

## ORIGINAL ARTICLE

OPEN

# Progression to cirrhosis is similar among all ages in nonalcoholic fatty liver disease, but liver-related events increase with age

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**Abstract**

**Background:** NAFLD is increasingly common among young people. Whether NAFLD carries a more benign course in younger adults is not known. We aimed to characterize genetic and metabolic risk factors for NAFLD and their effects on disease progression across age groups.

**Methods:** We conducted a retrospective study of adults with NAFLD seen within Michigan Medicine, a tertiary care center, between 2010 and 2021. NAFLD was defined by hepatic steatosis on imaging, biopsy, or transient elastography in the absence of other chronic liver diseases. Cirrhosis was determined by validated International Classification of Diseases-9/10 codes or imaging. Fine-Gray competing risk models were generated, with incident cirrhosis and liver-related events (LREs) as the primary outcomes and death without cirrhosis or LREs as a competing risk. The primary predictor was the age category.

**Results:** We included 31,505 patients with NAFLD, with 8,252 aged 18 to younger than 40, 15,035 aged 40 to younger than 60, and 8,218 aged 60 years or older years at diagnosis. Compared with older patients, young adults more often had obesity, higher ALT, and high-risk *PNPLA3* alleles, and fewer had prevalent cirrhosis, hypertension, hyperlipidemia, and diabetes. The 10-year risk of incident cirrhosis was similar between ages (3.4% in age 18 to <40 vs 3.7% in age 40 to <60 vs 4.7% in age  $\geq 60$ ;  $p = 0.058$ ). Predictors of LREs were advancing age and diabetes, with a significantly higher 10-year risk of LREs in the oldest age group (0.2% in age 18 to <40 vs 0.7% in age 40 to <60 vs 1.1% in age  $\geq 60$ ;  $p = 0.008$ ).

**Conclusions:** While the baseline prevalence of cirrhosis was higher among

**Abbreviations:** ALT, alanine transaminase; APRI, AST-to-platelet ratio index; AST, aspartate aminotransferase; BMI, body mass index; ICD, International Classification of Diseases; IQR, interquartile range; LRE, liver-related event; MGI, Michigan Genomics Initiative; ULN, upper limit of normal.

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older adults, the rate of NAFLD progression to cirrhosis was similar in young and older adults. Older patients were more likely to have LREs.

## INTRODUCTION

The prevalence of obesity has risen drastically since the mid-1970s.<sup>[1,2]</sup> Obesity increasingly affects children and young adults,<sup>[1]</sup> 40% of adults aged 20–39 years in the US have obesity, on par with older adults,<sup>[3]</sup> and young adults are increasingly affected by metabolic diseases, including diabetes mellitus and NAFLD.<sup>[4–7]</sup>

NAFLD is strongly associated with obesity and metabolic dysfunction and now affects 20%–30% of adults worldwide.<sup>[7–9]</sup> While NAFLD can progress to decompensated cirrhosis and is projected to become the leading indication for liver transplantation in the US,<sup>[10,11]</sup> only a minority of patients with NAFLD ultimately develop cirrhosis.<sup>[12,13]</sup> Identifying the subset of NAFLD patients who will progress to advanced fibrosis or cirrhosis has been an ongoing challenge. Age is a risk factor for disease-specific mortality in NAFLD.<sup>[14]</sup> However, this association may simply reflect longer exposure to hepatic steatosis and, therefore, a higher prevalence of cirrhosis in older patients. In contrast, among patients without cirrhosis, whether young adults with NAFLD have a more benign disease trajectory than older persons with NAFLD is unknown. Young adults with NAFLD may have a lower burden of metabolic diseases, notably diabetes.<sup>[15]</sup> However, young adults with NAFLD may be more likely to have genetic risk factors for NAFLD, such as *PNPLA3*-rs738409-G, which is associated with an increased risk of cirrhosis.<sup>[16]</sup> Notably, young patients with NAFLD potentially have decades of future “disease exposure” during which cirrhosis may develop. As the number of young adults with NAFLD grows, the global burden of cirrhosis and its complications is projected to be immense.<sup>[17]</sup> However, precise data on the rate of progression to cirrhosis across age groups are limited. This limitation in the literature is especially important given the increasing prevalence of NAFLD in young adults [ $>30\%$  of US adults aged 18–40 y<sup>[18]</sup>].

We aimed to compare young and older adults with NAFLD with respect to prevalent cirrhosis, risk of progression to cirrhosis, and liver-related events (LREs; including hepatic decompensation and HCC) and identify whether metabolic and laboratory-based risk factors demonstrate age-specific effects.

## METHODS

### Study design and cohort

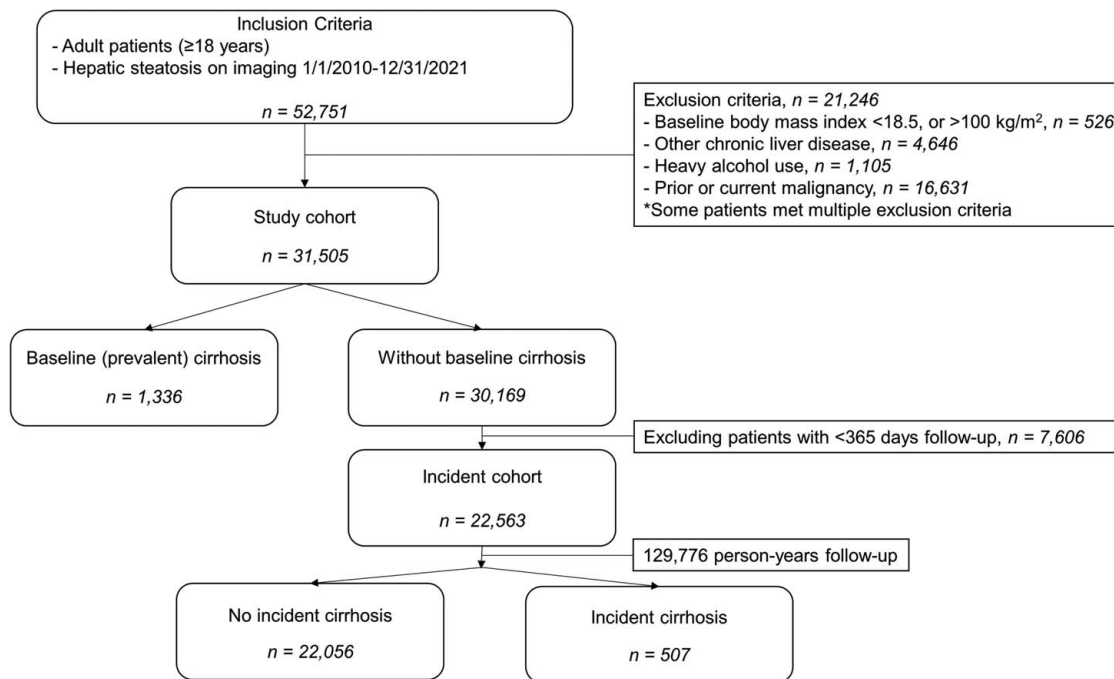
This is a retrospective study of adults ( $\geq 18$  y) with NAFLD seen at Michigan Medicine. We identified patients with hepatic steatosis based on liver biopsy, vibration-controlled transient elastography–controlled attenuation parameter  $>250$  db/m,<sup>[19]</sup> or imaging between January 1, 2010 and December 31, 2021. Identification of steatosis through imaging used a validated natural language processing algorithm,<sup>[20,21]</sup> which searches imaging reports for the term “steato” or “fat” in the same sentence as “liver” or “hepat” in the absence of a term denoting negation (eg, “no”) or evaluation (eg, “rule out”). We excluded patients with a history of cancer other than nonmelanoma skin cancer,<sup>[22]</sup> excess alcohol use ( $\geq 14/21$  standard drinks/week in women/men, respectively), or other chronic liver diseases<sup>[23]</sup> (Supplemental Table S1, <http://links.lww.com/HC9/A311>). The NAFLD index date was the date of the first study documenting the presence of hepatic steatosis. Patients were divided into 3 age groups based on age at the NAFLD index date: 18 to  $<40$  years (young), 40 to  $<60$  years (middle-aged), and  $\geq 60$  years (older).<sup>[12]</sup>

A subset of these patients was also participant in the Michigan Genomics Initiative (MGI), a prospective cohort of Michigan Medicine patients who underwent genotyping for research purposes. At the time of analysis,  $>80,000$  MGI participants had undergone genotyping using an Illumina HumanCoreExome v.12.1 array.<sup>[24]</sup>

The Institutional Review Board of the University of Michigan approved this study. All MGI participants provided written informed consent for the use of their genetic data. All research was conducted in accordance with both the Declarations of Helsinki and Istanbul.

### Diagnosis of cirrhosis and liver-related events

We defined cirrhosis based on imaging demonstrating cirrhosis, as described,<sup>[20]</sup> or validated International Classification of Diseases (ICD) codes (Supplemental Table S1, <http://links.lww.com/HC9/A311>) for cirrhosis



**FIGURE 1** Study flowchart.

or portal hypertensive complications with positive predictive values of 94%–96%.<sup>[25,26]</sup> We defined LREs based on ICD codes for ascites, variceal bleeding, hepatic encephalopathy, or HCC (Supplemental Table S1, <http://links.lww.com/HC9/A311>).<sup>[27]</sup> The earliest date of ICD diagnosis or imaging study demonstrating cirrhosis was used to define the date of cirrhosis diagnosis. Patients with cirrhosis diagnosed before or  $\leq 1$  year after the NAFLD index date were considered to have prevalent cirrhosis and those diagnosed  $> 1$  year after the NAFLD index date to have incident cirrhosis. For analyses of incident cirrhosis and LREs, we excluded patients with both prevalent cirrhosis or LREs (before or  $\leq 1$  y after the NAFLD index date). We chose to exclude patients with baseline cirrhosis from our analysis of incident LRE because the interest of our study was identifying progression from noncirrhotic NAFLD to LREs, rather than from compensated cirrhosis to decompensation. We evaluated the specificity of ICD codes for cirrhosis among those with presumed prevalent cirrhosis (vs imaging as the gold standard) and found that specificity was similar across age groups (99.2%, 98.8%, and 98.7% in young, middle-aged, and older).

## Genetic analyses

Among patients with available genetic data through MGI, we compared the distribution of genotypes of NAFLD risk alleles reported in a published study.<sup>[16]</sup> The risk alleles evaluated were *PNPLA3*-rs738409-G, *TM6SF2*-rs58542926-T, *GCKR*-rs1260326-C, *MBOAT7*-rs626283-

C, and *HSD17B13*-rs6834314-G (proxy for *HSD17B13*-rs72613567, which is not available in MGI;  $r^2 = 1.0$ ). For all alleles except the *TM6SF2* allele, we compared the proportion of patients with zero, 1, or 2 copies of the allele; for the *TM6SF2*-rs58542926 variant, we combined the CT and TT genotypes because the T allele has low allele frequency. We compared genotype distributions using a chi-squared test.

## Risk factors for prevalent and incident cirrhosis

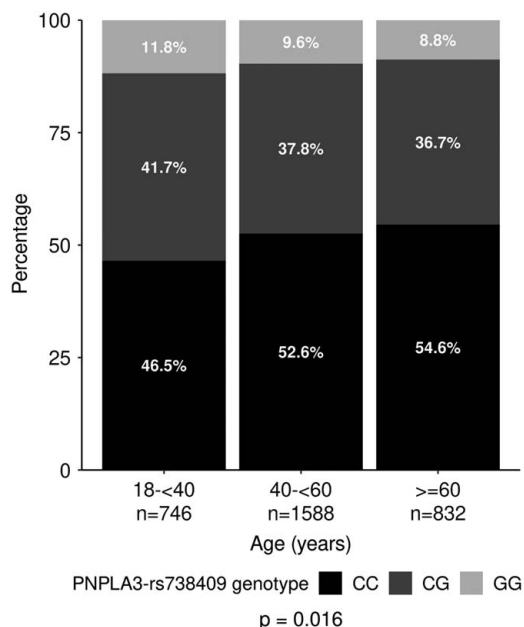
We identified factors associated with prevalent cirrhosis in the overall cohort and within each age group. First, we used univariable logistic regression to identify prespecified risk factors. Age and variables with  $p < 0.1$  on univariable analysis were included in the multivariate model, except that we did not include aspartate aminotransferase (AST) [alanine transaminase (ALT) was included instead] to avoid multicollinearity.

To identify risk factors associated with incident cirrhosis, we used Fine-Gray competing risk analyses with the development of cirrhosis as the primary event and death before the development of cirrhosis as the competing risk. Patients with prevalent cirrhosis or with follow-up  $< 365$  days were excluded from these analyses. The primary predictor was the age group. We conducted subgroup analyses based on baseline AST-to-platelet ratio index (APRI)<sup>[28]</sup> as a noninvasive marker for baseline fibrosis status, and diabetes, obesity, and baseline ALT because they were associated with

**TABLE 1** Baseline cohort characteristics by age group

Trait	Age 18 to <40 (n = 8252); %	Age 40 to <60 (n = 15035); %	Age; ≥ 60 (n = 8218); %	p
Age (y)	32.2 (27.0–36.4)	50.6 (45.7–55.2)	66.9 (63.2–72.1)	—
Male	49.0	49.4	46.5	<0.001
Race				
White	74.1	78.9	83.9	<0.001
Hispanic	7.0	4.1	2.1	—
Non-Hispanic Black	8.4	8.7	6.4	—
Asian	6.1	4.7	4.2	—
Other	4.4	3.7	3.4	—
Hypertension	24.0	48.0	63.3	<0.001
Hyperlipidemia	19.2	41.4	53.7	<0.001
Diabetes	16.1	29.6	36.9	<0.001
BMI (kg/m <sup>2</sup> )	32.9 (27.8–39.0)	32.5 (28.3–37.9)	30.8 (27.1–35.5)	<0.001
Normal	13.5	10.0	13.1	<0.001
Overweight	21.1	24.5	29.9	—
Class 1 obesity	24.8	28.2	29.7	—
Class 2 obesity	19.1	18.8	16.1	—
Class 3 obesity	21.5	18.5	11.2	—
Cirrhosis	2.3	4.3	6.4	<0.001
Aspirin use	16.6	38.4	61.5	<0.001
Statin use	15.6	45.4	65.3	<0.001
Metformin use	20.0	29.6	32.0	<0.001
Laboratory values				
Creatinine (mg/dL) (n = 26267)	0.8 (0.7–0.9)	0.8 (0.7–1.0)	0.9 (0.8–1.1)	<0.001
Hemoglobin A1c (%) (n = 9984)	5.6 (5.3–6.2)	5.9 (5.5–6.9)	6.2 (5.8–7.2)	<0.001
AST (U/L) (n = 25393)	32.0 (23.0–48.0)	31.0 (23.0–44.0)	30.0 (23.0–42.0)	<0.001
ALT (U/L) (n = 25460)	46.0 (26.0–76.5)	38.5 (26.0–60.0)	32.0 (22.0–49.0)	<0.001
< ULN	17.5	19.0	27.7	<0.001
1 to <2x ULN	37.0	45.0	44.5	—
2 to <5x ULN	34.9	29.6	22.1	—
≥ 5x ULN	10.6	6.5	5.7	—
Total bilirubin (mg/dL) (n = 25286)	0.5 (0.4–0.8)	0.5 (0.4–0.8)	0.6 (0.4–0.8)	<0.001
Alkaline phosphatase (U/L) (n = 25297)	80.5 (66.0–101.0)	84.0 (69.0–108.0)	87.0 (69.0–114.0)	<0.001
Albumin (g/dL) (n = 25495)	4.4 (4.1–4.6)	4.3 (4.1–4.5)	4.2 (3.8–4.5)	<0.001
Platelets (K/uL) (n = 24641)	255.0 (211.5–303.5)	241.0 (199.0–290.0)	221.0 (176.5–271.0)	<0.001
LDL (mg/dL) (n = 10834)	103.0 (82.0–127.0)	105.0 (81.0–129.0)	89.0 (66.0–116.0)	<0.001
HDL (mg/dL) (n = 11476)	41.0 (35.0–49.0)	44.0 (37.0–53.0)	45.0 (37.0–55.0)	<0.001
Triglycerides (mg/dL) (n = 12218)	167.0 (112.0–254.2)	162.0 (112.5–242.0)	147.5 (105.6–209.0)	<0.001

Note: Continuous variables are reported as median (interquartile range). The upper limit of normal for alanine transaminase was defined as 19 U/L for women or 30 U/L for men. Abbreviations: ALT, alanine transaminase; AST, aspartate aminotransferase; BMI, body mass index; ULN, upper limit of normal.



**FIGURE 2** Distribution of *PNPLA3*-rs738409 genotype across age groups.

prevalent cirrhosis. Of the commonly used fibrosis markers, APRI is the only one that can be applied consistently across age groups as it does not include age.

## Statistics

Quantitative variables were reported as median [interquartile range (IQR)] and categorical variables as numbers and percentages (%). Three-way comparisons were performed with Kruskal-Wallis statistics for continuous variables and the Fisher test for categorical variables.

A 2-sided  $p$  value  $< 0.05$  was used to determine statistical significance throughout.

## RESULTS

### Cohort and baseline characteristics

We included 31,505 patients with NAFLD (Figure 1), of whom 8252 (26.2%) were aged 18 to  $<40$  (young), 15,035 (47.7%) aged 40 to  $<60$  (middle-aged), and 8218 (26.1%) aged  $\geq 60$  years (older) at NAFLD index date. The first modality used to identify hepatic steatosis was imaging in 29,930 (95.0%), transient elastography in 916 (2.9%), and biopsy in 659 (2.1%). Young people were slightly more likely to have NAFLD diagnosed through imaging than middle-aged and older patients (95.6% in young and 94.8% in middle-aged and older,  $p < 0.05$ ).

The baseline characteristics of the study cohort are reported in Table 1. Obesity was more common in those  $<60$  years old (65.4%, 65.5%, and 57.0% in young, middle-aged, and older, respectively;  $p < 0.001$ ). There was a stepwise increase in the prevalence of other metabolic diseases with advancing age, including hypertension, hyperlipidemia, and diabetes mellitus (16.1%, 29.6%, and 36.9% in young, middle-aged, and older;  $p < 0.001$ ). Prevalent cirrhosis was also more frequent with advancing age (2.0, 4.0, and 6.2% in young, middle-aged, and older;  $p < 0.001$ ). The older group had the lowest triglycerides, lowest LDL, and highest HDL levels. There was a stepwise decrease in baseline ALT with age (median 46.0, 38.5, and 32.0 U/L in young, middle-aged, and older;  $p < 0.001$ ).

Genotypic data were available in 4,359 patients with similar availability in all age groups (9.4%, 10.6%, and 10.0% in young, middle-aged, and older, respectively). The frequency of the *PNPLA3*-rs738409-G allele was higher in the young (GG genotype 11.8%, 9.6%, and 8.8% in young, middle-aged, and older;  $p = 0.016$ ; Figure 2). The frequency of NAFLD risk alleles in *GCKR*, *HSD17B13*, *MBOAT7*, and *TM6SF2* was not different across age groups (Supplemental Figure S1, <http://links.lww.com/HC9/A311>).

### Factors associated with prevalent cirrhosis

Among patients presenting with cirrhosis, the percentage of decompensated cases was similar among ages (17.7% overall, with 19.8% in young, 17.5% in middle-aged, and 17.1% in older,  $p = 0.693$ ). Older patients were also more likely to have had decompensation at the time of NAFLD diagnosis (0.7% overall, with 0.4% in young, 0.7% in middle-aged, and 1.1% in older,  $p < 0.001$ ).

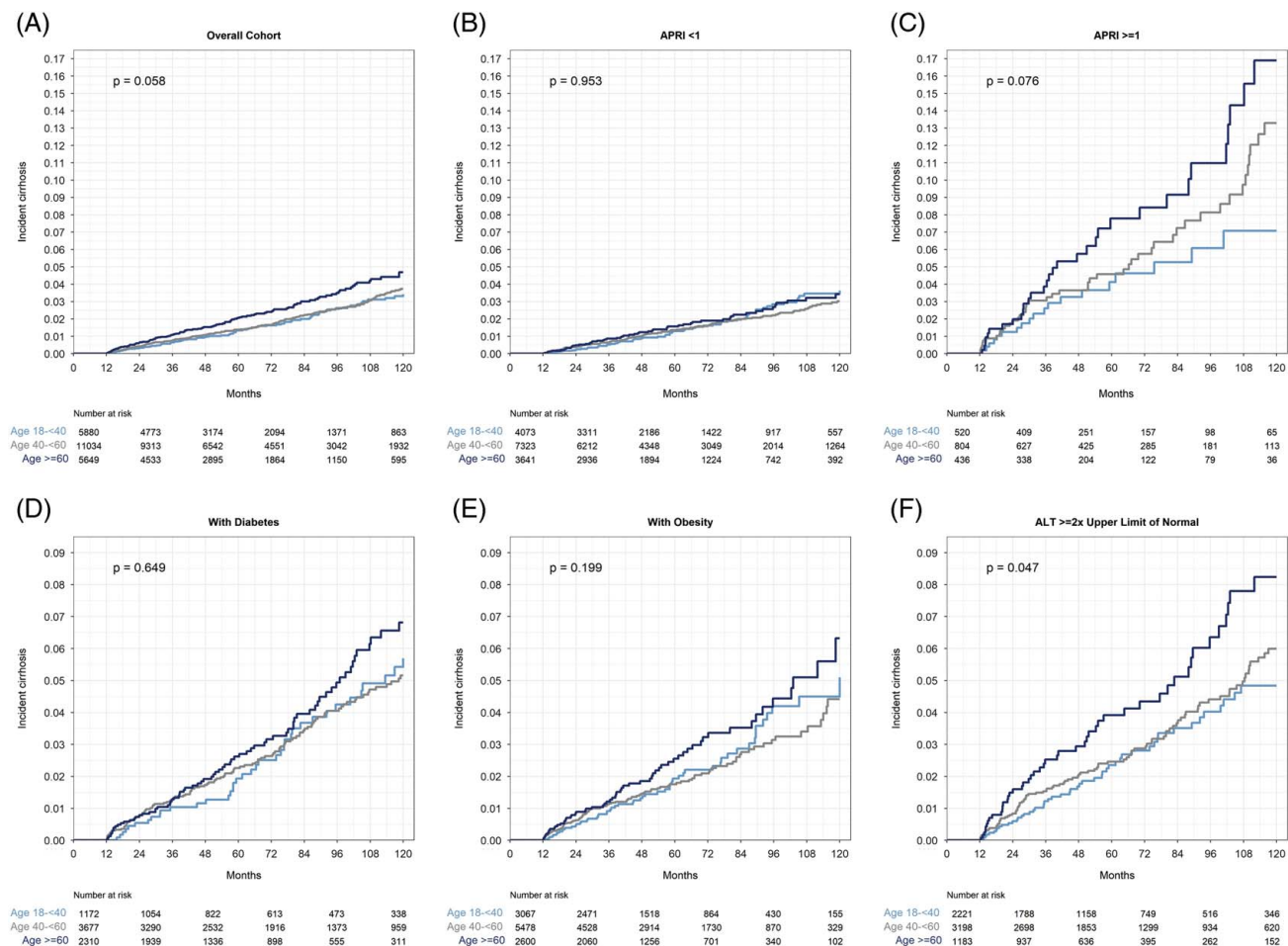
Univariate logistic regression analysis identified older age, diabetes, hypertension, class 3 obesity, elevated ALT, elevated AST, and AST-to-ALT ratio  $> 1$  to be associated with prevalent cirrhosis in the overall cohort (Supplemental Table S2, <http://links.lww.com/HC9/A311>, Supplemental Figure S2, <http://links.lww.com/HC9/A311>). Black and Asian patients were less likely to have prevalent cirrhosis overall (ORs: 0.39 and 0.36, respectively,  $p < 0.001$  in both). In multivariate analysis (Table 2, Supplemental Figure S3, <http://links.lww.com/HC9/A311>), older age, diabetes, and higher ALT were significantly associated with a higher prevalence of cirrhosis. Diabetes was strongly associated with prevalent cirrhosis in all age groups (ORs: 1.74, 2.75, and 2.17 in young, middle-aged, and older;  $p < 0.05$  in all). Similarly, higher ALT was associated with prevalent cirrhosis, but this effect was seen primarily in the older age group. Surprisingly, higher body mass index (BMI) was only strongly associated with a higher prevalence

**TABLE 2** Multivariate model for prediction of prevalent (baseline) cirrhosis

Factor	Overall		Age 18 to <40		Age 40 to <60		Age ≥ 60	
	OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p
Age (y)	1.02 (1.02–1.03)	< 0.001	1.00 (0.98–1.03)	0.734	1.04 (1.02–1.06)	0.000	0.98 (0.97–1.00)	0.084
Male (vs female)	1.03 (0.90–1.17)	0.679	1.19 (0.86–1.64)	0.294	0.95 (0.79–1.15)	0.611	1.06 (0.85–1.31)	0.620
Race								
White	Referent	—	Referent	—	Referent	—	Referent	—
Black	0.35 (0.25–0.49)	< 0.001	0.58 (0.30–1.12)	0.103	0.32 (0.20–0.51)	< 0.001	0.27 (0.14–0.53)	< 0.001
Asian	0.42 (0.28–0.64)	< 0.001	0.45 (0.18–1.12)	0.085	0.53 (0.30–0.93)	0.027	0.36 (0.17–0.77)	0.009
Hispanic	0.89 (0.66–1.21)	0.467	0.68 (0.35–1.30)	0.243	1.05 (0.70–1.58)	0.807	1.02 (0.54–1.94)	0.941
Other	0.69 (0.48–1.00)	0.052	0.60 (0.24–1.48)	0.268	0.73 (0.43–1.24)	0.247	0.68 (0.36–1.27)	0.224
Diabetes	2.44 (2.11–2.82)	< 0.001	1.74 (1.14–2.66)	0.011	2.75 (2.23–3.39)	< 0.001	2.17 (1.72–2.74)	< 0.001
Hypertension	0.92 (0.79–1.06)	0.241	1.10 (0.74–1.62)	0.637	0.92 (0.75–1.13)	0.403	0.84 (0.65–1.08)	0.170
Hyperlipidemia	0.64 (0.55–0.74)	0.000	0.85 (0.54–1.34)	0.489	0.65 (0.53–0.80)	< 0.001	0.56 (0.44–0.71)	< 0.001
BMI								
Normal	Referent	—	Referent	—	Referent	—	Referent	—
Overweight	0.92 (0.73–1.16)	0.501	0.56 (0.35–0.90)	0.016	1.01 (0.69–1.46)	0.978	1.21 (0.81–1.81)	0.363
Class 1 obesity	0.93 (0.74–1.17)	0.522	0.32 (0.19–0.53)	< 0.001	0.93 (0.64–1.34)	0.689	1.56 (1.05–2.31)	0.029
Class 2 obesity	1.08 (0.85–1.37)	0.542	0.36 (0.21–0.61)	< 0.001	1.23 (0.85–1.79)	0.271	1.61 (1.05–2.46)	0.029
Class 3 obesity	1.24 (0.97–1.57)	0.082	0.53 (0.33–0.86)	0.010	1.41 (0.97–2.04)	0.071	1.69 (1.08–2.66)	0.023
ALT								
<ULN	Referent	—	Referent	—	Referent	—	Referent	—
1 to <2× ULN	1.25 (1.05–1.50)	0.013	1.32 (0.81–2.16)	0.269	0.99 (0.77–1.29)	0.968	1.45 (1.09–1.93)	0.010
2 to <5× ULN	1.47 (1.21–1.78)	< 0.001	1.68 (1.03–2.74)	0.039	1.13 (0.86–1.50)	0.373	1.75 (1.27–2.40)	0.001
≥ 5× ULN	1.91 (1.48–2.45)	< 0.001	1.75 (0.97–3.18)	0.064	1.83 (1.28–2.62)	0.001	1.92 (1.22–3.02)	0.005

Note: ORs and 95% CI are reported. Normal body mass index was defined as body mass index <23 in Asians and body mass index <25 in non-Asian patients. The upper limit of normal for alanine transaminase was defined as 19 U/L for women or 30 U/L for men.

Abbreviations: ALT, alanine transaminase; BMI, body mass index; ULN, upper limit of normal.



**FIGURE 3** Cumulative incidence of cirrhosis, with death without cirrhosis modeled as a competing risk, stratified by age group. (A) Overall cohort. (B) Patients with APRI <1. (C) Patients with APRI ≥1. (D) Patients with diabetes. (E) Patients with obesity. (F) Patients with ALT ≥2 times the ULN, defined as 19 U/L for women or 30 U/L for men. Abbreviations: ALT, alanine transaminase; APRI, AST-to-platelet ratio index; ULN, upper limit of normal.

of cirrhosis in the older age group and was paradoxically associated with lower odds of prevalent cirrhosis in the young. Hyperlipidemia was not associated with cirrhosis in the young but was associated with lower odds of prevalent cirrhosis in the middle-aged and older groups (ORs: 0.65 and 0.56, respectively).

### Incidence and predictors of incident cirrhosis

During a median (IQR) follow-up of 4.6 (2.5–8.0) years, 507 (2.2%) of 22,563 patients without prevalent cirrhosis were diagnosed with incident cirrhosis. The diagnosis was made by both ICD and imaging in 32%, imaging alone in 30%, and ICD alone in 38%. Follow-up time was similar in each age group, with a median of 4.4 years in the young, 5.0 years in the middle-aged, and 4.1 years in the older group. Among patients who developed incident cirrhosis, median time-to-cirrhosis was (IQR) 5.2 (2.4–9.1) years overall, 5.5 (2.9–10.0) years in the

young, 6.1 (2.7–10.2) years in the middle-aged, and 3.8 (2.0–6.7) years in the older group. The cumulative 5 and 10-year incidence rates for cirrhosis were 1.5% and 3.9% overall, 1.3% and 3.4% for the young, 1.4% and 3.7% for the middle-aged, and 2.0% and 4.7% for the older age groups, respectively ( $p > 0.05$  for both comparisons; Figure 3).

In univariable analysis, diabetes, hypertension, hyperlipidemia, higher BMI, and higher baseline ALT level were associated with an increased risk of cirrhosis. While the oldest age group was at modestly increased risk of incident cirrhosis in univariable analysis [HR: 1.33 (1.03–1.71) vs youngest], in multivariable analysis, the age group was not associated with risk of incident cirrhosis (Table 3). In addition, diabetes, hypertension, and higher ALT remained associated with an increased risk of cirrhosis, while hyperlipidemia and higher BMI (except class 3 obesity) were not. Black patients were significantly less likely to develop cirrhosis. The strongest predictors of incident cirrhosis were diabetes [HR: 2.05 (1.58–2.64) vs no diabetes] and ALT

**TABLE 3** Univariate and multivariate predictors of incident cirrhosis

Predictor	Univariable		Multivariable	
	HR (95% CI)	<i>p</i>	HR (95% CI)	<i>p</i>
Age (y)				
18 to <40	Referent	—	Referent	—
40 to <60	1.12 (0.90–1.40)	0.304	0.86 (0.65–1.15)	0.321
≥60	1.33 (1.03–1.71)	0.026	1.03 (0.72–1.47)	0.881
Male (vs female)	0.97 (0.82–1.16)	0.776	1.21 (0.96–1.52)	0.110
Race				
White	Referent	—	Referent	—
Black	0.50 (0.32–0.77)	0.002	0.34 (0.18–0.64)	0.001
Asian	0.56 (0.33–0.93)	0.026	0.70 (0.38–1.30)	0.262
Hispanic	1.21 (0.80–1.82)	0.368	0.72 (0.40–1.29)	0.269
Other	0.69 (0.38–1.25)	0.216	0.49 (0.20–1.19)	0.113
Diabetes	2.16 (1.81–2.59)	<0.001	2.05 (1.58–2.64)	<0.001
Hypertension	1.70 (1.39–2.08)	<0.001	1.51 (1.14–2.01)	0.004
Hyperlipidemia	1.41 (1.17–1.70)	<0.001	1.07 (0.81–1.41)	0.623
BMI				
Normal	Referent	—	Referent	—
Overweight	1.56 (0.94–2.58)	0.084	1.33 (0.79–2.24)	0.288
Class 1 obesity	1.75 (1.07–2.87)	0.026	1.21 (0.72–2.04)	0.467
Class 2 obesity	1.59 (0.94–2.67)	0.082	1.01 (0.58–1.74)	0.982
Class 3 obesity	2.69 (1.64–4.41)	<0.001	1.81 (1.07–3.07)	0.028
ALT				
<ULN	Referent	—	Referent	—
1 to <2× ULN	1.51 (1.08–2.12)	0.017	1.70 (1.13–2.56)	0.011
2 to <5× ULN	2.58 (1.85–3.60)	<0.001	3.30 (2.21–4.94)	<0.001
≥5× ULN	4.50 (3.04–6.66)	<0.001	5.05 (3.13–8.16)	<0.001

Note: HRs and 95% CI are reported. Normal body mass index was defined as body mass index <23 in Asians and body mass index <25 in non-Asian patients. The upper limit of normal for alanine transaminase was defined as 19 U/L for women or 30 U/L for men.

Abbreviations: ALT, alanine transaminase; BMI, body mass index; ULN, upper limit of normal.

elevations [HR: 3.30 (2.21–4.94) for ALT 2 to <5 times upper limit of normal (ULN) and 5.05 (3.13–8.16) for ALT ≥ 5 times ULN vs < ULN; Table 3]. In several subgroup analyses, age group remained not associated with incident cirrhosis in patients with or without diabetes, obesity, or elevated baseline APRI (Figure 3, Supplemental Figure S4, <http://links.lww.com/HCG9/A311>). Older patients were modestly more likely to develop incident cirrhosis in the subgroup with baseline ALT ≥ 2 times ULN.

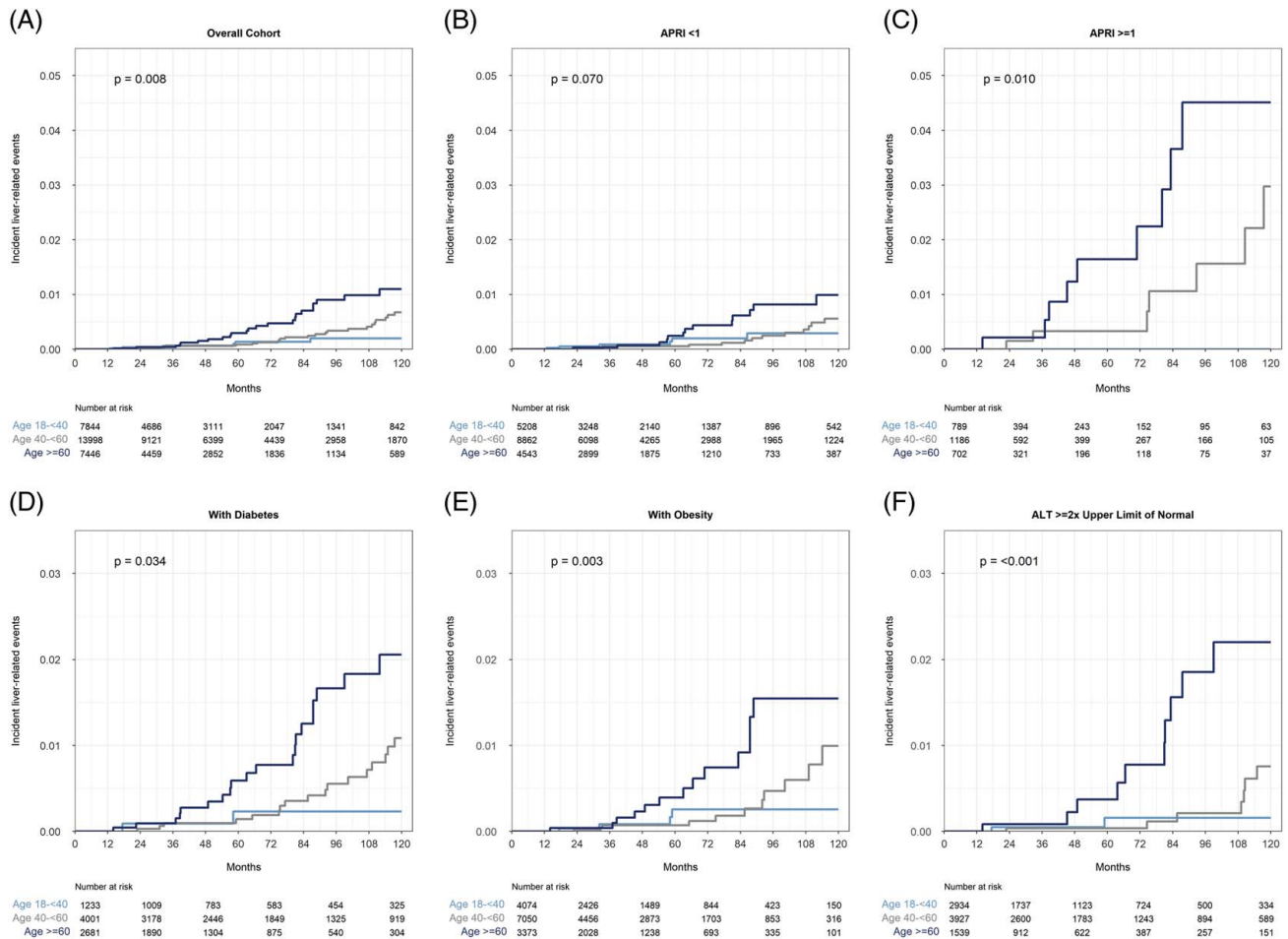
In the subset of patients with genetic data available and at least one year of follow-up (n = 3166), 71 patients developed incident cirrhosis. *PNPLA3*-rs738409-GG genotype was associated with an increased risk of incident cirrhosis (HR: 2.49 [1.29–4.79], *p* = 0.006) after adjustment for sex, age category, and genetic principal components 1–10. After additional adjustment for diabetes status, obesity, and ALT ≥ 2× ULN, the association between GG genotype

and incident cirrhosis was no longer significant [HR: 2.08 (0.94–4.63), *p* = 0.073], partly due to missingness in BMI values. The rs738409-CG genotype was not associated with an increased risk of incident cirrhosis.

### Incidence and predictors of liver-related events

During a median (IQR) follow-up of 4.6 (2.5–8.0) years, 74 (0.3%) of 22,121 patients had LREs [53 (71.6%) hepatic decompensation and 21 (28.4%) HCC] with cumulative 5 and 10-year incidences of 0.15% and 0.67% for the overall cohort. Among those who developed LREs, time-to-event was median (IQR) 7.2 (4.8–10.4) years, with 10.9 (4.9–16.5) years in the young, 8.1 (5.7–10.6) years in the middle-aged, and 5.7 (4.2–7.3) years in the older. The cumulative 5 and 10-year incidences of LREs were significantly higher in the





**FIGURE 4** Cumulative incidence of LREs, with death without hepatic decompensation modeled as a competing risk, stratified by age group. (A) Overall cohort. (B) Patients with APRI <1. (C) Patients with APRI ≥1. (D) Patients with diabetes. (E) Patients with obesity. (F) Patients with ALT ≥2 times the ULN, defined as 19 U/L for women or 30 U/L for men. Abbreviations: ALT, alanine transaminase; APRI, AST-to-platelet ratio index; LRE, liver-related event; ULN, upper limit of normal.

older age groups ( $p = 0.008$  in a 3-way comparison) and are given as follows: 0.14% and 0.20% for the young, 0.09% and 0.68% for the middle-aged, and 0.31% and 1.15% for the older age groups, respectively (Figure 4).

In both univariable and multivariable analyses, only diabetes and advancing age were associated with an increased risk of LREs (Table 4). *PNPLA3* genotype was not associated with incident LREs due to a small number of cases ( $n = 3$ ). In multivariable analysis, diabetes was the strongest predictor [HR: 4.48 (2.18–9.18) vs no diabetes] followed by age 60 years or older [HR: 3.11 (1.17–8.31)] vs age 18–<40 y]. Sex, race, elevated ALT, hypertension, and hyperlipidemia were not significantly associated with LREs. In most subgroups, including those with diabetes, obesity, elevated baseline ALT, and elevated APRI, advancing age was significantly associated with the risk of LREs (Figure 4, Supplemental Figure S5, <http://links.lww.com/HC9/A311>). Among subgroups of patients using versus not using aspirin, statins, or metformin, only metformin use was significantly associated with LREs in the oldest age

group though there was a trend toward increased LREs with advancing age in all subgroups (Supplemental Table S3, <http://links.lww.com/HC9/A311>).

## DISCUSSION

Among over 30,000 adults with hepatic steatosis, younger patients had a lower prevalence of diabetes but a higher prevalence of obesity, elevated ALT, and the *PNPLA3*-rs738409-G allele than their older counterparts. Progression to cirrhosis was similar in young, middle-aged, and older patients, but the risk of LREs was greater in older patients despite the exclusion of patients with baseline cirrhosis or a history of hepatic decompensation. Our finding that adult NAFLD patients of all ages demonstrate similar rates of progression to cirrhosis suggests that NAFLD is not necessarily benign in young patients. With >30% prevalence of NAFLD among Americans younger than 40 years,<sup>[18]</sup> this study provides direct evidence that the prevalence of NAFLD-related cirrhosis is likely to grow dramatically in the near

**TABLE 4** Univariate and multivariate predictors of LREs

Predictor	Univariable		Multivariable	
	HR (95% CI)	<i>p</i>	HR (95% CI)	<i>p</i>
Age (y)				
18 to <40	Referent	—	Referent	—
40 to <60	1.17 (0.63–2.16)	0.618	0.92 (0.36–2.35)	0.857
≥60	2.35 (1.25–4.41)	0.008	3.11 (1.17–8.31)	0.024
Male (vs female)	1.33 (0.84–2.11)	0.217	1.80 (0.94–3.46)	0.078
Race				
White	Referent	—	Referent	—
Black	0.65 (0.24–1.77)	0.395	0.70 (0.21–2.35)	0.564
Asian	0.25 (0.03–1.78)	0.165	0.74 (0.10–5.81)	0.779
Diabetes	4.83 (2.79–8.34)	<0.001	4.48 (2.18–9.18)	<0.001
Hypertension	1.38 (0.83–2.31)	0.214	0.82 (0.38–1.78)	0.616
Hyperlipidemia	1.32 (0.81–2.17)	0.266	0.67 (0.32–1.39)	0.280
BMI				
Normal	Referent	—	Referent	—
Overweight	0.40 (0.10–1.60)	0.195	0.46 (0.11–1.97)	0.292
Class 1 obesity	0.79 (0.24–2.57)	0.697	0.75 (0.21–2.70)	0.655
Class 2 obesity	1.30 (0.41–4.15)	0.657	1.11 (0.31–4.05)	0.871
Class 3 obesity	2.12 (0.71–6.35)	0.181	2.25 (0.64–7.85)	0.204
ALT				
<ULN	Referent	—	Referent	—
1 to <2× ULN	1.02 (0.49–2.11)	0.964	1.04 (0.43–2.56)	0.924
2 to <5× ULN	1.29 (0.62–2.71)	0.500	1.41 (0.52–3.83)	0.505
≥5× ULN	1.98 (0.72–5.41)	0.185	1.59 (0.38–6.72)	0.526

Note: HRs and 95% CI are reported. Normal body mass index was defined as body mass index <23 in Asians and body mass index <25 in non-Asian patients. The upper limit of normal for alanine transaminase was defined as 19 U/L for women or 30 U/L for men. Abbreviations: ALT, alanine transaminase; BMI, body mass index; LRE, liver-related event; ULN, upper limit of normal.

future. Prevalent cirrhosis was more than 3 times as common in older than young patients (6.3% vs 2.3%), which may reflect a longer average duration of NAFLD exposure.<sup>[29,30]</sup>

Few studies have focused on evaluating NAFLD disease trajectory in young adults compared with older adults. One recent territory-wide study of people with NAFLD and type 2 diabetes in Hong Kong found that age 50 years or older was associated with a higher incidence of LREs versus age younger than 40 years.<sup>[31]</sup> While our study found the progression to cirrhosis overall to be similar across ages, we likewise found that the risk of LREs increased with advancing age and the presence of diabetes. Our study had important differences from the study in Hong Kong. First, we included both patients with and without diabetes to assess its impact on cirrhosis development and LRE, which is important as diabetes increases the risk of cirrhosis in NAFLD.<sup>[12,32]</sup> Next, we excluded patients with baseline cirrhosis from our time-to-event analyses for hepatic decompensation, mitigating biases that prolonged cirrhosis may have on subsequent decompensation.

Finally, our cohort had a higher proportion of young patients (26% vs 11%), increasing the sample of young patients who may decompensate.

The prevalence of metabolic and genetic risk factors for NAFLD differed considerably based on age group. Younger patients tended to have higher BMI and baseline ALT but less often had hypertension, hyperlipidemia, and diabetes. This is consistent with prior work in NAFLD demonstrating an inverse correlation between age and both obesity and ALT,<sup>[33,34]</sup> and the general trend of increased metabolic comorbidities with age.<sup>[4–6]</sup> These differences in metabolic profile have important prognostic significance, as both diabetes and obesity are linked to disease progression.<sup>[31,35]</sup> Carriage of high-risk *PNPLA3* alleles has been associated with earlier age of NAFLD diagnosis<sup>[16]</sup> and with cirrhosis/advanced fibrosis<sup>[36]</sup> and HCC.<sup>[16,37]</sup> There is growing evidence that these variants are associated with disease progression in patients with established NAFLD.<sup>[38]</sup> The higher prevalence of *PNPLA3* risk alleles, obesity, and liver enzyme elevations in our young patients may “cancel out” their lower prevalence of diabetes and presumably shorter

duration of steatosis resulting in a similar rate of incident cirrhosis as the older patients.

Strengths of our study include its large sample size of > 30,000 patients, with a balanced representation of young and older adults, and a long-follow up period: a median of nearly 5 years and a total of > 130,000 person-years. Furthermore, genotypic data were available in a large number of patients ( $n = 4359$ ). There were several limitations to our study. First, this study was based on a single tertiary center with a predominantly White population, and the results may not be representative of the general population in the US or other countries. As a referral center, the incidence of cirrhosis and LREs in our patients is expected to be higher than in primary or secondary care settings. Whether our findings are generalizable to lower risk populations is unclear. Second, while we made every effort to identify the earliest date at which there was objective evidence of NAFLD, it was not possible to define the exact date at which NAFLD first developed. Third, while we made every effort to exclude patients with heavy alcohol use and other causes of chronic liver diseases, we relied on ICD codes and patient self-report in the medical record rather than standardized tools, such as AUDIT-C or biomarkers, which is a limitation inherent in a retrospective cohort of this size. Fourth, patients in our cohort had NAFLD determined primarily by imaging studies, and there is a possibility of referral bias, given that indications for abdominal imaging in younger patients may differ from older patients. Finally, due to the retrospective nature of this study, it can be challenging to identify when NAFLD first developed: routine screening for hepatic steatosis with imaging is not recommended, so we simply used the earliest date that there was evidence of steatosis in our medical system. Similarly, the exact date of cirrhosis development may be unclear if patients were not regularly monitored, and ICD codes and imaging may not be sensitive in identifying patients with compensated cirrhosis though this would apply across all age groups. We reported that the sensitivity of ICD codes for cirrhosis in our cohort was 46%,<sup>[39]</sup> so there likely were cases of cirrhosis which were missed. We partially addressed this by evaluating LREs as an outcome, which are less likely to be underdiagnosed as they result in symptoms. We mitigated this by excluding patients with clear confounding indications for obtaining imaging, most notably cancers other than nonmelanoma skin cancer.

In conclusion, young adults with NAFLD demonstrated similar rates of progression to cirrhosis as older patients but experienced a significantly lower risk of LREs during a median follow-up of 4.6 years. Given the increasing prevalence of NAFLD in children and young adults, simple and reliable noninvasive strategies to assess baseline fibrosis have importance across all age groups. Our findings that older patients are at the highest

risk of LREs in the short to medium term are consistent with current guidelines focusing on older patients. However, the increasing prevalence of NAFLD in children and young adults, and a similarly high rate of incident cirrhosis in younger patients compared with older ones forewarn a wave of NAFLD-related cirrhosis and related complications hitting younger persons in the future.

## CONFLICTS OF INTEREST

This study was supported in part by a Clinical, Translational, and Outcomes Research Award from the AASLD to Vincent L. Chen. Vincent L. Chen and Anna S. Lok received research support from KOWA and Astra Zeneca (to University of Michigan). Anna S. Lok serves on the DSMB of Novo Nordisk. The remaining authors have no conflicts to report.

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**How to cite this article:** Miller MJ, Harding-Theobald E, DiBattista JV, Zhao Z, Wijarnpreecha K, Lok AS, et al. Progression to cirrhosis is similar among all ages in nonalcoholic fatty liver disease, but liver-related events increase with age. *Hepatol Commun*. 2023;7:e0148 <https://doi.org/10.1097/HC9.000000000000148>