Gastro Hep Advances 2024;3:122–127

ORIGINAL RESEARCH—CLINICAL

Advanced Fibrosis in Metabolic Dysfunction-Associated Steatotic Liver Disease Is Independently Associated With Reduced Renal Function

Carolina Villarroel,[1] Gres Karim,[2] Mantej Sehmbhi,[3] Jake Debroff,[1] Ilan Weisberg,[2] and Amreen Dinani[4,5]

[1]Department of Medicine, Mount Sinai Beth Israel Medical Center, Icahn School of Medicine at Mount Sinai, New York, New York; [2]Division of Gastroenterology, NewYork-Presbyterian Brooklyn Methodist Hospital, New York, New York; [3]Department of Medicine, Mount Sinai Morningside and West Hospitals, Icahn School of Medicine at Mount Sinai, New York, New York; [4]Division of Liver Diseases, Icahn School of Medicine at Mount Sinai, New York, New York; and [5]Division of Gastroenterology, Duke University, Durham, North Carolina

BACKGROUND AND AIMS: The large global population of patients with metabolic dysfunction-associated steatotic liver disease (MASLD) has recently been shown to have an association with chronic kidney disease (CKD) due to a host of proposed mechanisms, one of which being lipoprotein dysmetabolism. Furthermore, metabolic comorbidities have been concurrently prevalent in MASLD and CKD independently. This study aimed at analyzing risk and predictive traits among an obese population for both MASLD and CKD. **METHODS:** A retrospective chart review of 546 obese patients with a diagnosis of either MASLD or metabolic dysfunction-associated steatohepatitis between January 2020 and June 2021 was performed. Markers of liver and kidney function in addition to demographic data and renoprotective medications were recorded. Both univariable and multivariable linear regression analyses were performed to understand possible associations between MASLD markers, renal function, and markers of metabolic derangements. **RESULTS:** Univariate analysis revealed that increased age ($P < .001$), elevated alanine aminotransferase (defined as alanine aminotransferase $\geq$ 30 IU/L, $P = .01$), low albumin ($P = .011$), and increasing fibrosis-4 (FIB-4) ($P = .005$) were statistically associated with a reduced renal function. A reduction in glomerular filtration was associated with an increase in FIB-4 (effect size [beta] of a one-unit increase in glomerular filtration on FIB-4 $= -0.013$, $P < .001$) in univariate linear regression. In multivariate linear regression, type 2 diabetes (T2D) was independently associated with increased liver fibrosis (effect size of T2D on FIB-4 $= 0.387925$, $P < .02$). **CONCLUSION:** Our study shows that in a patient population with obesity and a diagnosis of MASLD, advanced fibrosis is independently associated with reduced renal function.

Keywords: Hepatic Steatosis; Liver Inflammation; Chronic Kidney Disease; Obesity; Metabolic Syndrome

Introduction

Metabolic dysfunction associated steatotic liver disease (MASLD) is characterized by fat infiltration of the liver in the absence of secondary causes of hepatic steatosis.[1] Its global impact is staggering, affecting more than a quarter of the world population while being the fastest growing cause of hepatocellular carcinoma[2] and a rapidly increasing indication for liver transplantation.[3] Liver fibrosis as a result of MASLD is associated with major adverse liver outcomes and all-cause mortality,[4,5] with atherosclerotic cardiovascular disease being the principal cause of death in patients with MASLD.[6]

Metabolic comorbidities and individual components of metabolic syndrome: visceral obesity, type 2 diabetes (T2D), hypertension (HTN), and atherogenic dyslipidemia are prevalent in MASLD.[7–9] Recently, it has been established that there is a strong association between MASLD and chronic kidney disease (CKD), regardless of the presence of potential confounding metabolic risk factors such as obesity, HTN, and T2D. Both MASLD and CKD are associated with visceral obesity, T2D, metabolic syndrome, and insulin resistance (IR). The severity of metabolic dysfunction-associated steatohepatitis (MASH) histology is associated with decreased kidney function independent of IR and other components of the metabolic syndrome.[10] Moreover, a meta-analysis showed that the presence and severity of MASLD were associated with increased risk and severity of CKD.[11] Mechanisms proposed to account for how MASLD might potentiate renal injury include lipoprotein

Abbreviations used in this paper: **ACEi, angiotensin-converting enzyme inhibitor; ALT, alanine aminotransferase; ARB, angiotensin receptor blocker; AST, aspartate aminotransferase; BMI, body mass index; CKD, chronic kidney disease; EMR, electronic medical record; GFR, glomerular filtration rate; HTN, hypertension; ICD, International Classification of Diseases; IR, insulin resistance; MASH, metabolic dysfunction-associated steatohepatitis; MASLD, metabolic dysfunction-associated steatotic liver disease; T2D, type 2 diabetes.**

Most current article

2772-5723
https://doi.org/10.1016/j.gastha.2023.09.008

dysmetabolism and altered hepatic secretion of fibroblast growth factor-21, fetuin-A, insulin-like growth factor-1, and syndecan-1.[12] Conversely, CKD may mutually aggravate MASLD and associated metabolic disturbances through altered intestinal barrier function and microbiota composition, accumulation of uremic toxic metabolites, and alterations in prereceptor glucocorticoid metabolism. The liver and kidney express all components of the RAS system including both systemic and local ACE-AT2-AT1 which supports the pathogenesis of MASLD and CKD.[13]

CKD is defined as a sustained reduction in the glomerular filtration rate (GFR) or evidence of structural or functional abnormalities of the kidneys based on urinalysis, biopsy, or imaging.[14,15] CKD has many potential causes, which vary in frequency between different populations. In developed countries, older age, HTN, T2D, obesity, and dyslipidemia are consistently associated with CKD.[14,15] Patients with CKD exhibit an elevated risk for the development of cardiovascular disease.

The aim of this study was to explore the association and identify risk factors between MASLD and CKD in a cohort of patients with obesity (defined by a body mass index (BMI) $\geq$ 30 kg/m^2), a population at high risk for developing both MASLD and CKD.

Methods

Patient Selection

Using an electronic medical record (EMR), we identified patients aged 18 years and older with a BMI $\geq$ 30 kg/m^2 and a diagnosis of MASLD or MASH, as determined by International Classification of Diseases (ICD)-10 codes, (K76.0 or K75.8), seen in a specialty gastroenterology and hepatology clinic between January 2020 and June 2021. Patients in these outpatient clinical sites were seen for both liver and nonliver-related medical conditions. Patients were excluded if they had additional causes of liver disease including viral hepatitis, biliary obstruction, hepatocellular carcinoma, Wilson's disease, Budd Chiari syndrome, autoimmune hepatitis, alcoholic liver disease, alcohol use (>20g/day women, >30g/day men), aspartate aminotransferase (AST) or alanine aminotransferase (ALT) > 300 U/L, current use of steatogenic medications (amiodarone, methotrexate, tamoxifen, and corticosteroids), pregnant, or with a history of liver transplantation. The study was approved by the institutional review board of the Icahn School of Medicine at Mount Sinai and was performed in accordance with the Declaration of Helsinki.

Study Design

A retrospective manual chart review of the EMR-identified patients was conducted to capture the following patient characteristics: demographic data including age, sex, race, and ethnicity. Presence of metabolic comorbidities and BMI was recorded. Laboratory values were documented during the initial study visit, with a margin of 3 months before or after that visit. Markers of liver inflammation (aminotransferases [ALT, AST], alkaline phosphatase, gamma-glutamyl transferase) and synthetic function [albumin and platelet count] were collected and recorded. Estimated GFR (eGFR), which is a calculation recorded in medical records, was observed as a surrogate of renal function and will hereby be referenced as equivalent to GFR. Proteinuria, albuminuria, and urinary biomarkers were not evaluated, given that these markers are generally not included in the routine testing during visits to gastroenterology and hepatology clinics. HTN and T2D were documented using ICD-10 codes from the EMR of each patient; as a result, distinct markers of metabolic dysfunction were not directly observed. This study also looked to see if there was an association between patients who were already on an angiotensin-converting enzyme inhibitor (ACEi), angiotensin receptor blocker (ARB), or metformin and its effect on renal function. To assess the degree of fibrosis, the fibrosis-4 (FIB-4) score was calculated. A FIB-4

Table 1. Patient Baseline Characteristics

Patient baseline characteristics	
N = 546	Mean (standard deviation)
Age (y)	55.63 (12.8)
BMI (kg/m^2)	35.73 (5.5)
Laboratory values	
FIB-4	1.60 (1.69)
GFR (mL/min)	88.95 (22.91)
ALT (IU/L)	45.32 (48.12)
AST (IU/L)	36.85 (32.36)
Albumin (g/dL)	4.08 (0.48)
ALP (U/L)	90.74 (38.36)
GGT (U/L)	58.92 (103.89)
Platelet count (10-9/L)	236.15 (70.98)
Cholesterol (mg/dL)	179.05 (40.70)
HDL (mg/dL)	48.34 (20.21)
LDL (mg/dL)	103.56 (35.36)
	n (%)
Sex	
Male	226 (41.4%)
Female	320 (58.6)
Ethnicity	
Hispanic	131 (24.0)
Non-Hispanic	259 (47.4)
Unknown/not recorded	156 (28.6)
Race	
White	207 (37.9%)
Black	83 (15.2%)
Asian	14 (2.6%)
Unknown	101 (18.5)
Other	141 (25.8)
Comorbidities	
Hypertension	271 (49.6%)
Diabetes	190 (34.9)
CAD	57 (10.4)
Use of ACE/ARB	204 (37.36%)
Use of metformin	163 (29.9)
FIB-4 < 1.30	302 (57.2)
FIB-4 [1.30–2.67]	167 (31.6)
FIB-4 > 2.67	59 (11.2)

ALP, alkaline phosphatase; CAD, coronary artery disease; GGT, gamma-glutamyl transferase; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

Table 2. Univariate Analysis

Univariate analysis

GFR (mL/min)	>90		[60–89.99]		[45–59.99]		[30–49.99]		<30		
N	228		234		44		5		4		*P*
Age (y) (mean|σ)	51.9	12.2	57.2	12.0	66.7	7.6	69.0	5.8	69.3	8.9	<.001
Sex											
Male (#|%)	88	39%	104	44%	19	43%	1	20%	3	75%	.371
Female (#|%)	140	61%	130	56%	25	57%	4	80%	1	25%	
Ethnicity											.466
Hispanic (#|%)	58	25%	59	25%	8	18%	0	0%	1	25%	
Non-Hispanic (#|%)	98	43%	111	47%	24	55%	5	100%	2	50%	
Unknown (#|%)	72	32%	64	27%	12	27%	0	0%	1	25%	
AST (IU/L) (mean|σ)	40.0	36.8	35.3	29.6	32.3	25.5	23.0	9.1	23.8	15.4	.285
ALT (IU/L) (mean|σ)	51.6	55.1	42.9	43.2	29.3	20.0	18.4	7.1	13.8	5.1	.015
Albumin (mean|σ)	4.1	0.5	4.1	0.5	4.0	0.5	3.4	0.4	4.0	0.6	.013
Platelet (#×10-9/L)	244.3	71.1	233.4	70.4	214.8	67.8	233.0	104.0	208.0	99.6	.096
Mean FIB-4	1.5	1.9	1.6	1.2	2.3	2.4	2.3	2.2	3.7	4.8	.005

<1.3 was considered as a low risk of significant fibrosis (<F2 fibrosis), values ≥ 1.3 to 2.67 was considered as intermediate risk (≥F2 fibrosis), and values ≥ 2.67 was considered high risk.

Statistical Analysis

Data were described and summarized using means and standard deviations for continuous variables and frequencies and proportions for categorical variables. Comparisons between independent variables were examined using *t*-tests for continuous variables and chi-squared or Fisher's exact tests (for sample sizes with < 15 observations in any cell) for categorical variables. Univariate and multivariate linear and logistic regression models were constructed to identify factors contributing to the stage of fibrosis. Confounders, including T2D, HTN, race/ethnicity, and medications, were included in multivariate regression models to account for their effects in the relationship between CKD and degree of fibrosis. A *P* value of < .05 was considered statistically significant.

Results

A total of 546 individuals with a diagnosis of MASLD were identified from a cohort of patients with obesity (n = 1896, BMI ≥ 30 kg/m^2) from January 2020 to June 2021. The demographic and clinical characteristics of individuals at baseline are outlined in Table 1. The majority of the patients were female (58.6%), the mean age was 56 years ± 12.7 years, and the mean BMI was 35.7 kg/m^2 ± 5.49 kg/m^2, consistent with class 2 obesity. The majority of the individuals included in this study identified as White, constituting 37.9%, 24% of the patients were Hispanic, and 15.2% were Black. The most common metabolic comorbidities were HTN (49.6%) and T2D (34.9%). It is also important to note that 204 (37.36%) of the participants were on an ACEi/ARB and 163 (29.9%) were on metformin. 302 of the patients had a FIB-4 score < 1.30, 167 had a FIB-4 score between 1.30 and 2.67, and 59 had a FIB-4 score ≥ 2.67 (see Table 1).

In univariate analysis (Table 2), increased age (*P* < .001), elevated ALT (defined as ALT ≥ 30 IU/L, *P* = .01), low albumin (*P* = .011), and increasing FIB-4 (*P* = .005) were statistically associated with a reduced renal function, characterized as a consistent measurement lasting for a duration of 3 months or more, where the value of eGFR <60 ml/min/1.73 m^2. In univariate linear regression (Table 2), a reduction in GFR was associated with an increase in FIB-4 (effect size [beta] of a one-unit increase in GFR on FIB-4 = −0.013, *P* < .001).

In multivariate linear regression (Table 3), T2D was independently associated with increased liver fibrosis, defined as equivalent to an increase in FIB-4 (effect size of T2D on FIB-4 = 0.387925, *P* < .02). After adjustment for T2D, the relationship between GFR and FIB-4 was maintained (beta −0.012; *P* < .001). HTN did not significantly change the relationship between GFR and FIB-4 in this model (*P* > .05). To assess the impact of race and ethnicity

Table 3. Multivariate Analysis

Multivariate analysis

	Estimate (beta)	*P* value
GFR	−0.0129	<.001
HTN	0.055	.730
T2DM	0.365	.027
White race	Reference	N/A
Black race	−0.387	.088
Asian race	−0.435	.385
Other race	0.057	.763
Unknown race	0.020	.924

Table 4. Distribution of FIB-4 Based on Ethnicity and Race

Distribution of FIB-4 based on ethnicity and race

	FIB-4 Avg	ALT (IU/L)	AST (IU/L)	FIB-4 1	FIB-4 2	FIB-4 3
Hispanic ethnicity	1.87	48.5	38.6	53%	30%	17%
White race	1.65	45.8	36.9	52%	36%	13%
Black race	1.35	37.3	34.1	67%	23%	10%
Asian race	1.05	80.6	53.7	77%	23%	0%
Other race	1.69	45.7	36.5	58%	27%	15%
Unknown race	1.62	45.5	37.2	57%	38%	5%

on the relationship between GFR and FIB-4, the effect size was calculated (Table 4). Patients of Black race had a lower FIB-4 (effect size of Black race, FIB-4 = −0.442) compared to White race ($P < .05$). Patients of Black race did not have evidence of worse baseline renal function at baseline compared to races of other patients included in this study (see Figure). Furthermore, there was no difference in FIB-4 between races ($P > .05$). Adjusting for race did not alter the underlying relationship between GFR and FIB-4.

Patients on ACEi, ARB, metformin, or combination of these medications were not found to have a significant difference in renal function ($P > .05$).

Discussion

In our cohort study of individuals with obesity and MASLD, 56% of the population was found to reduced renal function (GFR<60 mL/min/1.73m^2), with the majority having stage 2 CKD (GFR 60–89 mL/min/1.73m^2). We observed a notable decrease in ALT levels alongside a progression of fibrosis, as evidenced by an upward trajectory in FIB-4 scores, in the presence of impaired renal function. Hepatocellular liver injury (indicated by aminotransferases), age, albumin, and FIB-4 were associated with changes in GFR. T2D was identified as an independent risk factor of impaired renal function.

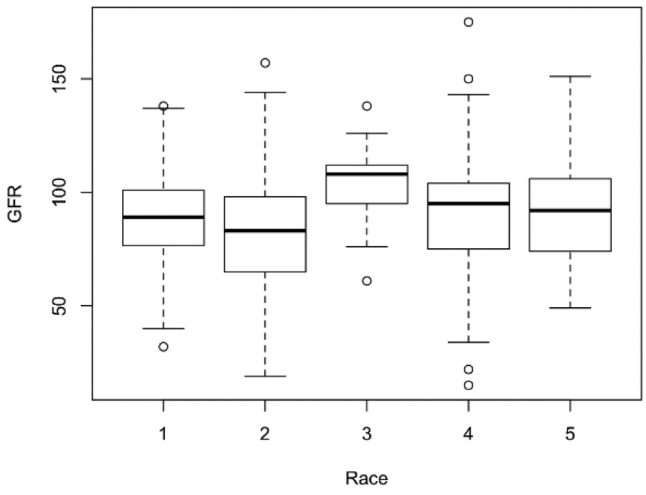

Figure. GFR levels stratified by race. Races: (1) White; (2) Black; (3) Asian; (4) Other; (5) Unknown.

Obesity has been clearly identified as one of the leading risk factors for MASLD, with approximated prevalence rates as high as 50%–90%, and significantly higher rates with increasing obesity classification.[4] Several studies have demonstrated the strong correlation of obesity with MASLD, including advanced disease (MASH, MASH-related cirrhosis, and hepatocellular carcinoma). On the basis of recent publications, the prevalence of CKD has significantly increased among patients with MASLD. This has sparked interest in trying to understand the relationship between CKD and MASLD, MASLD fibrosis, and cirrhosis. Our study shows that in a patient population with obesity and a diagnosis of MASLD, advanced fibrosis is independently associated with reduced renal function.

Similar studies have elucidated similar conclusions. In a cross-sectional study conducted in China including 3872 individuals with MASLD (defined by abdominal ultrasonography), the prevalence of CKD was higher in individuals with MASLD than in those without MASLD (15.8% vs 11.9%, $P < .001$). In this study, MASLD was shown to be associated with a 1.31 times higher risk of prevalent CKD after adjusting for common variables such as age, sex, and presence of T2D.[16] Results of this study, similar to ours, show that T2D stands out as an independent risk factor for higher FIB-4 and reduced renal function. These observations were made in a Chinese population with an imperfect method of diagnosing MASLD fibrosis (ultrasound imaging was employed to detect fibrotic changes); our approach involves using FIB-4, a widely accepted and validated noninvasive test for assessing fibrosis, despite it not being the gold standard method. Furthermore, our population is a robust representation of the general population with inclusion of populations that are commonly underrepresented with MASLD studies (ie Black population accounted for 15% of the total population).

Common generalizations about the predilection of MASLD have been challenged with a growing body of literature suggesting that there are racial and ethnic disparities in MASLD prevalence. The Hispanic population is commonly associated with high rates of MASLD and liver fibrosis, influenced by the increased prevalence of genetic variants such as PNPLA3 mutation and the presence of

metabolic comorbidities.[17] In contrast, Blacks are reported to have lower MASLD prevalence and severity compared to non-Hispanic Whites and Hispanic populations.[17] In our study, the Black population represented 15% of the entire cohort. The mean FIB-4 was 1.35 with a standard deviation of 0.80.

In a study by Browning et al, 287 subjects from multiple ethnicities (32% White, 48% Black, and 18% Hispanic), using proton magnetic resonance spectroscopy, one third of the population had hepatic steatosis of which Hispanics made up 45% compared to 33% in Whites and 24% in Blacks. In our study, of the patients with documented ethnicity, Whites represented the majority of the population with obesity and MASLD and Hispanics constituted just under half the population. Our study also showed that when compared to White race, only patients of Black race had a lower FIB-4 (effect size of Black race on FIB-4 $= -0.442$ compared to White race, $P < .05$). In a systematic review and meta-analysis by Rich et al, the highest burden on MASLD was found in Hispanics and the lowest burden was in Blacks.[17]

The observations made about renal dysfunction and hepatofibrosis in our cohort of patients with obesity and MASLD are noteworthy. However, the authors acknowledge the study's intrinsic limitations. These encompass the retrospective study design, the challenges tied to electronic medical record data, the precision of fibrosis measurements, and the approach of involving the continuous analysis of eGFR and FIB-4. Notably, the identification of MASLD relied on ICD-10 codes (specifically K76.0 and K75.8), a method that may not fully capture the actual prevalence of MASLD within this high-risk population. The study cohort was derived from a solitary tertiary care center, characterized by a substantial immigrant demographic. This context likely contributes to the nearly equivalent representation of White and Hispanic individuals within the cohort. However, as in other investigations into MASLD, the Black population remains underrepresented. Furthermore, the utilization of FIB-4 as a fibrosis indicator could potentially introduce misclassification in specific cases, given its potential limitations in distinguishing distinct fibrosis stages effectively. Our choice to employ eGFR and FIB-4 as continuous variables in the analysis stemmed from a comprehensive evaluation of the overall data set. This assessment highlighted the limitations within certain binary variable categories. Notably, the cohort exhibited limited representation of patients with advanced CKD (only N = 4 for GFR<30 mL/min), emphasizing the need for cautious interpretation. Shifting the focus to liver fibrosis, it's pertinent to note that a FIB-4 score exceeding 2.67 was present in 59 patients, constituting 11.2% of the entire study population. While this score aids in assessing risk, its capacity to discriminate among diverse fibrosis stages requires careful consideration. With a larger cohort, representing diverse populations, the authors suspect the associations between reduced renal function and fibrosis will reveal interesting trends revealing unique patient phenotypes and opportunities for therapeutics. In addition, the liver AT2 promotes IR and pro-inflammatory cytokine production which contributes to the development of MASLD. In the kidney, ACE-AT2 activation formulates renal ectopic lipid disposition and leads to obesity-associated CKD development.[13]

Conclusion

Both MASLD and CKD are major public health problems and the prevalence and incidence is growing. MASLD and CKD share many important cardiometabolic risk factors; however, understanding their overlapping pathways is presently incomplete. Our data support a growing body of literature that shows that there is likely a strong correlation between development of CKD in MASLD, independent of classic metabolic risk factors. Secondarily, we observed that the degree and distribution of CKD may be ethnicity specific, further supporting the racial and ethnic disparities in MASLD prevalence that go beyond socioeconomic status but may in fact be influenced by intrinsic pathophysiology.

References

1. Rinella ME, Neuschwander-Tetri BA, Siddiqui MS, et al. AASLD practice guidance on the clinical assessment and management of nonalcoholic fatty liver disease. Hepatology 2023;77:1797–1835.
2. Younossi ZM, Stepanova M, Ong J, et al. Nonalcoholic steatohepatitis is the most rapidly increasing indication for liver transplantation in the United States. Clin Gastroenterol Hepatol 2021;19(3):580–589.e5.
3. Dulai PS, Singh S, Patel J, et al. Increased risk of mortality by fibrosis stage in nonalcoholic fatty liver disease: systematic review and meta-analysis. Hepatology 2017;65(5):1557–1565.
4. Sanyal AJ, Van Natta ML, Clark J, et al. Prospective study of outcomes in adults with nonalcoholic fatty liver disease. N Engl J Med 2021;385(17):1559–1569.
5. Targher G, Day CP, Bonora E. Risk of cardiovascular disease in patients with nonalcoholic fatty liver disease. N Engl J Med 2010;363(14):1341–1350.
6. de Alwis NMW, Day CP. Non-alcoholic fatty liver disease: the mist gradually clears. J Hepatol 2008;48(Suppl 1):S104–S112.
7. Marchesini G, Moscatiello S, Di Domizio S, et al. Obesity-associated liver disease. J Clin Endocrinol Metab 2008;93(11 Suppl 1):S74–S80.
8. Vuppalanchi R, Chalasani N. Nonalcoholic fatty liver disease and nonalcoholic steatohepatitis: selected practical issues in their evaluation and management. Hepatology 2009;49(1):306–317.
9. Targher G, Bertolini L, Rodella S, et al. Non-alcoholic fatty liver disease is independently associated with an increased prevalence of chronic kidney disease and proliferative/laser-treated retinopathy in type 2 diabetic patients. Diabetologia 2008;51(3):444–450.

10. Musso G, Gambino R, Tabibian JH, et al. Association of non-alcoholic fatty liver disease with chronic kidney disease: a systematic review and meta-analysis. PLoS Med 2014;11(7):e1001680.
11. Musso G, Cassader M, Cohney S, et al. Emerging liver-kidney interactions in nonalcoholic fatty liver disease. Trends Mol Med 2015;21(10):645–662.
12. de Vries APJ, Ruan XZ, et al. Fatty kidney: emerging role of ectopic lipid in obesity-related renal disease. Lancet Diabetes Endocrinol 2014;2(5):417–426.
13. James MT, Hemmelgarn BR, Tonelli M. Early recognition and prevention of chronic kidney disease. Lancet 2010; 375(9722):1296–1309.
14. Sarnak MJ, Levey AS, Schoolwerth AC, et al. Kidney disease as a risk factor for development of cardiovascular disease: a statement from the American Heart Association Councils on kidney in cardiovascular disease, high blood pressure research, clinical Cardiology, and epidemiology and prevention. Hypertension 2003;42(5):1050–1065.
15. Divella R, Mazzocca A, Daniele A, et al. Obesity, nonalcoholic fatty liver disease and adipocytokines network in promotion of Cancer. Int J Biol Sci 2019;15(3):610–616.
16. Rich NE, Oji S, Mufti AR, et al. Racial and ethnic disparities in nonalcoholic fatty liver disease prevalence, severity, and outcomes in the United States: a systematic review and meta-analysis. Clin Gastroenterol Hepatol 2018;16(2):198–210.e2.
17. Browning JD, Kumar KS, Saboorian MH, et al. Ethnic differences in the prevalence of cryptogenic cirrhosis. Am J Gastroenterol 2004;99(2):292–298.

Received May 9, 2023. Accepted September 18, 2023.

Correspondence:
Address correspondence to: Amreen Dinani, MD, FRCPC, Division of Gastroenterology, Duke University, 40 Duke Medicine Cir Clinic 2J, Durham, North Carolina 27710. e-mail: amreen.dinani@gmail.com.

Authors' Contributions:
Conception and design: Amreen Dinani. Administrative support: Amreen Dinani. Provision of study material or patients: Amreen Dinani, Gres Karim, Carolina Villarroel, Jake Debroff, Mantej Sehmbhi, Ilan Weisberg. Collection and assembly of data: Amreen Dinani, Gres Karim, Carolina Villarroel, Jake Debroff, Ilan Weisberg. Data analysis and interpretation: Amreen Dinani, Gres Karim, Carolina Villarroel, Jake Debroff, Mantej Sehmbhi, Ilan Weisberg. Manuscript writing: Amreen Dinani, Gres Karim, Carolina Villarroel, Jake Debroff, Mantej Sehmbhi, Ilan Weisberg. Final review of manuscript: Amreen Dinani, Gres Karim, Carolina Villarroel, Jake Debroff, Mantej Sehmbhi, Ilan Weisberg.

Conflicts of Interest:
These authors disclose the following: Ilan Weisberg is a speaker for Gilead. Amreen Dinani is a consultant for Guidepoint, LCN NIH funding. The remaining authors disclose no conflicts.

Funding:
The authors report no funding.

Ethical Statement:
The study was approved by the IRB of the Icahn School of Medicine at Mount Sinai and was in accordance with the Declaration of Helsinki. The corresponding author, on behalf of all authors, jointly and severally, certifies that their institution has approved the protocol for any investigation involving humans or animals and that all experimentation was conducted in conformity with ethical and humane principles of research.

Data Transparency Statement:
Data, analytic methods, and study materials will not be made available to other researchers.

Reporting Guidelines:
Helsinki Declaration.