver Stiffness. (A) Predicting cirrhosis. (B) Predicting decompensation.

Supplementary Table 1. Codes for NAFLD Inclusion, Exclusion, Cirrhosis, and Decompensation

NAFLD inclusion codes		
I9	571.5	CIRRHOSIS OF LIVER WITHOUT MENTION OF ALCOHOL
I9	571.8	OTHER CHRONIC NONALCOHOLIC LIVER DISEASE
I9	571.9	UNSPECIFIED CHRONIC LIVER DISEASE WITHOUT MENTION OF ALCOHOL
I10	K74.60	UNSPECIFIED CIRRHOSIS OF LIVER
I10	K74.69	CIRRHOSIS CRYPTOGENIC (HCC)
I10	K75.81	NONALCOHOLIC STEATOHEPATITIS (NASH)
I10	K76.0	FATTY (CHANGE OF) LIVER, NOT ELSEWHERE CLASSIFIED
NAFLD exclusion codes		
I9	303.00-03	Acute alcoholic intoxication
I9	303.90-93	OTHER AND UNSPECIFIED ALCOHOL DEPENDENCE
I9	571.0-3	CHRONIC ALCOHOLIC LIVER DISEASE
I9	571.1	ACUTE ALCOHOLIC HEPATITIS
I9	571.6	Biliary cirrhosis
I9	275.01	HEREDITARY HEMOCHROMATOSIS
I9	070.0-9	VIRAL HEPATITIS
I9	072.71	MUMPS HEPATITIS
I9	091.62	Secondary syphilitic hepatitis
I9	130.5	Hepatitis due to toxoplasmosis
I9	571.42	Autoimmune hepatitis
I9	571.49	OTHER CHRONIC HEPATITIS
I9	573.1	HEPATITIS IN VIRAL DISEASES CLASSIFIED ELSEWHERE
I9	573.2	Hepatitis in other infectious diseases classified elsewhere
I9	573.3	HEPATITIS, UNSPECIFIED
I9	V02.60-9	Carrier or suspected carrier of viral hepatitis
I9	576.1	CHOLANGITIS
I10	F10.1-99	ALCOHOL ABUSE
I10	K70.0-9	ALCOHOLIC LIVER DISEASE
I10	K74.3	Cirrhosis Biliary Primary (HCC)
I10	K74.4	SECONDARY BILIARY CIRRHOSIS
I10	K74.5	Cirrhosis Biliary (HCC)
I10	K76.89	OTHER SPECIFIED DISEASES OF LIVER
I10	K76.9	LIVER DISEASE, UNSPECIFIED
I10	E83.110-9	HEMOCHROMATOSIS
I10	A18.83	Tuberculosis of digestive tract organs, not elsewhere classified
I10	A51.45	Secondary syphilitic hepatitis
I10	B00.81	Herpesviral hepatitis
I10	B15-19	VIRAL HEPATITIS
I10	B25.1	Cytomegaloviral hepatitis
I10	B26.81	Mumps hepatitis
I10	B58.1	Toxoplasma hepatitis

Supplementary Table 1. Continued

I10	B94.2	Sequelae of viral hepatitis
I10	K71.2-6	TOXIC LIVER DISEASE WITH HEPATITIS
I10	K73.0-9	Chronic hepatitis, not elsewhere classified
I10	K75.2	Nonspecific reactive hepatitis
I10	K75.3	GRANULOMATOUS HEPATITIS, NOT ELSEWHERE CLASSIFIED
I10	K75.4	Hepatitis Autoimmune
I10	O98.413	Viral hepatitis complicating pregnancy, childbirth and the puerperium
I10	P35.3	Congenital viral hepatitis
I10	Z22.50-9	Carrier of viral hepatitis
I10	K83.0	Cholangitis Acute
CIRRHOSIS codes		
I9	571.5	CIRRHOSIS OF LIVER WITHOUT MENTION OF ALCOHOL
I10	K74.60	UNSPECIFIED CIRRHOSIS OF LIVER
I10	K74.69	Cirrhosis Cryptogenic (HCC)
DECOMPENSATION codes		
I9	785.59	OTHER SHOCK WITHOUT MENTION OF TRAUMA
I9	456.0	Esophageal Varix With Bleeding
I9	456.20	ESOPHAGEAL VARICES IN DISEASES CLASSIFIED ELSEWHERE, WITH BL
I9	155.1	MALIGNANT NEOPLASM OF INTRAHEPATIC BILE DUCTS
I9	155.0	MALIGNANT NEOPLASM OF LIVER, PRIMARY
I9	572.2	HEPATIC ENCEPHALOPATHY
I9	572.4	HEPATORENAL SYNDROME
I9	567.23	SPONTANEOUS BACTERIAL PERITONITIS
I9	50.59	Other Transplant of Liver
I9	996.82	COMPLICATIONS OF TRANSPLANTED LIVER
I9	V42.7	LIVER REPLACED BY TRANSPLANT
I9	456.0	Esophageal Varix With Bleeding
I9	456.1	ESOPHAGEAL VARICES WITHOUT MENTION OF BLEEDING
I9	456.20-1	ESOPHAGEAL VARICES IN DISEASES CLASSIFIED ELSEWHERE
I10	R18.8	Other ascites
I10	I85.01	ESOPHAGEAL VARICES WITH BLEEDING
I10	I85.11	Secondary esophageal varices with bleeding (HCC)
I10	C22.1	Cholangiocarcinoma (HCC)
I10	C22.0	Malignant Neoplasm Of Liver Hepatocellular (HCC)
I10	K72.91	HEPATIC FAILURE, UNSPECIFIED WITH COMA
I10	K76.7	HEPATORENAL SYNDROME
I10	I85.00	Varix Esophageal (HCC)
I10	I85.10	Secondary esophageal varices without bleeding (HCC)
I10	K65.2	Spontaneous bacterial peritonitis (HCC)
I10	0FY00Z0-2	TRANSPLANTATION OF LIVER
I10	T86.40	Complication Liver Transplant (HCC)
I10	T86.41	LIVER TRANSPLANT REJECTION

Supplementary Table 1. Continued

I10	T86.42	Liver transplant failure (HCC)
I10	T86.43	LIVER TRANSPLANT INFECTION
I10	T86.49	Other complications of liver transplant (HCC)
I10	Z94.4	LIVER TRANSPLANT STATUS
I10	I85.00	Varix Esophageal (HCC)
I10	I85.01	ESOPHAGEAL VARICES WITH BLEEDING
I10	I85.10	Secondary esophageal varices without bleeding (HCC)
I10	I85.11	Secondary esophageal varices with bleeding (HCC)

HCC, hepatocellular carcinoma.

Supplementary Table 2. Distribution of Baseline Non-cirrhotic Patients With Matched LSM and Fibrosis Stage Per Biopsy

		Fibrosis stage				
		0	1	2	3	4
LSM	<3	2	5	3	0	0
	3–3.5	3	2	1	0	0
	3.5–4	1	2	1	1	0
	4–5	0	0	1	7	0
	5+	0	0	3[a]	0	0

LSM, liver stiffness measurement.
[a]Of the 3 patients with fibrosis stage 2 and LSM >5 kPa had superimposed conditions in addition to nonalcoholic steatohepatitis (1 had sarcoidosis, 1 had a 2.4-cm focal nodular hyperplasia) while 1 had cross-sectional imaging supportive of cirrhosis and suboptimal liver sample with 4 portal tracts). Spearman correlation = 0.6.

Supplementary Table 3. Distribution of Baseline Compensated Cirrhotic Patients With Matched LSM and Fibrosis Stage Per Biopsy

		Fibrosis stage				
		0	1	2	3	4
LSM	<3					
	3–3.5					
	3.5–4			0	0	1
	4–5			0	1	4
	5+			1[a]	6[a]	19

LSM, liver stiffness measurement.
[a]Among the 7 patients with LSM >5 kPa and fibrosis stage <4, all had cross-sectional imaging supportive of cirrhosis (nodular liver, portal hypertension, splenomegaly), supporting the underestimation of fibrosis stage by biopsy.