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MAJOR ARTICLE

Steatosis Rates by Liver Biopsy and Transient Elastography With Controlled Attenuation Parameter in Clinical Experience of Hepatitis C Virus (HCV) and Human Immunodeficiency Virus/HCV Coinfection in a Large US Hepatitis Clinic

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Background. Steatosis contributes to liver fibrosis in hepatitis C virus (HCV) and human immunodeficiency virus (HIV)/HCV coinfection. Liver biopsy (LB) is the reference standard for grading steatosis and staging fibrosis, yet recent advances in noninvasive modalities have largely supplanted LB, which may limit recognition of steatosis. We evaluated steatosis rates by LB and transient elastography (TE) with controlled attenuation parameter (CAP) among HCV-infected and HIV/HCV-coinfected patients in a US clinic.

Methods. Patients with chronic HCV infection during pretreatment evaluation by LB (n = 421; December 2001 through May 2014) and TE with CAP (n = 1157; May 2016 through May 2017) were included. Fibrosis and steatosis rates by LB and TE with CAP were stratified by HCV versus HIV/HCV coinfection status.

Results. Steatosis was not reported in 26.1% of LBs. Moderate to severe steatosis (grade ≥S2) was detected more often with CAP than with LB (in 24.0% vs 11.4% of patients, respectively). Median CAP values were higher in patients with HCV monoinfection than in those with coinfection (230 vs 215.5 dB/m, respectively; $P < .001$). With TE, the rate of advanced fibrosis (values F3–F4) was higher in HCV monoinfection than in coinfection (25.9% vs 14.8%, respectively; $P < .001$). With both LB and TE, advanced fibrosis (F3–F4) was significantly associated with moderate to severe steatosis (S2–S3) in HCV monoinfection compared with HIV/HCV coinfection (33.3% vs 4.4%, respectively for LB [$P = 0.003$] and 36.0% vs 29.0% for TE [$P = 0.008$]).

Conclusions. In patients with chronic HCV undergoing liver fibrosis staging, steatosis was detected more often with CAP than LB, with median CAP values higher in HCV monoinfection than HIV/HCV coinfection. Steatosis severity may be increasing in the modern HCV treatment era.

Keywords. HIV; Hepatitis C; steatosis; fibrosis; controlled attenuation parameter.

Nonalcoholic fatty liver disease (NAFLD) is a common cause of liver disease in Western adult populations and an increasingly important cause of disease and death [1, 2]. High prevalence of NAFLD has been recorded in both human immunodeficiency virus (HIV)– and hepatitis C virus (HCV)–infected populations, including those with coinfection [3–5]. NAFLD is one of the leading causes of progressive liver disease and comprises a wide spectrum of presentations, including hepatic steatosis (HS), nonalcoholic steatohepatitis (NASH), and cirrhosis. There are few indicated treatments for NAFLD, with weight loss as the foundation of current recommendations [6]. Metabolic factors are important considerations for development, most notably obesity, type 2 diabetes mellitus, and dyslipidemia. Ethnicity and sex are also important considerations, with the highest prevalence seen in men and Hispanic populations [1, 2, 7]. Patients with advanced fibrosis from NAFLD have an increased likelihood of death, mostly attributed to decompensated liver disease and cardiovascular disease [8, 9]. With HCV cure initiatives currently underway, NAFLD will probably cause the greatest burden of chronic liver disease within the next decade.

For persons living with HIV (PLWH) the mortality rate from HIV/AIDS has substantially decreased with effective antiretroviral therapy, thus elevating the importance of identifying chronic comorbid conditions, such as HCV infection and NAFLD. The progression to liver fibrosis is common and appears to be similar in HCV monoinfected and HIV/HCV coinfected patients [10–12]. Despite this, HCV coinfection,

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compared with HIV monoinfection, has been associated with an increased risk of death in large cohort studies [13–15].

PLWH may have more severe steatosis, with the reported prevalence of NAFLD ranging from 15% to 54% [4, 16]. Factors associated with NAFLD in HIV and HIV/HCV coinfection include male sex, increased body mass index (BMI), metabolic syndrome, diabetes, abnormal cholesterol levels, and lipodystrophy [3, 5, 17, 18]. Interestingly, HIV-related factors have not been consistently demonstrated as risk factors for development of NAFLD [3]. Outcomes data are mostly limited to treatment of HCV coinfection, because historically PLWH have been excluded from NAFLD studies [5]. The prevalence and natural history of NAFLD in PLWH are not currently well defined.

HCV is a common coinfection in PLWH owing to shared transmission routes, which can also contribute to HS. Previous estimates suggest a coinfection rate of 15%–30% [19, 20]. Patients with HIV/HCV coinfection have been reported to have high prevalence of steatosis associated with more advanced fibrosis, especially in older age groups [5, 21, 22]. Coinfected patients with underlying NASH were also at increased risk of fibrosis progression that was not influenced by HIV viral suppression [12]. More advanced fibrosis is associated with increased risk of end-stage liver disease, hepatocellular carcinoma (HCC), or death [23]. Steatosis rates vary based on study population, ranging from 46.3% to 59% for HCV monoinfection and from 47% to 72.1% for HIV/HCV coinfection [17, 18, 21].

Diagnosis of NAFLD requires imaging or histologic evidence of HS. Liver biopsy (LB) is considered the reference standard in diagnosis. This allows concomitant evaluation of fibrosis, steatosis, and inflammation [8]. However, biopsy is an invasive procedure that may have limited availability and potential adverse outcomes. Thus, there has been a significant effort to develop noninvasive testing to follow progression of disease over time and to diagnose HS. Currently, no serum biomarkers are approved for clinical use to detect HS or NASH [24].

Useful imaging techniques to quantify HS and fibrosis include ultrasonography- and magnetic resonance imaging–based modalities, with ultrasonography the most widely available. Transient elastography (TE) with controlled attenuation parameter (CAP) has increasingly been used as a noninvasive means of assessing the steatosis grade. TE with CAP simultaneously measures the degree of ultrasound attenuation by hepatic fat and liver stiffness as an indication of fibrosis [25]. CAP has also been validated by cross-sectional studies in patients with HIV, HCV, and HIV/HCV infection [26], although cross-sectional trends in steatosis over time remain poorly studied in patients with chronic HCV and HIV infection.

Because most previous data for steatosis rates in liver fibrosis staging were collected and analyzed based on LB results, our study aimed to evaluate TE-CAP as a noninvasive method of evaluation in these patients. The objective of the current study was to evaluate steatosis and fibrosis rates by LB and TE-CAP in HCV-monoinfected and HIV/HCV-coinfected patients in 2 cross-sectional eras at a large US hepatitis clinic.

MATERIALS AND METHODS

Study Population

This single-center retrospective study selected patients from HCV-monoinfected and HIV/HCV-coinfected populations engaged in care at the Cook County CORE Center hepatitis clinic in Chicago, Illinois. Unique patients with chronic HCV infection (either monoinfected or coinfected) during pretreatment evaluation were analyzed. All patients were >18 years of age and had positive HCV RNA results by commercial assay. TE replaced LB for fibrosis staging in June 2014 in our clinic, and CAP was added to TE in May 2016.

The analysis included patients engaged in care from December 2001 to May 2014 (n = 421) who had an LB result. For patients with multiple available biopsy results, only the last collected result was included. This report probably represents the most recent HCV pretreatment staging procedure, because LBs were not typically performed after HCV therapy. Also included in the analysis were patients engaged in care from May 2016 to May 2017 with documented TE-CAP (n = 1157). For those with multiple TE-CAP results, only the initial measurement was analyzed, because treatment of HCV infection was more easily offered after initial staging, and follow-up TE is commonly performed in our clinic after sustained virologic response (SVR) to determine fibrosis regression. Patients were excluded from analysis if they had a history of autoimmune hepatitis or hepatitis B coinfection.

Demographic data were extracted for each patient including age, sex, race, ethnicity, and HIV status. Before LB or TE-CAP evaluation, each patient underwent standard biochemical testing. For the LB population, the variables included aspartate aminotransferase (AST), alanine aminotransferase (ALT), platelets, albumin, α-fetoprotein (AFP), international normalized ratio (INR), cholesterol, creatinine, total bilirubin, and in patients with HIV coinfection CD4 cell count nadir and at the time of LB. For the TE-CAP population, variables included probe size, AST and ALT, and, when available for nonreferred patients receiving care at the Cook County Health & Hospital System (CCHHS), platelets, albumin, AFP, INR, cholesterol, creatinine, total bilirubin, CD4 cell count nadir, and last CD4 cell count before TE-CAP. The study was approved by the CCHHS Institutional Review Board.

Liver Histopathology

LB specimens were obtained in the usual fashion and were scored by local pathologists at CCHHS according to the METAVIR fibrosis stage (F0–F4) [27]; the scale used to classify fibrosis was as follows: F0 represents no fibrosis; F1, perisinusoidal/pericellular fibrosis only; F2, perisinusoidal/pericellular fibrosis with periportal fibrosis; F3, perisinusoidal/pericellular fibrosis

with periportal fibrosis and bridging fibrosis; and F4, cirrhosis. Steatosis was scored based on the necroinflammatory grading system, with assignment of a steatosis grade (S0–S3). The scale used to classify steatosis grade was as follows: S0, no steatosis; S1, mild (<10% hepatocytes); S2, moderate (10%–30% hepatocytes); and S3, severe (>30% hepatocytes). Reports that did not comment on steatosis were documented as "not reported."

TE-CAP Protocol

All TE was performed in our clinic by certified operators according to manufacturer instructions (FibroScan, Echosens, Paris), using either the medium-sized (3.5-Hz frequency) or extra-large (XL) (2.5-Hz frequency) probe. The XL probe was used when the distance from skin to liver capsule exceeded 2.5 cm, as measured by sonographic imaging, and/or when BMI was >30. Cutoff values were assigned according to manufacturer recommendations. For HCV monoinfection and HIV/HCV coinfection, fibrosis stages are assigned as follows: F0–F1 indicates no to mild scarring (2–7 kPa); F2, mild fibrosis (7.1–9.4 kPa); F3, severe fibrosis (9.5–12.4 kPa); and F4, cirrhosis (≥12.5 kPa). Patients were also assigned a steatosis grade (S0–S3) (based on CAP scores in decibels per meter, which is a calculation of the attenuation of ultrasonic signals used for TE) as described elsewhere by Sasso et al [28]. The grades are assigned as follows: S0, no steatosis (0%–10% fat; 0–237 dB/m); S1, mild steatosis (11%–33% fat; 238–259 dB/m); S2, moderate steatosis (34%–66% fat; 260–292 dB/m); and S3, severe steatosis (>67% fat; ≥293 dB/m).

Statistical Analysis

Two binary logistical regression analyses were performed. The first analysis considered steatosis determined by LB. A dichotomous variable was derived by coding those patients with S3 results as 1, and those with S1–S2 results as 0. The second dependent variable in the analysis was fibrosis as determined by TE-CAP. This variable was similarly coded, with TE-CAP results of F3–F4 coded as 1, and F0–F2 results coded as 0. For LB, independent variables in the analysis are included in Table 1. For TE-CAP, the demographics considered are included in Table 2. When applicable, health-related indicators were categorized into clinical reference ranges, as follows: ALT ≥1.5 the upper limit of normal (≥52 U/L), AST ≥1.5 the upper limit of normal (≥60 U/L), platelets ≤130 000/μL, AFP ≥10 ng/mL, and INR ≥1.2.

RESULTS

Baseline Characteristics

A total of 1578 unique patients were included in this study, 13 of whom had both LB and TE-CAP performed within the respective time periods. There were 421 patients in the LB group, 73.6% male, with a median age of 50 years; 57.6% (n = 243) were coinfected, and 42.4% (n = 178) were HCV monoinfected. There was a slight predominance of males in the coinfection subgroup (80.7% vs 64% in the monoinfection subgroup) (Table 1). There were 1157 patients in the TE-CAP group, 66.6% male, with a median age of 57 years; 20.5% (n = 237) were coinfected, and 79.5% (n = 919) were HCV monoinfected (Table 2). The median age increased by 7 years from the LB era to the era of TE-CAP assessment. With TE-CAP, the XL probe (BMI >30) was used significantly more often in HCV-monoinfected patients than in coinfected patients (12.2% vs 5.5%, respectively; $P = .002$).

Steatosis

In 26.1% of LB reports, steatosis histopathology was not recorded. Moderate-severe steatosis (≥S2) was detected more often with CAP than with LB (24.0% vs 11.4%, respectively) among recorded results, and with LB this rate of S2–S3 steatosis was higher in HCV monoinfection than in HIV/HCV coinfection (15.7% vs 8.6%; $P = .002$) (Table 1). Similar steatosis rates were seen in coinfected and monoinfected populations for S0–S1 steatosis by LB and S1 steatosis by CAP. With CAP, the rate for "no steatosis" (S0) was slightly higher for HIV/HCV coinfection than for HCV monoinfection (70.5% vs 57.1%; $P = .002$). Median CAP scores were significantly higher in HCV monoinfection than in HIV/HCV coinfection (230 vs 215.5 dB/m; $P < .001$), with higher CAP scores (S3) associated with HCV monoinfection (11.8% vs 4.6% for coinfection; $P < .001$) (Table 2).

Fibrosis

Fibrosis rates with LB were similar in HCV-monoinfected and HIV/HCV-coinfected patients for all stages (F0–F4) (Table 1). With TE, rates of advanced fibrosis (F3–F4) (38.4%) were significantly higher in HCV monoinfection (for F4, 25.9% vs 14.8% in coinfection; $P < .001$). With TE, HIV/HCV coinfection was associated with lower fibrosis stage (F0–F1) (46.4% vs 38.4% for HCV monoinfection; $P = .03$) (Table 2). With both LB and TE, advanced fibrosis (F3–F4) was significantly associated with moderate-severe steatosis (S2–S3) in HCV monoinfection, compared with HIV/HCV coinfection (33.3% vs 4.4%, respectively, for LB [$P = .003$] and 36.0% vs 29.0% for TE [$P = .008$]). With LB and TE, lower stages of fibrosis (F0–F1) were significantly more associated with lower grades of steatosis (S0–S1) in coinfection than in HCV monoinfection (96.3% vs 86.7% for LB [$P = .02$] and 90.0% vs 81.0% for TE [$P = .002$], respectively) (Tables 1 and 2).

Logistic Regression Analysis

With LB, lower ALT levels (odds ratio [OR], 0.067; $P = .03$) and age 40–49 years (OR, 0.058; $P = .03$) were correlated with moderate-severe steatosis (grade S1–S2). For fibrosis a correlation was found between lower ALT levels (OR, 0.080; $P = .01$) and lower levels of fibrosis (score F0–F1). For TE-CAP, higher AST levels were associated with F3–F4 fibrosis (OR, 1.033; $P < .001$), and lower ALT levels with F1–F2 fibrosis (OR, 0.986;

Table 1. Steatosis and Fibrosis Rates Associated With Hepatitis C Virus (HCV) Monoinfection and Human Immunodeficiency Virus/HCV Coinfection by Liver Biopsy

Variable	All Patients, No. (%) (n = 421)[a]	*P* Value	HIV/HCV-Coinfected Patients, No. (%)[a] (n = 243)	HCV-Monoinfected Patients, No. (%)[a] (n = 178)	*P* Value
Age, median, y	50.0	…	50.0	51.0	…
Sex					
Male	310 (73.6)	…	196 (80.7)	114 (64.0)	<.001
Female	111 (26.4)		47 (19.3)	64 (36.0)	
Race and ethnicity[b]					
African American	270 (64.0)	…	168 (69.1)	102 (57.3)	.45
White	116 (27.5)	…	65 (26.7)	51 (28.7)	.26
Asian	10 (2.4)	…	10 (4.1)	0 (0.0)	.008
Hispanic or Latino	73 (17.3)	…	47 (19.3)	26 (14.6)	.24
Other/unknown	12 (2.9)	…	5 (5.7)	7 (4.0)	.33
Fibrosis stage[c]					
F0	35 (8.3)	…	22 (9.1)	13 (7.3)	.31
F1	136 (32.3)	…	85 (35.0)	51 (28.7)	.09
F2	136 (32.3)	…	73 (30.0)	63 (35.4)	.16
F3	77 (18.2)	…	43 (17.7)	34 (19.1)	.42
F4	35 (8.3)	…	18 (7.4)	17 (9.6)	.28
Steatosis grade (hepatocytes)[c]					
S0 (0%)	125 (29.7)	…	87(35.8)	38 (22.2)	.002
S1 (<10%)	138 (32.7)	…	77 (31.7)	61 (34.2)	.17
S2 (11%–30%)	32 (7.6)	…	13 (5.3)	19 (10.7)	.02
S3 (>30%)	16 (3.8)	…	7 (2.9)	9 (5.1)	.14
Not reported	110 (26.1)	…	59 (24.3)	51 (28.7)	.18
S2–S3	48 (11.4)	…	21 (8.6)	28 (15.7)	.02
F0–F1 (n = 127)		<.001			
S0–S1	118 (93.7)		79 (96.3)	39 (86.7)	.02
S2–S3	9 (7.1)	…	3 (3.7)	6 (1.3)	.18
F2–F4 (n = 184)		<.001			
S0–S1	145 (78.8)		85 (79.4)	60 (77.9)	.68
S2–S3	39 (21.2)	…	22 (20.6)	17 (22.1)	.19
F3–F4 (n = 78)		.72			
S0–S1	65 (83.3)	…	43 (95.6)	22 (66.7)	.13
S2–S3	13 (16.7)		2 (4.4)	11 (33.3)	.003

Numbers in this section (F0–F1, F2–F4 and F3–F4) represent the totals for available steatosis reports.

Abbreviations: HCV, hepatitis C virus; HIV, human immunodeficiency virus.

[a]Data represent no. (%) of patients unless otherwise specified.

[b]Note: 52 patients identified as both Latino and white, and 7 as both Latino and other.

[c]See Liver Histopathology for explanation of fibrosis staging and steatosis grading systems.

$P < .001$). Medium probe size was associated with F1–F2 fibrosis (OR, 0.020; $P = .51$). With TE, HCV monoinfection was correlated with F3–F4 fibrosis (OR, 1.787; $P = .02$).

DISCUSSION

In patients with chronic hepatitis C undergoing liver fibrosis staging, we identified steatosis more often with CAP than with LB, with higher median CAP scores in HCV monoinfection than in HIV/HCV coinfection. We also found that rates of advanced fibrosis and severe steatosis were significantly higher in HCV monoinfection than in coinfection in our population. With both LB and TE, HIV/HCV coinfection with advanced fibrosis was associated with moderate-severe steatosis. Importantly, no histopathologic record of steatosis was reported in >25% of LBs in this clinical setting.

Several previous studies have shown increased prevalence and severity of steatosis and fibrosis in HIV/HCV-coinfected patients than in those with either HIV or HCV monoinfection. It is postulated that HIV may act in synergy with HCV to cause steatosis by disrupting lipid metabolism, resulting in more severe disease in coinfected patients [21]. However, other researchers have also previously shown lower disease severity in coinfected patients. Comparison of liver fibrosis progression using TE-CAP in HIV monoinfection or HCV monoinfection versus coinfection in a Canadian prospective cohort found that HS and liver fibrosis progressed faster in HIV monoinfection than in those with HIV/HCV coinfection. In that study HCV

Table 2. Steatosis and Fibrosis Rates Associated With Hepatitis C Virus (HCV) Monoinfection and Human Immunodeficiency Virus/HCV Coinfection by Transient Elastography With Controlled Attenuation Parameter

	All Patients, No. (%)[a] (n = 1157)	*P* Value	HIV/HCV-Coinfected Patients, No. (%)[a] (n = 237)	HCV-Monoinfected Patients, No. (%) (n = 919)[a] (%)	*P* Value
Age, median, y	57	…	57	59	…
Sex					
Male	771 (66.6)	…	184 (77.6)	585 (63.7)	<.001
Female	379 (32.7)		48 (20.3)	331 (36.0)	
Probe size					
Medium	997 (86.1)	…	217 (91.6)	778 (84.7)	…
XL (BMI ≥30)	125 (10.8)	…	13 (5.5)	112 (12.2)	.002
Race and ethnicity					
African American	817 (70.6)	…	171 (72.2)	646 (70.3)	.63
White	174 (15.0)	…	25 (10.5)	149 (16.2)	.03
Asian	31 (2.7)	…	1 (0.4)	31 (3.4)	.01
Hispanic or Latino	132 (11.4)	…	40 (16.9)	92 (10.0)	.004
Other/unknown	3 (0.19)	…	1 (0.4)	2 (0.22)	>.99
Fibrosis stage[b]					
F0–F1 (<7.1 kPa)	463 (40.1)	…	110 (46.4)	353 (38.4)	.03
F2 (7.1–9.4 kPa)	277 (23.9)	…	65 (27.4)	212 (23.1)	.17
F3 (9.5–12.4 kPa)	142 (12.3)	…	27 (11.4)	115 (12.5)	.03
F4 (≥12.5 kPa)	273 (23.7)	…	35 (14.8)	238 (25.9)	<.001
CAP score, median, dB/m	226	…	215.5	230	<.001
Steatosis grade (CAP score)[b]					
S0 (0–237 dB/m)	692 (59.8)	…	167 (70.5)	525 (57.1)	<.001
S1 (238–259 dB/m)	187 (16.2)	…	33 (13.9)	154 (16.8)	.32
S2 (260–292 dB/m)	158 (13.7)	…	26 (11.0)	132 (14.4)	.20
S3 (≥293 dB/m)	119 (10.3)	…	11 (4.6)	108 (11.8)	<.001
F0–F1 (n = 463)		<.01			
S0–S1	385		99 (90.0)	286 (81.0)	.002
S2–S3	78	…	11 (10.0)	67 (19.0)	.19
F2–F4 (n = 692)		.02			
S0–S1	494	…	101 (79.5)	393 (69.6)	<.001
S2–S3	198		26 (20.5)	172 (30.4)	.005
F3–F4 (n = 415)		<.001			
S0–S1	270	…	44 (71.0)	226 (64.0)	.058
S2–S3	145		18 (29.0)	127 (36.0)	.008

Abbreviations: BMI, body mass index; CAP, controlled attenuation parameter; HCV, hepatitis C virus; HIV, human immunodeficiency virus; TE, transient elastography; XL, extra large.

[a]Data represent no. (%) of patients unless otherwise specified.

[b]See TE-CAP Protocol for explanation of fibrosis stages and steatosis grades (CAP scores).

coinfection was an independent negative predictor of HS progression [29].

We suspect that the lower rates of severe steatosis in our coinfected patients reflects increased long-term engagement in healthcare that may mitigate contributory metabolic factors for steatosis, together with higher rates of obesity in HCV-monoinfected patients. Many monoinfected patients came into care during our TE-CAP study period owing to new availability of healthcare access through the Affordable Care Act. A high proportion of patients at our facility are part of undeserved and low-income communities with disparities in healthcare access. In contrast, many coinfected patients in this study were already engaged in care at our facility and thus internally referred for viral hepatitis therapy. It is plausible that patients already engaged in care may have had better control of chronic health conditions, including obesity.

As LBs have become less desirable, assessment for NAFLD and HS with reliable noninvasive modalities has been an area of extensive development. Repeating CAP measurements longitudinally may detect worsening steatosis in subgroups of patients in whom it is associated with progressive fibrosis [29]. Scoring tools using proprietary algorithms such as the enhanced liver fibrosis (ELF) score, investigational biomarkers such as pro-pepticed of type III collagen (Pro-C3) and routine serum markers of liver function, including ALT, AST, platelets, and γ-glutamyltransferase (for the AST-to-platelet ratio index and fibrosis-4 (FIB-4)) have been evaluated to estimate HS but have generally lacked validation owing to frequently normal levels in HS and poor correlation with histopathologic findings [30–33]. Identification of factors associated with HS or fibrosis progression after treatment of HCV infection in monoinfected

and coinfected patients may be helpful in monitoring the clinical course after SVR.

The advance of direct-acting antiviral therapy has revolutionized the treatment of HCV infection. Risk of liver failure, HCC, and death dramatically decrease with SVR [34–37]. As markers of inflammation and fibrosis, transaminase levels often normalize with SVR in both HCV monoinfection and HIV/HCV coinfection, and elevated transaminase levels after SVR may signal persistent homeostatic abnormalities in hepatic inflammation and architecture, including steatosis. Cirrhosis and baseline elevated TE-CAP results have been associated with persistent transaminase elevation and slower decrease in TE values that was independent of HIV status [38]. Certain patient populations require ongoing surveillance after SVR; patients with baseline advanced fibrosis or cirrhosis before direct-acting antiviral treatment still require periodic imaging to detect HCC after SVR, because HCC emergence is not completely eliminated with cure of HCV infection [37]. However, these imaging techniques, usually liver ultrasonography or magnetic resonance imaging, do not demonstrate steatosis if not equipped with specialized probes or software. In HCV-infected patients with hepatosteatosis, better understanding of the natural history of NAFLD and improved noninvasive diagnostics will help guide monitoring and treatment of these patients after curative therapy for HCV infection.

Our study had several limitations. First, a large proportion of biopsy reports did not record steatosis findings, potentially underestimating the burden of steatosis before the availability of TE-CAP. For the LB cohort, the original intent of biopsy was for staging of fibrosis, not assessment of steatosis. For the LB cohort, BMI was not ascertained, because a proportion of LBs predated the implementation of our electronic medical record for BMI data abstraction. Comorbidity information was also not universally collected in our database, so was not available for analysis. In addition, patients referred for LB were often carefully selected and may not be representative of the overall population. It is possible that using the noninvasive TE-CAP method invited more comprehensive representation of the population being evaluated.

Finally, the steatosis grading system for LB was based on that of the French METAVIR Groupe, rather than the current internationally used algorithm for steatosis and NAFLD activity score introduced in 2005, which postdated our LB specimens collected in 2001–2004 [39]. However, there were advantages to using these criteria for our study: The French cutoffs were widely used in previous HIV/HCV coinfection cohorts [40], our pathologists were not uniformly recording other histologic features (eg, ballooning and intralobular inflammation) that factor into the NAFLD activity score, and sensitivity for steatosis severity detection may have increased, given the degree of pathologists' underreporting for any presence of steatosis.

In conclusion, steatosis contributes to liver fibrosis in both HCV and HIV/HCV coinfection. Recent advances in noninvasive imaging for staging have largely supplanted LB in HCV infection, which may limit recognition of underlying steatosis. In this study, any histopathologic record of steatosis was not reported in >25% of LBs. Steatosis in this study was more often detected with CAP than with LB. Median CAP scores were significantly higher in HCV-monoinfected than in coinfected patients. The severity of NAFLD may be increasing in the modern HCV treatment era, particularly in HCV monoinfection. With both LB and TE, advanced fibrosis was associated with moderate to severe steatosis, with stronger associations in the HCV-monoinfected population. In clinical settings that may not have access to elastographic techniques validated for steatosis, improved biomarkers are needed to serially assess HCV-infected patients with significant steatosis after curative therapy for HCV infection.

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