



Association of Components of Metabolic Syndrome and the Progression of Nonalcoholic Fatty Liver Disease

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Abstract

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CONFLICTS OF INTEREST

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INTRODUCTION: The effects of metabolic syndrome (MetS), its individual components, and baseline liver histology, on the rates of progression and regression of nonalcoholic fatty liver disease (NAFLD), were evaluated.

METHODS: We conducted a post hoc analysis of a multicenter prospective cohort study using the noninterventional registry of the Nonalcoholic Steatohepatitis Clinical Research Network (2002–2022). We included patients aged 18 years or older with biopsy-proven NAFLD. Outcomes included progression/regression of histology defined by changes in NAFLD Activity Score, nonalcoholic steatohepatitis, or fibrosis. Crude incidence rates were compared among patients with MetS vs those without using Kaplan-Meier curves and log-rank test. Cox proportional hazard models were used to estimate effects of MetS and its components on the fibrosis progression/regression.

RESULTS: We included 452 patients; the mean age was 51 years, one-third was male, and 85% was White. The median follow-up was 4.3 (range: 1–15.6) years. At baseline, patients with MetS, large waist circumference, and impaired glucose tolerance/diabetes had worse ballooning and fibrosis scores and a higher prevalence of definite nonalcoholic steatohepatitis than those without. MetS was not associated with fibrosis progression or regression. Impaired glucose tolerance/diabetes was associated with a higher risk of fibrosis progression (adjusted hazard ratio = 1.61; 95% confidence interval: 1.11–2.34) whereas hypertension was associated with a lower risk (adjusted hazard ratio = 0.64; 95% confidence interval: 0.43–0.96).

DISCUSSION: In the cohort of patients with NAFLD, MetS was associated with greater histological severity at baseline but was not a risk factor of disease progression or regression. Impaired glucose/diabetes was associated with a higher rate and hypertension with a lower rate of fibrosis progression.

Keywords

metabolic syndrome; nonalcoholic fatty liver disease; disease progression; nonalcoholic steatohepatitis

INTRODUCTION

Between one-fourth and one-third of the global adult population are estimated to have nonalcoholic fatty liver disease (NAFLD) (1,2). NAFLD is present in two-thirds of patients with T2DM or obesity (3,4). Among patients with T2DM undergoing liver biopsy, half had nonalcoholic steatohepatitis (NASH) and one-third had advanced fibrosis (5). NAFLD is currently the second most common indication for liver transplantation in the United States (2,6–9).

Metabolic syndrome (MetS) is characterized by the presence of 3 or more of the following factors: large waist circumference, impaired fasting glucose or diabetes, low high-density lipoprotein (HDL), hypertriglyceridemia, and hypertension (10). The prevalence of MetS in US adults increased from 25% in 1988–1994 to 34% in 2007–2012 (11). Patients with MetS compared with those without MetS have greater risk of developing T2DM, cardiovascular disease, advanced fibrosis, NASH, and hepatocellular carcinoma (12–14). However, little is known about the impact of MetS or its individual components on rates of progression

and regression of NAFLD. Identifying risk factors of NAFLD progression will help identify high-risk populations and design effective screening programs for early interventions to reduce the overall burden of NAFLD and its consequences (15,16). In this study, we aimed to identify the impact of MetS and its components and baseline liver histology on the rates of progression and regression of NAFLD in adult patients in the NASH Clinical Research Network (NASH CRN) database.

PATIENTS AND METHODS

Study design and study population

We used data from the noninterventional registry of NASH CRN which included participants from NAFLD Databases 1–3 ([NCT01030484](#) for database 2 and [NCT04454463](#) for database 3) (from 2002 to 2022) and those in the placebo arms of the Pioglitazone versus Vitamin E versus Placebo for the Treatment of Nondiabetic Patients with Nonalcoholic Steatohepatitis (PIVENS) ([NCT00063622](#)) and Farnesoid X nuclear receptor ligand obeticholic acid for non-cirrhotic, non-alcoholic steatohepatitis (FLINT) ([NCT01265498](#)) trials (17,18). All participants were outpatient. The institutional review board at each participating clinical center and data coordinating center approved the study. Written informed consents were obtained from all patients.

Participants aged 18 years or older with biopsy-proven NAFLD were eligible if they also had paired biopsies (1 year apart) and MetS data, with physical examination and laboratory findings within 6 months of biopsies. Participants who consumed on average >14 and >7 alcohol drinks/wk for men and women, respectively, based on the Alcohol Use Disorders Identification Test questionnaire were excluded, as were those who had non-evaluable biopsy samples, were enrolled in the active arms of the PIVENS and FLINT trials, or had bariatric surgery, liver transplant, hepatocellular carcinoma, viral hepatitis or other chronic liver diseases, and missing data. The terminology for NAFL, NAFLD, or NASH has been recently changed to MASL, MASLD, or MASH (19). However, our results are unchanged because only 7 of 3,343 patients (0.021%) in the database did not have the metabolic risk factors used in the new terminology.

Clinical and laboratory data

Based on the National Cholesterol Education Program's Adult Treatment Panel III report, MetS was defined as having at least 3 of the following 5 risk factors: waist circumference ≥35 inches for women and ≥40 inches for men; a fasting blood sugar level ≥100 mg/dL, having a diagnosis of or being on medicine for diabetes; fasting HDL cholesterol <50 mg/dL for women and <40 mg/dL for men or being on medicine to treat low HDL cholesterol; fasting triglycerides ≥150 mg/dL or having a diagnosis of and being on medicine for hyperlipidemia; and systolic blood pressure (BP) ≥130 mm Hg or diastolic BP ≥85 mm Hg or having a diagnosis of and being on medicine for hypertension (20).

Outcome measures

Study outcomes included rates of fibrosis progression and regression, change in the NASH diagnosis, and overall histological change. Details on histological assessment are in the

Supplementary Digital Content, see <http://links.lww.com/AJG/D626>. Fibrosis progression was defined as an increase of 1 point and regression as a reduction of 1 point in fibrosis stage between biopsies (17,18,21). NASH progression were defined as the development of either borderline (among patients with no NASH at baseline) or definite NASH (among patients with no/borderline NASH at baseline), and regression as having no or borderline NASH at follow-up (for patients with definite NASH at baseline) or having no NASH at follow-up (for patients with borderline NASH or definite NASH at baseline). Regarding overall histological change, progression was defined as an increase by 2 points of NAFLD Activity Score (NAS) with 1 of which was increase in ballooning and regression as a decrease by 2 NAS points with 1 of which was decrease in ballooning and without worsening of fibrosis. NAS was calculated as the sum of steatosis, lobular inflammation, and hepatocellular ballooning scores (21).

Statistical analysis

Descriptive statistics, including the Fisher exact test for categorical variables and analysis of variance or *t* test for continuous variables, were used to compare characteristics between patients with and without baseline MetS. The rate of progression/regression was estimated using crude incidence rate (IR) and 95% confidence interval (CI), calculated as the number of new events divided by the total number of person-years. The follow-up duration was from October 2004 to March 2022. The time to event was defined as the time from enrollment (baseline) to the earliest date of event. Patients who did not experience an event at the end of follow-up were censored. Crude IR and incidence rate ratio with 95% CIs were compared between those with vs without MetS and with vs without each MetS component. The difference between groups was examined using Kaplan-Meier curves and the log-rank test. We excluded patients with baseline fibrosis stage 4 (F4) from the analysis for fibrosis progression and patients with F0 from the analysis for regression. We also excluded patients with baseline definite NASH from the analysis for NASH progression and those without NASH from the analysis for regression. Finally, we excluded patients with a baseline NAS of 7 or a ballooning score of 2 from the analysis for overall histological progression and patients with a ballooning score of 0 or F4 from the analysis for regression.

Cox proportional hazard models were used to estimate the effect of baseline MetS on fibrosis progression/regression, adjusted for patients' characteristics. We assessed 3 different exposures of interest: MetS (yes/no), 5 individual MetS components (5 yes/no responses) together, and number of MetS components. For each set of exposure, we generated 3 models: (i) unadjusted, (ii) adjusted for demographics (age, sex, race, ethnicity), and (iii) adjusted for demographics and histological variables (baseline fibrosis stage and NASH status). As a change in MetS status and its components over time could affect disease progression/regression, we conducted a secondary analysis for the fibrosis outcome. Specifically, we estimated crude IRs by MetS status. Patients were considered to have MetS improved if they had 3 MetS criteria at baseline but <3 at follow-up and worsened if they had <3 criteria at baseline and 3 at follow-up. We also ran 3 Cox models: a. including temporal changes in waist circumference, glucose, HDL, triglyceride, and systolic BP as independent variables; b. further adjusting for demographics; and c. further adjusting for demographics and histology. Statistical significance was defined as a *P* value of <0.05,

and no adjustments were made for multiple comparisons. We assessed the proportionality assumption by using the Schoenfeld and scaled Schoenfeld residuals and used Stata v.16.1.

RESULTS

Sample characteristics

Among 452 included patients, 85.4% had MetS, two-thirds had definite NASH, and half had F 2 at baseline (Table 1). The mean follow-up duration was 4.3 (range: 1–15.6) years. The mean age was 51.1 years, one-third were male, and 85.4% were White. The mean body mass index was 34.8 kg/m², and 46.7% had T2DM. Compared with patients without MetS, those with MetS were older; less likely to be Hispanic/Latino; had higher body mass index; used more metformin, lipid-lowering, and hypertension medication; and had lower HDL cholesterol and higher triglycerides, glucose, insulin, and Homeostatic Model Assessment of Insulin Resistance (all *P* values <0.05). Histologically, patients with MetS had worse mean scores for ballooning (1.20 vs 0.98; *P* value = 0.039) and fibrosis (1.74 vs 1.32; *P* value = 0.003) and higher prevalence of definite NASH (68.9% vs 54.5%; *P* value = 0.001) than those without MetS. Further details on patient characteristics are presented in S.Tables 1–5

Progression and regression of fibrosis

Overall, 150 patients (33.2%) experienced fibrosis progression and 103 (22.8%) had regression. We included 431 patients for progression analysis and 357 patients for regression analysis (see Supplementary Table 6, <http://links.lww.com/AJG/D626>).

In patients with MetS, the cumulative incidence of fibrosis progression was 26.6%, 59.6%, and 95.4% whereas that of fibrosis regression was 25.5%, 55.2%, and 71.5% after 5, 10, and 15 years of follow-up, respectively. Fibrosis progression rate did not differ between patients with vs without MetS (0.079 vs 0.074/person-year; *P* value = 0.92) or between those with vs without each individual MetS component (Table 2, Figure 1), neither did regression rates (all *P* values >0.05).

In both adjusted and unadjusted analyses, baseline MetS was not associated with fibrosis progression (adjusted hazard ratio [aHR] = 0.90; 95% CI: 0.56–1.45) or regression (aHR = 1.01; 95% CI: 0.54–1.90) (Table 3). Having more MetS components was also not associated with progression or regression. When individual components were included together, impaired glucose/diabetes was associated with a higher risk of fibrosis progression (aHR = 1.61; 95% CI: 1.11–2.34) whereas hypertension was associated with a lower risk (aHR = 0.64; 95% CI: 0.43–0.96) (Table 3). In addition, having definite NASH at baseline was a risk factor of fibrosis progression, whereas being Hispanic and having a higher baseline fibrosis stage were associated with a decreased risk (see Supplementary Table 7, <http://links.lww.com/AJG/D626>). No individual MetS component was associated with fibrosis regression. Older ages, being White, and having borderline or definite NASH were associated with a decreased rate, whereas a higher baseline fibrosis stage was associated with an increased rate of regression (see Supplementary Table 8, <http://links.lww.com/AJG/D626>).

In secondary analysis, we included 419 patients of whom 37 (8.8%) did not have MetS at baseline and follow-up, 26 (6.2%) developed MetS, and 31 (7.4%) no longer had MetS at follow-up. Three-fourth of patients (N = 325) remained having MetS during the study period. MetS status change was not associated with fibrosis progression, but patients whose MetS did not improve (or worsened) had a lower incidence of regression than those whose MetS improved or who never had MetS ($P = 0.017$) (see Supplementary Tables 9 and 10, <http://links.lww.com/AJG/D626>). In the fully adjusted model, a one unit increase in systolic BP over time were associated with slower regression rate (aHR = 0.98; 95% CI: 0.97–0.99) (see Supplementary Table 11, <http://links.lww.com/AJG/D626>).

Progression and regression of NASH

In total, 67 (14.8%) developed NASH and 129 (28.5%) had NASH regression. We included 150 and 383 patients for progression and regression analysis, respectively. During a mean follow-up of 5.0 (SD = 3.3) and 4.2 (SD = 3.0) years, respectively, the overall incidence of NASH progression was 0.089/person-year (95% CI: 0.070–0.113), whereas that of NASH regression was 0.074/person-year (95% CI: 0.062–0.089). Patients with MetS had a similar incidence of NASH progression (0.092 vs 0.079/person-year; P value = 0.58) and regression (0.073 vs 0.084/person-year; P value = 0.46) as those without MetS, respectively (Table 4, Figure 1). No individual MetS components were associated with either progression or regression.

Progression and regression of overall histology

In total, 35 patients (7.7%) progressed histologically (as defined by a change in NAS) and 92 (20.4%) regressed. We finally included 253 patients for histological progression analysis and 317 patients for regression. During a mean follow-up of 4.5 years (SD = 3.1), the overall incidence of histological progression was 0.031/person-year (95% CI: 0.022–0.043) whereas during a mean follow-up of 4.2 years (SD = 2.9), the incidence of histological regression was 0.069/person-year (95% CI: 0.057–0.085). Patients with MetS had similar rates of histological progression (0.033 vs 0.023/person-year; P value = 0.48) and regression (0.067 vs 0.090/person-year; P value = 0.16) as those without MetS (Table 5, Figure 1). No MetS components were associated with histological progression, but patients with hypertension regressed more slowly than those without hypertension (0.063 vs 0.101/person-year, P value = 0.01) (see Supplementary Fig. 1, <http://links.lww.com/AJG/D626>).

DISCUSSION

In this study, we found that although MetS was associated with more advanced disease at baseline, MetS and a higher number of components were not significantly associated with fibrosis progression or regression. Impaired glucose/diabetes was associated with a higher risk whereas hypertension was associated with a lower risk of fibrosis progression after controlling for all MetS components and individual factors. In addition, having definite NASH at baseline was a significant risk factor of fibrosis progression, whereas being Hispanic and having a higher baseline fibrosis stage were associated with a decreased risk. By contrast, no individual MetS component was associated with fibrosis regression. Older age, White ethnicity, and having borderline/definite NASH were associated with decreased

rates of regression, whereas a higher baseline fibrosis stage was associated with an increased rate. In secondary analysis, MetS status change did not affect fibrosis progression, but a lack or an improvement in MetS was associated with faster regression. In addition, an increase in systolic BP over time was associated with slower regression rate. These findings suggest that individual components of MetS and the actual changes in biomarkers may have variable effects on disease progression. Patients with impaired glucose/diabetes should have targeted surveillance and more intensive management. It is also important to assess specific metabolic factors independently, rather than relying solely on the presence of MetS to guide risk stratification. Our study also underscores the importance of baseline histology, especially definite and borderline NASH, in predicting fibrosis progression and regression. As an increase in fibrosis stage is known to predict a higher risk of mortality, transplantation, and liver-related events, early intervention to address NASH may be crucial in preventing worse long-term outcomes (22–24). As details on antihypertensive medications are not consistently available, it is possible that previous reports of the potential beneficial effects of angiotensin inhibitors in NASH can explain our surprising observation regarding the protective effect of hypertension on fibrosis progression (25,26).

Previous studies have shown that patients with MetS were more likely to have advanced fibrosis, cirrhosis, liver cancer, and liver-related and overall mortality than those without. Moreover, these risks increased with the increasing number of MetS components (13,15,27–29). Higher levels of blood glucose, plasma triglycerides, and waist circumference were independently associated with both incidence and prevalence of NAFLD (30–32). Yet, few studies have explored the association between MetS and fibrosis progression and regression longitudinally (33). A meta-analysis revealed that MetS was not significantly associated with progressive fibrosis (OR = 0.63; 95% CI: 0.32–1.25) while hypertension was (34). Meanwhile, the effect of T2DM on fibrosis progression was inconsistent because it was significant in one study (adjusted odds ratio = 6.25; 95% CI: 1.88–20.00) (35) but not in another (OR = 1.05; 95% CI: 0.64–1.72) (34). However, these studies did not report time-to-event analysis as shown in our study, which may explain the difference in findings. Using the NASH CRN database, a recent study did not directly incorporate the temporal aspect of the data (36) while another reported that T2DM was significantly associated with an increased risk of fibrosis progression but not regression (37). Neither of these studies, however, examined MetS, individual components in the presence of all other components, or temporal changes of the 5 biomarkers. Our study is among the first to report this relationship while controlling for potential confounders, but it needs to be confirmed in future research.

We also found a lack of association between MetS and NASH progression/regression. In cross-sectional studies, patients with MetS or diabetes had increased odds of NASH compared with those without and the probability of definite NASH increased with the increasing number of MetS components (13,29,38). A potential explanation for our nonsignificant finding was the higher rate of statin use in patients with MetS than in those without MetS (36% vs 7.6%), as statins were shown to decrease the risk of NAFLD-related complications (39–41).

In our patient cohort, histological regression was more common than progression (20% vs 8%, respectively), consistent with a previous meta-analysis (42). There was also no

significant association between MetS or individual components and histological progression or regression, except for hypertension, which was associated with slower regression rate in unadjusted analysis. The underlying mechanism remains unclear, although hypertension can increase oxidative stress, which can increase inflammation and fibrosis in the liver. Sample size and event occurrence limitations prevented multivariable modeling to confirm whether the inverse association between hypertension and histological regression would hold.

Our study has several strengths. First, we included more than 450 well-characterized patients with biopsy-proven NAFLD, which is one of the largest cohorts of prospectively followed patients to date. Second, we used a rigorous methodology to define and diagnose NAFLD, including the use of liver biopsies and expert pathologists. Third, we had a mean follow-up of 4.4 years, allowing us to capture both short-term and long-term outcomes. Fourth, we carefully assessed changes in several histological aspects and adjusted for potential confounding factors. Finally, we conducted sensitivity analysis to preliminarily explore the impact of changes in MetS status on fibrosis progression/regression.

Limitations include the lack of representativeness of the NASH CRN database which comprised patients being outpatient and referred from large academic medical centers, selection bias with all subjects selected for liver biopsy who often had higher rate of advanced liver disease and differed systematically from those managed noninvasively, and potential misclassification of patients with metabolic dysfunction-associated steatotic liver disease and moderate-to-high alcohol consumption. With >85% of the cohort having MetS at baseline and an overall low rate of fibrosis progression, there was a potential for a type II error. As a result, null findings in our analyses should be interpreted with caution. Some factors influencing disease progression, such as dietary habits and physical activity, and patient adherence to lifestyle recommendations are not available. Subjects who died after baseline and without follow-up biopsies may bias the results. Adjusted analysis for NASH and overall histological change could not be performed because of limited sample size. Treatments for comorbidities that patients received during follow-up could not be accounted for fully. Finally, the mean follow-up of 4.4 years may not be enough to observe a shift in fibrosis stages.

In conclusion, MetS and its individual components were not significantly associated with progression/regression of fibrosis, NASH, or overall histology in patients with biopsy-proven NAFLD. When all 5 individual components were controlled for together, impaired glucose/diabetes was associated with a higher risk, whereas hypertension was associated with less risk of fibrosis progression. Although MetS is a known risk factor of developing NAFLD, its status at baseline may not play a major role in disease progression or regression. However, change of MetS status may be important and warrants further investigation. An increase in systolic BP was associated with slower fibrosis regression. The findings underscore the importance of accounting for baseline histology in predicting disease progression and addressing individual metabolic abnormalities in NAFLD management.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Potential competing interests:

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Study Highlights

WHAT IS KNOWN

- Metabolic syndrome (MetS) is associated with higher risk of nonalcoholic steatohepatitis, advanced fibrosis, and liver cancer.
- The risk of liver-related complications increases with an increasing number of MetS components.

WHAT IS NEW HERE

- MetS was not associated with the progression/regression of nonalcoholic fatty liver disease.
- Impaired fasting glucose/type 2 diabetes and hypertension were associated with higher and lower risk of fibrosis progression, respectively.
- Neither MetS nor any components were associated with progression/regression of nonalcoholic steatohepatitis or overall histology.

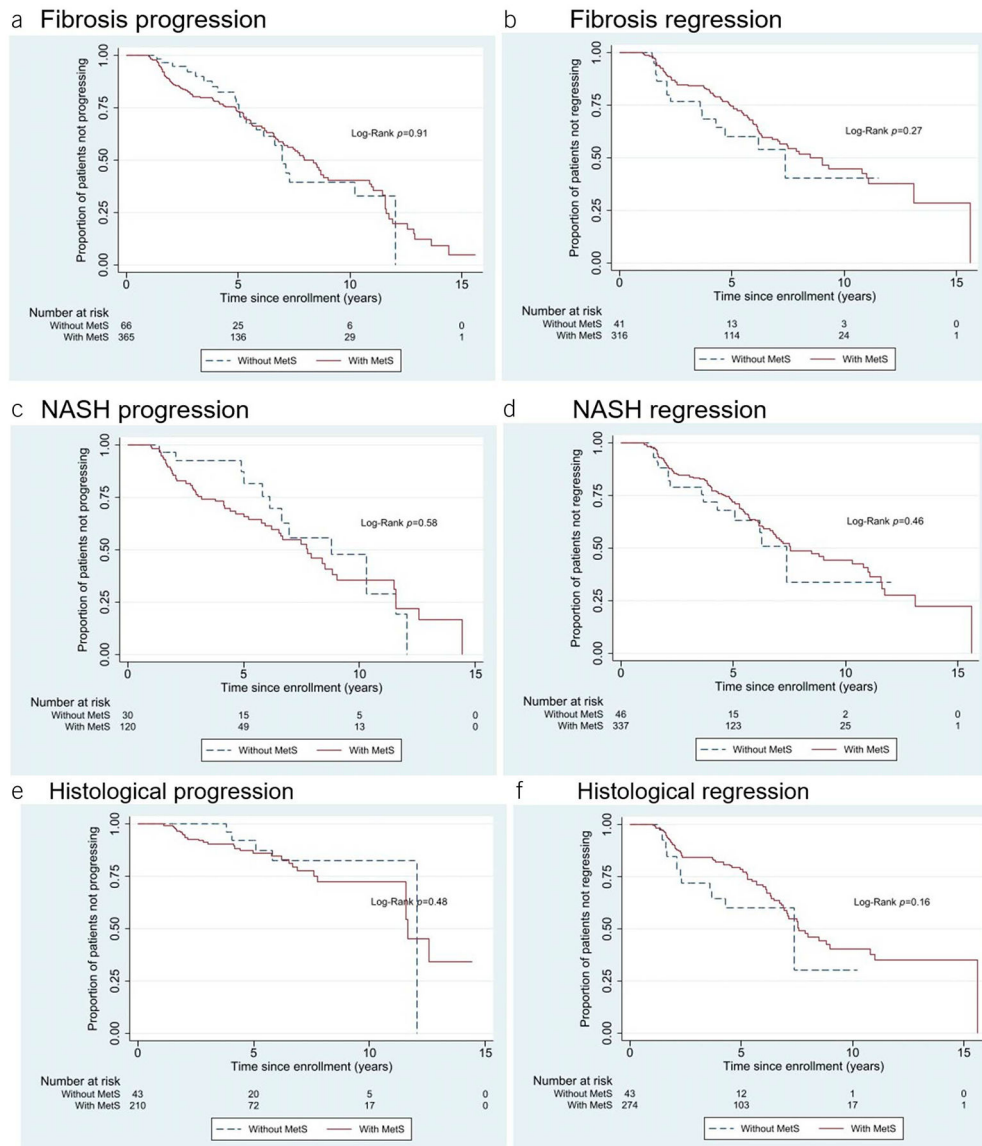


Figure 1. Kaplan-Meier curves of progression and regression by metabolic syndrome status. Fibrosis progression was defined as an increase of 1 point and regression as a reduction of 1 point on fibrosis score between biopsies. NASH progression was defined as the development of either borderline (among patients with no NASH at baseline) or definite NASH (among patients with no or borderline NASH at baseline), and regression as having no or borderline NASH at a follow-up liver biopsy (for patients with definite NASH at baseline) or having no NASH at follow-up (for patients with borderline NASH at baseline). Histological progression was defined as an increase by 2 points of NAS with 1 of which was increase in ballooning and regression as a decrease by 2 NAS points with 1 of which was decrease in ballooning and without worsening of fibrosis. NAFLD, nonalcoholic fatty liver disease; NAS, NAFLD Activity Score; NASH, nonalcoholic steatohepatitis.

Table 1.

Baseline characteristics by the presence of metabolic syndrome

Patient characteristics	Without metabolic syndrome (N = 66)	With metabolic syndrome (N = 386)	Total (N = 452)	P value
Demographics				
No.	66	386	452	
Age at biopsy, mean (SD), y	47.9 (12.1)	51.6 (11.4)	51.1 (11.6)	0.02
Male, no. (%)	27 (40.9)	134 (34.7)	161 (35.6)	0.33
White race, no. (%)	56 (84.8)	330 (85.5)	386 (85.4)	0.85
Hispanic or Latino, no. (%)	14 (21.2)	33 (8.5)	47 (10.4)	<0.01
MetS component count, no. (%)				
Increased waist	45 (68.2)	356 (92.2)	401 (88.7)	<0.01
Impaired glucose/diabetes	14 (21.2)	270 (69.9)	284 (62.8)	<0.01
Low HDL cholesterol, mg/dL	15 (22.7)	339 (87.8)	354 (78.3)	<0.01
Hypertriglyceridemia	11 (16.7)	291 (75.4)	302 (66.8)	<0.01
Hypertension	29 (43.9)	325 (84.2)	354 (78.3)	<0.01
Type 2 diabetes, no. (%)	9 (13.6)	202 (52.3)	211 (46.7)	<0.01
Smoking history, no. (%)				
Current smoker	5 (7.6)	33 (8.5)	38 (8.4)	1.00
Ever smoked	30 (45.5)	188 (48.7)	218 (48.2)	0.69
Clinical and laboratory data				
BMI, mean (SD), kg/m ²	32.2 (6.4)	35.2 (6.2)	34.8 (6.3)	<0.01
ALT, mean (SD), U/L	88.1 (70.6)	76.7 (52.4)	78.3 (55.5)	0.12
AST, mean (SD), U/L	55.7 (36.6)	56.6 (41.5)	56.4 (40.8)	0.87
Alkaline phosphatase, mean (SD), U/L	80.9 (21.3)	84.4 (28.1)	83.9 (27.2)	0.33
Cholesterol, mean (SD), mg/dL				
LDL	116.5 (28.8)	115.7 (38.1)	115.8 (36.9)	0.87
HDL	53.9 (15.2)	41.4 (9.6)	43.2 (11.5)	<0.01
Triglycerides	118.1 (57.2)	183.3 (98.7)	173.8 (96.5)	<0.01
Glucose, mean (SD), mg/dL	90.9 (13.3)	112.8 (38.8)	109.6 (37)	<0.01
Insulin, mean (SD), μ U/mL	17.8 (12.5)	25.2 (22.4)	24.2 (21.4)	0.01
HOMA-IR, mean (SD)	4.1 (3.2)	7.4 (7.7)	6.9 (7.3)	<0.01

Patient characteristics	Without metabolic syndrome (N = 66)		With metabolic syndrome (N = 386)		Total (N = 452)	P value
	no. (%)		no. (%)			
Medication use, no. (%)						
Metformin	34 (51.5)		318 (82.4)		352 (77.9)	<0.01
Lipid lowering	7 (10.6)		134 (34.7)		141 (31.2)	<0.01
Statins	8 (12.1)		179 (46.4)		187 (41.4)	<0.01
Hypertension	5 (7.6)		139 (36)		144 (31.9)	<0.01
Vitamin E	17 (25.8)		254 (65.8)		271 (60)	<0.01
Vitamin E	2 (3)		64 (16.6)		66 (14.6)	<0.01
Histologic findings						
Hepatic steatosis (numeric score), no. (%)						
0 (5%)	1 (1.5)		11 (2.8)		12 (2.7)	0.24
1 (5%–33%)	25 (37.9)		128 (33.2)		153 (33.8)	
2 (34%–66%)	17 (25.8)		144 (37.3)		161 (35.6)	
3 (66%)	23 (34.8)		103 (26.7)		126 (27.9)	
Lobular inflammation score, foci per 20× high power field, no. (%)						
0 (none)	0 (0)		2 (0.5)		2 (0.4)	0.93
1 (<2)	29 (43.9)		178 (46.1)		207 (45.8)	
2 (2–4)	27 (40.9)		153 (39.6)		180 (39.8)	
3 (>4)	10 (15.2)		53 (13.7)		63 (13.9)	
Ballooning, no. (%)						
0 (none)	23 (34.8)		92 (23.8)		115 (25.4)	0.12
1 (few)	21 (31.8)		122 (31.6)		143 (31.6)	
2 (many)	22 (33.3)		172 (44.6)		194 (42.9)	
Portal inflammation score, no. (%)						
0 (none)	12 (18.2)		38 (9.8)		50 (11.1)	0.11
1 (mild)	37 (56.1)		253 (65.5)		290 (64.2)	
2 (more than mild)	17 (25.8)		94 (24.4)		111 (24.6)	
Baseline NAFLD activity score, mean (SD)	4.6 (1.6)		4.8 (1.6)		4.7 (1.6)	0.59
Fibrosis stage, no. (%)						
0 (none)	25 (37.9)		70 (18.1)		95 (21)	<0.01
1 (mild/moderate)	12 (18.2)		104 (26.9)		116 (25.7)	
2 (zone 3 and periportal)	12 (18.2)		91 (23.6)		103 (22.8)	
3 (bridging)	17 (25.8)		100 (25.9)		117 (25.9)	

Patient characteristics	Without metabolic syndrome (N = 66)	With metabolic syndrome (N = 386)	Total (N = 452)	P value
4 (cirrhosis)	0 (0)	21 (5.4)	21 (4.6)	
Interval between biopsies, mean (SD), yr	4.5 (3)	4.3 (3.1)	4.4 (3.1)	0.64
Biopsy length, mean (SD), mm	19.9 (11.2)	20.2 (9.3)	20.2 (9.6)	0.85
Steatohepatitis diagnosis				
NAFLD (not NASH)	20 (30.3)	49 (12.7)	69 (15.3)	<0.01
Borderline NASH	10 (15.2)	71 (18.4)	81 (17.9)	
Definite NASH	36 (54.5)	266 (68.9)	302 (66.8)	

P values derived from the Fisher exact test for categorical variables and analysis of variance for continuous variables.

ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; HDL, high-density lipoprotein; HOMA-IR, Homeostatic Model Assessment of Insulin Resistance; LDL, low-density lipoprotein; MetS, metabolic syndrome; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis.

Table 2. Incidence (per person-year) and incidence rate ratio of fibrosis progression and regression by metabolic syndrome status

Exposure	Without the exposure		With the exposure		Crude rate difference (95% CI)	Incidence rate ratio (95% CI)	P value
	No. of events	Incidence rate (95% CI)	No. of events	Incidence rate (95% CI)			
Fibrosis progression							
Metabolic syndrome	22	0.074 (0.048 to 0.112)	128	0.079 (0.067 to 0.094)	0.006 (-0.028 to 0.039)	1.080 (0.683 to 1.784)	0.37
Increased waist	16	0.064 (0.039 to 0.105)	134	0.081 (0.068 to 0.096)	0.020 (-0.018 to 0.051)	1.297 (0.748 to 2.267)	0.19
Impaired glucose/diabetes	52	0.067 (0.051 to 0.088)	98	0.087 (0.071 to 0.106)	0.025 (-0.005 to 0.045)	1.391 (0.917 to 1.852)	0.06
Low HDL cholesterol	32	0.077 (0.054 to 0.109)	118	0.079 (0.066 to 0.095)	0.002 (-0.028 to 0.032)	1.027 (0.690 to 1.570)	0.45
Hypertriglyceridemia	51	0.078 (0.060 to 0.103)	99	0.079 (0.065 to 0.096)	0.000 (-0.026 to 0.027)	1.003 (0.709 to 1.435)	0.50
Hypertension	34	0.087 (0.062 to 0.122)	116	0.076 (0.064 to 0.092)	-0.011 (-0.044 to 0.021)	0.873 (0.591 to 1.320)	0.24
Fibrosis regression							
Metabolic syndrome	14	0.086 (0.051 to 0.145)	89	0.066 (0.054 to 0.081)	-0.0198 (-0.067 to 0.027)	0.769 (0.435 to 1.464)	0.18
Increased waist	11	0.058 (0.032 to 0.105)	92	0.070 (0.057 to 0.085)	0.012 (-0.026 to 0.049)	1.198 (0.639 to 2.484)	0.30
Impaired glucose/diabetes	38	0.071 (0.052 to 0.098)	65	0.066 (0.052 to 0.085)	-0.005 (-0.032 to 0.023)	0.935 (0.617 to 1.434)	0.37
Low HDL cholesterol	22	0.073 (0.048 to 0.111)	81	0.067 (0.054 to 0.083)	-0.006 (-0.04 to 0.028)	0.919 (0.568 to 1.546)	0.36
Hypertriglyceridemia	38	0.078 (0.057 to 0.108)	65	0.063 (0.05 to 0.081)	-0.015 (-0.045 to 0.014)	0.806 (0.532 to 1.236)	0.15
Hypertension	22	0.085 (0.056 to 0.129)	81	0.065 (0.052 to 0.08)	-0.0207 (-0.059 to 0.018)	0.757 (0.468 to 1.274)	0.13

Fibrosis progression was defined as an increase of 1 point and regression as a reduction of 1 point on fibrosis score between biopsies.

CI, confidence interval; HDL, high-density lipoprotein.

Table 3.

Association between metabolic syndrome and its components and the progression and regression of fibrosis

	Progression HR (95% CI)	Regression HR (95% CI)
Model 1: unadjusted		
Metabolic syndrome (yes/no)	1.03 (0.65–1.61)	0.73 (0.42–1.29)
All 5 MetS components together		
Increased waist	1.48 (0.86–2.54)	1.27 (0.66–2.42)
Impaired glucose/diabetes	1.44 (1.02–2.04)	1 (0.67–1.5)
Low HDL cholesterol	0.96 (0.63–1.47)	0.92 (0.55–1.54)
Hypertriglyceridemia	1.07 (0.75–1.54)	0.87 (0.56–1.36)
Hypertension	0.73 (0.49–1.08)	0.72 (0.44–1.16)
No. of MetS components	1.08 (0.93–1.26)	0.91 (0.76–1.09)
Model 2: adjusted for demographics		
Metabolic syndrome (yes/no)	0.93 (0.59–1.47)	0.77 (0.43–1.38)
All 5 MetS components together		
Increased waist	1.46 (0.81–2.62)	2.08 (0.99–4.38)
Impaired glucose/diabetes	1.46 (1.02–2.09)	1.08 (0.71–1.66)
Low HDL cholesterol	0.93 (0.61–1.43)	0.78 (0.46–1.31)
Hypertriglyceridemia	1.12 (0.78–1.62)	0.94 (0.59–1.47)
Hypertension	0.71 (0.47–1.05)	0.84 (0.51–1.36)
No. of MetS components	1.08 (0.92–1.26)	0.97 (0.8–1.17)
Model 3: adjusted for demographics and histology		
Metabolic syndrome (yes/no)	0.9 (0.56–1.45)	0.9 (0.49–1.63)
All 5 MetS components together		
Increased waist	1.36 (0.75–2.47)	2.02 (0.97–4.21)
Impaired glucose/diabetes	1.61 (1.11–2.34)	1.11 (0.72–1.72)
Low HDL cholesterol	0.95 (0.62–1.47)	0.86 (0.51–1.45)
Hypertriglyceridemia	1.03 (0.71–1.5)	0.93 (0.59–1.47)
Hypertension	0.64 (0.43–0.96)	0.85 (0.52–1.39)
No. of MetS components	1.06 (0.9–1.24)	0.99 (0.82–1.2)

Demographics include age, sex, race, and ethnicity. Histology includes baseline fibrosis stage and NASH status (no, borderline, definite).

HDL, high-density lipoprotein; HR, hazard ratio, MetS, metabolic syndrome, NASH, nonalcoholic steatohepatitis.

Table 4. Incidence (per person-year) and incidence rate ratio of NASH progression and regression by metabolic syndrome status

Exposure	Without the exposure			With the exposure			Crude rate difference (95% CI)	Incidence rate ratio (95% CI)	P value
	No. of events	Incidence rate (95% CI)	No. of events	Incidence rate (95% CI)	No. of events	Incidence rate (95% CI)			
NASH progression									
Metabolic syndrome	13	0.079 (0.046 to 0.135)	54	0.092 (0.07 to 0.12)	0.013 (-0.036 to 0.063)	1.17 (0.63 to 2.34)	0.31		
Increased waist	9	0.067 (0.035 to 0.130)	58	0.094 (0.072 to 0.121)	0.026 (-0.024 to 0.076)	1.388 (0.683 to 3.187)	0.18		
Impaired glucose/diabetes	33	0.083 (0.059 to 0.117)	34	0.096 (0.068 to 0.134)	0.013 (-0.03 to 0.055)	1.15 (0.691 to 1.915)	0.28		
Low HDL	15	0.078 (0.047 to 0.130)	52	0.093 (0.071 to 0.121)	0.014 (-0.033 to 0.061)	1.181 (0.655 to 2.259)	0.29		
Hypertriglyceridemia	20	0.067 (0.043 to 0.104)	47	0.103 (0.077 to 0.137)	0.036 (-0.006 to 0.077)	1.528 (0.888 to 2.722)	0.05		
Hypertension	18	0.088 (0.056 to 0.140)	49	0.09 (0.067 to 0.118)	0.001 (-0.047 to 0.049)	1.013 (0.580 to 1.848)	0.49		
NASH regression									
Metabolic syndrome	15	0.084 (0.051 to 0.139)	106	0.073 (0.061 to 0.089)	-0.011 (-0.055 to 0.034)	0.874 (0.507 to 1.617)	0.30		
Increased waist	16	0.085 (0.052 to 0.138)	105	0.073 (0.060 to 0.089)	-0.011 (-0.055 to 0.032)	0.866 (0.509 to 1.570)	0.29		
Impaired glucose/diabetes	40	0.07 (0.051 to 0.095)	81	0.077 (0.062 to 0.096)	0.007 (-0.02 to 0.034)	1.102 (0.746 to 1.653)	0.31		
Low HDL	22	0.068 (0.045 to 0.104)	99	0.076 (0.062 to 0.092)	0.008 (-0.025 to 0.04)	1.112 (0.695 to 1.854)	0.33		
hypertriglyceridemia	45	0.084 (0.063 to 0.113)	76	0.07 (0.056 to 0.087)	-0.014 (-0.043 to 0.015)	0.830 (0.567 to 1.228)	0.16		
Hypertension	28	0.093 (0.064 to 0.134)	93	0.07 (0.057 to 0.086)	-0.022 (-0.059 to 0.015)	0.759 (0.493 to 1.203)	0.10		

NASH progression were defined as the development of either borderline (among patients with no NASH at baseline) or definite NASH (among patients with no or borderline NASH at baseline), and regression as having no or borderline NASH at follow-up (for patients with definite NASH at baseline) or having no NASH at follow-up (for patients with borderline NASH at baseline). CI, confidence interval; HDL, high-density lipoprotein; NASH, nonalcoholic steatohepatitis.

Table 5.

Incidence (per person-year) and incidence rate ratio of the progression and regression of the overall histological change by metabolic syndrome status

Exposure	Without the exposure			With the exposure			Incidence rate ratio (95% CI)	P value
	No. of events	Incidence rate (95% CI)	No. of events	Incidence rate (95% CI)	Crude rate difference (95% CI)			
Histologic progression								
Metabolic syndrome	5	0.023 (0.010 to 0.056)	30	0.033 (0.023 to 0.047)	0.01 (-0.014 to 0.033)	1.417 (0.544 to 4.678)	0.25	
Increased waist	6	0.033 (0.015 to 0.074)	29	0.031 (0.021 to 0.044)	-0.003 (-0.032 to 0.026)	0.917 (0.374 to 2.701)	0.41	
Impaired glucose/diabetes	12	0.024 (0.013 to 0.041)	23	0.037 (0.025 to 0.056)	0.014 (-0.006 to 0.034)	1.592 (0.760 to 3.510)	0.10	
Low HDL	10	0.038 (0.020 to 0.070)	25	0.029 (0.020 to 0.043)	-0.009 (-0.035 to 0.017)	0.769 (0.357 to 1.795)	0.24	
Hypertriglyceridemia	11	0.028 (0.015 to 0.051)	24	0.032 (0.022 to 0.049)	0.005 (-0.016 to 0.026)	1.169 (0.551 to 2.644)	0.34	
Hypertension	5	0.020 (0.008 to 0.047)	30	0.034 (0.024 to 0.049)	0.015 (-0.007 to 0.036)	1.743 (0.669 to 5.752)	0.12	
Histologic regression								
Metabolic syndrome	14	0.090 (0.053 to 0.151)	78	0.067 (0.053 to 0.083)	-0.023 (-0.072 to 0.026)	0.745 (0.418 to 1.424)	0.16	
Increased waist	13	0.091 (0.053 to 0.157)	79	0.067 (0.054 to 0.083)	-0.025 (-0.076 to 0.027)	0.732 (0.404 to 1.434)	0.15	
Impaired glucose/diabetes	34	0.075 (0.054 to 0.105)	58	0.066 (0.051 to 0.086)	-0.009 (-0.04 to 0.021)	0.88 (0.567 to 1.386)	0.28	
Low HDL	20	0.079 (0.051 to 0.123)	72	0.067 (0.053 to 0.084)	-0.012 (-0.050 to 0.026)	0.847 (0.510 to 1.468)	0.25	
Hypertriglyceridemia	29	0.070 (0.048 to 0.100)	63	0.069 (0.054 to 0.089)	-0.000 (-0.031 to 0.030)	0.997 (0.632 to 1.605)	0.49	
Hypertension	23	0.101 (0.067 to 0.152)	69	0.063 (0.050 to 0.079)	-0.038 (-0.082 to 0.006)	0.621 (0.382 to 1.043)	0.03	

Histological progression was defined as an increase by 2 points of NAFLD activity score (NAS) with 1 of which was increase in ballooning and histological regression as a decrease by 2 NAS points with 1 of which was decrease in ballooning and without worsening of fibrosis.

CI, confidence interval; HDL, high-density lipoprotein; NAFLD, nonalcoholic fatty liver disease.