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MASLD IN PEOPLE WITH HIV EXHIBITS HIGHER FIBROSIS STAGE DESPITE LOWER DISEASE ACTIVITY THAN IN MATCHED CONTROLS

Dr. Daniela Allende[1], **Dr. Oscar Cummings**[2], **Ms. Alice L Sternberg**[3], **Dr. Cynthia A. Behling**[4], **Dr. Danielle Carpenter**[5], **Dr. Ryan M. Gill**[6], **Dr. Cynthia D. Guy**[7], **Dr. Matthew M. Yeh**[8], **Dr. Samer Gawrieh**[9], **Dr. Richard K. Sterling**[10], **Dr. Susanna Naggie**[11], **Dr. Rohit Loomba**[12], **Dr. Jennifer C. Price**[13], **Mrs. Mary McLaughlin**[14], **Dr. Colleen Hadigan**[14], **Mrs. Holly Crandall**[2], **Ms. Patricia Belt**[3], **Ms. Laura Wilson**[3], **Dr. Naga P. Chalasani**[9], **Dr. David E Kleiner**[15], **HIV NASH and NASH Clinical Research Groups**

[1]Cleveland Clinic, Cleveland, OH, United States

[2]Department of Pathology, Indiana University School of Medicine, Indianapolis, IN, United States

[3]Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, United States

[4]Pacific Rim Pathology, San Diego, CA, United States

[5]Saint Louis University, St. Louis, MO, United States

[6]University of California San Francisco, San Francisco, CA, United States

[7]Duke University, Durham, NC, United States

[8]University of Washington, Seattle, WA, United States

[9]Department of Medicine, Indiana University School of Medicine, Indianapolis, IN, United States

[10]Virginia Commonwealth University Health System, Richmond, VA, United States

[11]Duke Clinical Research Institute, Durham, NC, United States

[12]University of California San Diego, San Diego, CA, United States

[13]University of California San Francisco, San Francisco, CA, United States

[14]National Institute of Allergy and Infectious Disease (NIAID), Bethesda, MD, United States

[15]Laboratory of Pathology, National Cancer Institute, Bethesda, MD, United States

Corresponding author: David E Kleiner MD PhD, Laboratory of Pathology, National Cancer Institute, Bethesda, MD, United States, kleinerd@mail.nih.gov, Address: Building 10 - Magnuson CC, Room 2B44, Bethesda, MD 20892.

Conflict of interest:

Dr. Behling's institution provides contract services for ICON, Covance and Sharp Healthcare Laboratories. Dr. Behling has received speaker fees from Pfizer and Alimentiv for NASH related topics.

Dr. Chalasani reports no conflicts of interest relevant for this paper. For full disclosure, he reports paid consulting agreements with Madrigal, Zydus, Ipsen, Pfizer, Merck, Altimmune, BioMea and GSK, He receives research grant support from Exact Sciences and Zydus. He reports equity interest in Avant Sante Therapeutics, LLC, a contract clinical research organization and Heligenics, a drug discovery start-up.

Other authors report no conflicts related to this paper.

Summary

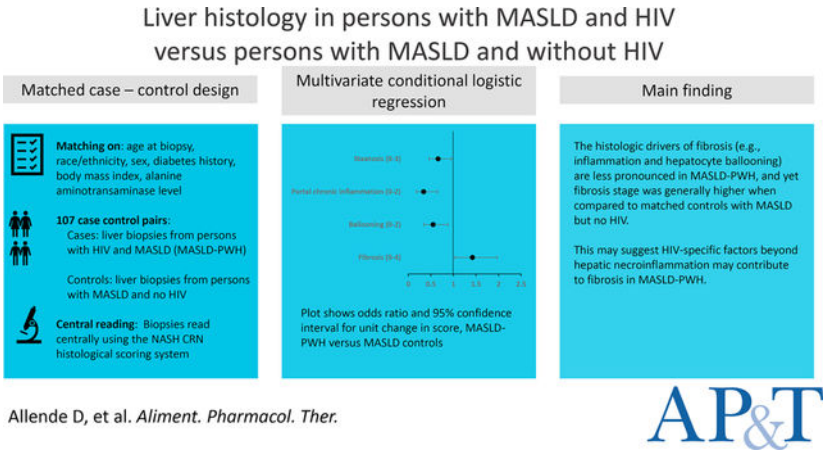
Background: Metabolic dysfunction-associated steatotic liver disease (MASLD) is common in people with HIV (PWH). The morphologic spectrum of MASLD compared to matched controls and of the correlation between the NAFLD activity score (NAS) and fibrosis stage in PWH remains unknown.

Methods: 107 liver biopsies from PWH with MASLD (MASLD-PWH) were matched to 107 biopsies from individuals with MASLD and without HIV (MASLD controls) on age at biopsy, race/ethnicity, sex, type 2 diabetes, body mass index (BMI), and alanine aminotransferase (ALT) level. Biopsies were scored using NAS.

Results: Compared to MASLD-controls, MASLD-PWH had lower steatosis grade (OR 0.65, 95%CI (0.47, 0.90), P=0.01), lower lobular inflammation grade (OR 0.55, 95%CI (0.34, 0.89), P=0.02), less portal inflammation (OR 0.42, 95%CI (0.25, 0.72), P=0.002), and less ballooned hepatocytes (OR 0.60, 95%CI (0.41, 0.88), P=0.01). Thus, NAS was lower in MASLD-PWH (OR 0.69, 95%CI (0.56, 0.85), P<0.001) than in MASLD controls. There was a trend towards lower prevalence of steatohepatitis in MASLD-PWH (OR 0.84, 95%CI (0.68, 1.03), P=0.09). A multivariate analysis demonstrated that MASLD-PWH cases had significantly less steatosis (OR 0.66, P=0.03), portal inflammation (OR 0.34, P=0.001), and ballooned hepatocytes (OR 0.55, P=0.01), yet higher stage fibrosis (OR 1.42, P=0.03) compared to MASLD controls.

Conclusion: The NAS and histologic drivers of fibrosis (e.g., inflammation and hepatocyte ballooning) are less pronounced in MASLD-PWH, and yet fibrosis stage was generally higher when compared to matched controls with MASLD ~~but~~ without HIV. This suggests HIV-specific factors beyond hepatic necroinflammation may contribute to fibrosis progression in MASLD-PWH.

Graphical Abstract:



Keywords

HIV; PWH; MASLD; Ballooned hepatocytes; Fibrosis

Background

People with Human Immunodeficiency Virus (PWH) are at risk for acute and chronic liver injury including alcohol and metabolic disorders and drug induced liver injury. Studies in metabolic dysfunction-associated steatotic liver disease (MASLD) have historically excluded patients with other coexisting diseases, such as Human Immunodeficiency Virus (HIV). The available data suggest that PWH may show MASLD in 20–63% of cases [1–12]. Some of these studies [13–14] have focused on clinical manifestations and/or faced limitations in the number of patients included (and used methodology that precluded extrapolating their results to larger populations). Further, the morphologic spectrum of histopathological findings and the correlation between the NAFLD activity score (NAS) and fibrosis stage, in PWH, remain to be explored.

Aim

In this study, we compared the histological findings from liver biopsies of MASLD in individuals with and without HIV who were matched on demographic and health characteristics.

Methods

The study was approved by the institutional review board at each participating site and the data coordinating center (DCC). Liver biopsies were obtained from the NASH Clinical Research Network (NASH CRN) and the HIV NASH Clinical Research Network, an ancillary study of the NASH CRN.

Terminology

Of the 3,343 adult patients ever enrolled in NASH CRN observational studies or treatment trials as of January 1, 2024 under the historical clinical and histological definitions of nonalcoholic fatty liver disease (NAFLD) and nonalcoholic steatohepatitis (NASH), only 7 patients (0.02%) did not have at least 1 metabolic risk factor. Consequently, we will use the new MASLD or MASH nomenclature in this paper to describe the NASH CRN patients previously identified as having NAFLD or NASH, respectively, and will also use this nomenclature for the HIV NASH CRN patients previously identified as having NAFLD or NASH, despite limited information on their metabolic risk factors.

Biopsies and clinical data

Liver biopsies in PWH were obtained from the Duke University, Indiana University, University of California at San Diego, University of California at San Francisco, Virginia Commonwealth University sites of the HIV NASH Clinical Research Network and from the NIAID intramural research program. Eligible biopsies were historical and obtained on PWH at least 18 years of age (any duration since HIV diagnosis) and without acute or other chronic liver disease and obtained under consent for use for research. The biopsies from NIAID come from a variety of NIAID clinical and research studies [14]. Clinical data for the MASLD-PWH patients were obtained by chart review; clinical data for the biopsies provided by NIAID were obtained from NIAID files.

Liver biopsies and clinical data from adults with MASLD and without HIV (MASLD-controls) were obtained from the NASH CRN which has studied MASLD in persons without HIV since 2002 (NCT01030484, NCT01061684, NCT00063622, NCT01265498, NCT00063635, NCT01529268, NCT03467217, NCT04454463, NCT04801849). Eligible liver biopsies were those obtained on participants ever enrolled in a NASH CRN study, at least age 18 at biopsy and without acute or other chronic liver disease, and prior to any NASH CRN study treatment for MASLD. Each NASH CRN study consent includes consent to use study biopsy material and data for research.

Histologic parameters were evaluated based on methods developed by Kleiner et al [15] by the NASH CRN Pathology Committee during quarterly in-person review at a multiheaded microscope. Consensus scores for each histologic feature were recorded.

Statistical analysis

Each biopsy was characterized with respect to self-reported race and ethnicity (3 categories: Hispanic/Latino ethnicity regardless of race, Non-Hispanic/Latino ethnicity and Black race, all other race/ethnicity combinations including missing), sex at birth (male, female), and diabetes (3 categories: type I, type II, non-diabetic). The MASLD-PWH biopsies were then grouped per their combined race/ethnicity, sex, and diabetes categorization, as were the MASLD-control biopsies. Each MASLD-PWH biopsy was then reviewed for matches within the corresponding MASLD-control race/ethnicity, sex, and diabetes group on age (±10 years), BMI (±4 points), and ALT (±50%); if more than one MASLD-control biopsy was identified as matching to MASLD-PWH biopsy on these additional criteria, the set of matching MASLD-control biopsies was put in random order and then a single MASLD-control biopsy was paired to the MASLD-PWH biopsy per the random ordering. Unique matching case (MASLD-PWH) and control (MASLD-controls) pairs were thus identified.

Differences between paired cases and controls on clinical and histologic features were assessed using McNemar's test (binary categorical variables), the Stuart-Maxwell generalization of McNemar's test (non-binary categorical variables), or the paired t-test (continuous variables). Univariate conditional logistic regression was used to assess trend in differences between the paired case and controls on ordered categories of histologic features.

Conditional multiple logistic regression with best variable subsets selection using the Akaike information criterion (AIC) was used to identify the optimal set of histologic features for distinguishing MASLD-PWH cases from MASLD-control cases; best variable subsets selection identifies the subset of predictors that best predicts the outcome out of all possible subsets of predictors [16–17]. The lower the Akaike information criterion level, the better the model fit and the simpler the model; hence the Akaike information criterion is used to identify a model that balances model fit with model complexity. The set of candidate histologic features was limited to those available for each case and control biopsy that were not a combination of features (e.g., NAS and steatohepatitis diagnosis are composite variables and were not included) and consisted of steatosis grade, microvesicular steatosis contiguous patches, lobular inflammation score, portal chronic inflammation score, ballooned hepatocyte score, Mallory-Denk bodies score, and fibrosis score [15].

All analyses were conducted in SAS version 9.4 (Cary, NC) or STATA version 15 (College Station, TX).

Results

Populations and matching.

126 MASLD-PWH biopsies were obtained from the HIV NASH CRN. One each was excluded for age at biopsy less than 18 years, repeat biopsy of an individual already included, and biopsy tissue inadequate for scoring, leaving 123 cases for matching to the MASLD-control population. The MASLD-PWH patients were 13.7 ± 8.0 years from HIV infection diagnosis on average and had mean reported CD4+ count of 659.1 ± 362.6 cells/mm^3 (Table S1). The overall prevalence of MASLD by biopsy score was 86%, with 50% diagnosed as MASLD but not definite MASH and 36% as definite MASH (Table S2).

3244 liver biopsies collected by the NASH CRN met the criteria for inclusion. The overall prevalence of MASLD by biopsy score was 96%, with 40% diagnosed as MASLD but not definite MASH and 57% as definite MASH (Table S2).

Differences of note between the MASLD-PWH and MASLD-controls populations include larger proportion Hispanic/Latino in the PWH population (25% versus 12%), much smaller proportion female (19% versus 62%), lower mean BMI (30 versus 34 kg/m^2), higher mean ALT (108 vs 68 U/L), and higher mean AST (68 versus 50 U/L) (Table S1).

Applying the matching protocol to these datasets, 107 matched case-control pairs were obtained. As required by the matching protocol, the MASLD-PWH and MASLD-control groups had the same proportion Hispanic/Latino ethnicity (26%), male (79%), and type 2 diabetics (24%; none of the 107 cases had type 1 diabetes) (Table 1). The range matching on age at biopsy (± 10 years) and BMI (± 5 points) resulted in qualitatively similar mean values for cases and controls (49 vs 47 years, respectively; 31 vs 32 kg/m^2). Mean ALT and AST levels were higher in MASLD-PWH cases (94 and 60 U/L respectively) than in controls (74 and 46 U/L respectively), while AST/ALT ratio and total bilirubin were not different (Table 1). Additional details on the quality of the case-control matches are shown in Table S3. Histologic features of the 16 cases that could not be matched to a MASLD-control were compared to the 107 cases that were matched; no significant differences were noted (Table S4).

Histologic features of cases versus controls, univariate analysis.

Compared to the control group, MASLD-PWH had lower steatosis grade (odds ratio [OR] 0.65, 95% Confidence Interval [95%CI] (0.47, 0.90), P=0.01), lower lobular inflammation grade (OR 0.55, 95%CI (0.34, 0.89), P=0.02), less portal inflammation (OR 0.42, 95%CI (0.25, 0.72), P=0.002) and less ballooned hepatocytes (OR 0.60, 95%CI (0.41, 0.88), P=0.01) (Table 2). As a result, NAS was lower in MASLD-PWH (OR 0.69, 95%CI (0.56, 0.85), P<0.001; mean ± SD, 3.2 ±1.6 versus 4.0 ± 1.6, P<0.001). There was a trend toward less steatohepatitis diagnosis in MASLD-PWH vs MASLD-controls (OR 0.84, 95%CI (0.68, 1.03), P=0.09).

Most cases and controls had a steatosis location categorization of zone 3 predominant distribution (64% and 53%, respectively). Microvesicular steatosis was uncommon and similar in cases and controls (OR 0.38, 95%CI (0.10, 1.41), P=0.15). 67% of MASLD-PWH cases revealed fibrosis, with 21% having advanced fibrosis (13.1% stage 3 and 7.5% stage 4). On univariate analysis, fibrosis stage did not differ between cases and controls (OR 1.01, 95%CI (0.79, 1.28), P=0.95). Iron deposition (hepatocellular and nonhepatocellular) was most commonly minimal or mild (if present) and not different between cases and controls.

Histologic features of cases versus controls, multivariate analysis.

Conditional multiple logistic regression with best variable subsets selection by means of the Akaike information criterion identified the optimal model of histologic features distinguishing MASLD-PWH from MASLD-controls; MASLD-PWH cases were more likely than MASLD-controls to have less steatosis (OR 0.66,95%CI (0.46, 0.95), P=0.03), portal inflammation (OR 0.34, 95%CI (0.18, 0.65), P=0.001), and ballooned hepatocytes (OR 0.55, 95%CI (0.34, 0.88), P=0.01) and greater fibrosis (OR 1.42, 95%CI (1.03, 1.97), P=0.03) (Table 3).

Conclusion

Overall prevalence of MASLD and MASH based on NASH CRN consensus biopsy interpretation was high in the MASLD-PWH group (85% and 37% respectively; Table 2) and in keeping with other studies published in the field [1–11]. Advanced fibrosis was noted in 21% of these cases (Table 2). This result is in concordance with data reported by Vodkin et al [9], who observed a 18.2% of cases with biopsy proven diagnosis of MASLD and advanced fibrosis among MASLD-PWH. Morse et al published a study on 62 MASH-PWH patients in which the authors reported bridging fibrosis in 17% of the entire cohort [14]. Other studies [6, 12] have also reported bridging fibrosis in 13–14% of MASH-PWH cases. Studies using exclusively imaging studies for diagnosis [5, 10, 18] have reported a much lower prevalence of advanced fibrosis (less than 10%) in their populations suggesting that imaging studies may underestimate the degree of clinically impactful fibrosis seen in these patients.

As opposed to prior studies in the field, the NAS score and histologic drivers of fibrosis (e.g., inflammation and ballooned hepatocytes) are less pronounced in MASLD-PWH cases in our cohort. Yet, fibrosis stage was generally higher in MASLD-PWH when compared to matched controls with MASLD (without HIV) in our study when controlling for steatosis, portal inflammation and ballooning. This is in concordance with Torgersen et al that showed that PWH had less severe steatosis assessed by transient elastography than controls after adjusting for multiple covariables [5]. Upon review of the literature, a single study [9] was noted that showed the opposite findings, a greater number of patients with MASH diagnosis in the MASH-PWH groups and no differences in fibrosis stage when compared to controls. This study included a smaller number of cases and a single pathologist in the study design, so it is possible that some of the findings may relate to lack of sufficient power and interobserver consensus.

This suggests that HIV-specific factors beyond hepatic necroinflammation may contribute to fibrosis in HIV-associated MASLD. Some studies have cited genetic factors predisposing to fibrosis in patients with HIV-associated MASLD [19].

Demographics of our cases are similar to other studies and included mostly middle aged non-Hispanic white males [18]. MASLD-PWH cases showed higher elevation of liver enzymes than MASLD controls, which is consistent with published data [9, 14].

Our study strengths include a large sample size, carefully matched, with comprehensive data collection and established inclusion/exclusion criteria. Furthermore, cases and controls were evaluated centrally by the same group, using a standardized scoring system (NAS) in consensus readings by experienced NASH CRN Pathology Committee members.

Limitations include the retrospective and cross-sectional nature of the analysis. Availability of certain behavioral and clinical parameters (smoking, alcohol consumption, complete medication and infections history prior to the biopsy) was limited in some cases. Worth highlighting is the inability to gather a detailed history of toxins and medications consumed by the patients, including ongoing treatment related to HIV or other diseases. Drugs/toxins could potentially be associated with drug induced liver injury and fibrosis. Demographic differences between populations of PWH and the NASH CRN MASLD population created challenges that were only partially overcome by the case-control methodology. A potential referral bias on the patient selection for biopsies cannot be entirely excluded.

MASLD in PWH remains a significant issue, affecting the great majority of these patients and manifesting as MASH in a third of them. In this biopsy-proven study, advanced fibrosis is present in higher proportions than reported in imaging-based studies (21% of our MASLD-PWH cases). This is both concerning and puzzling, considering that MASLD-PWH cases demonstrated lower NAS scores in comparison to controls, suggesting that alternative mechanisms may drive fibrosis progression in PWH.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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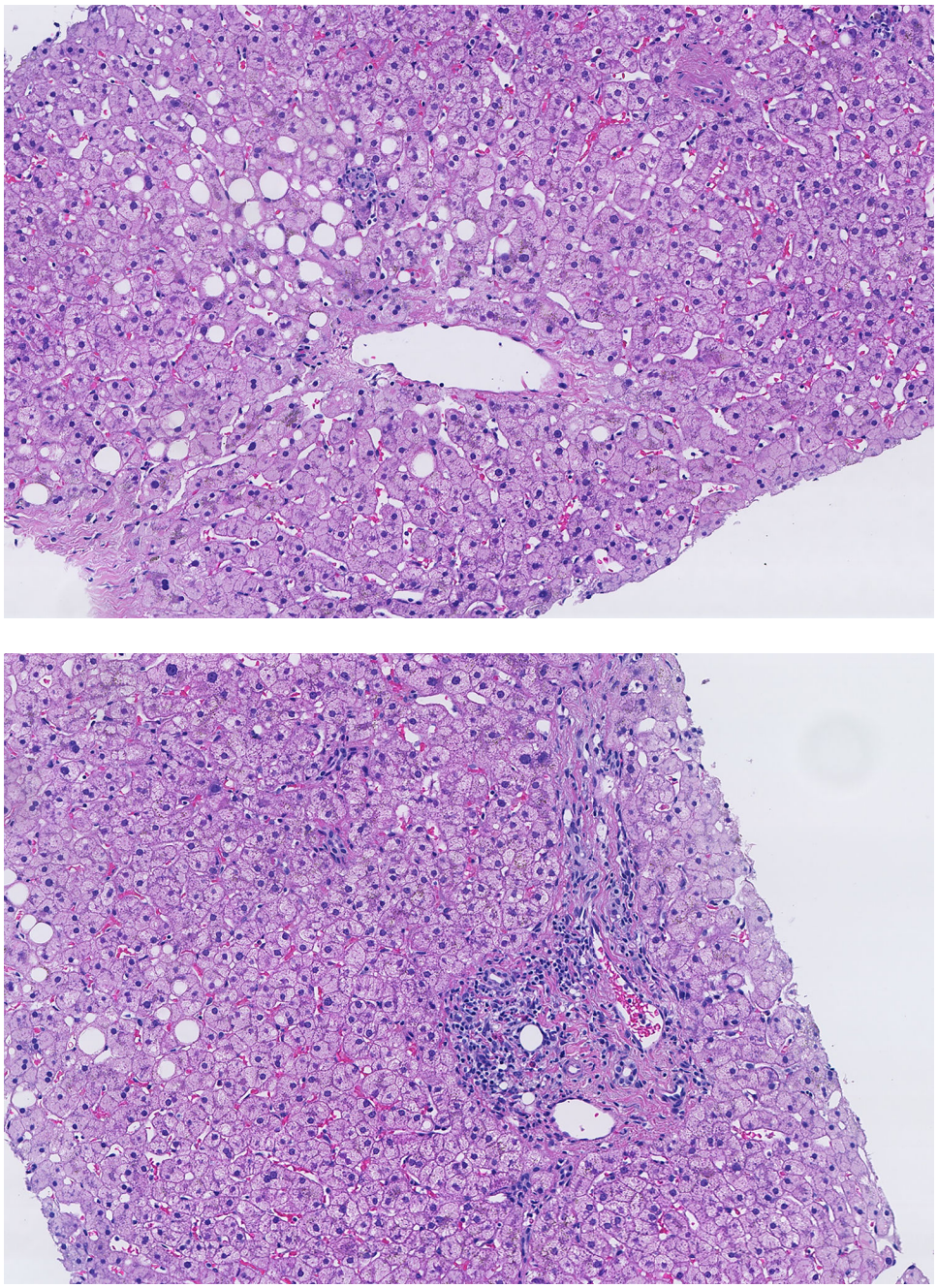


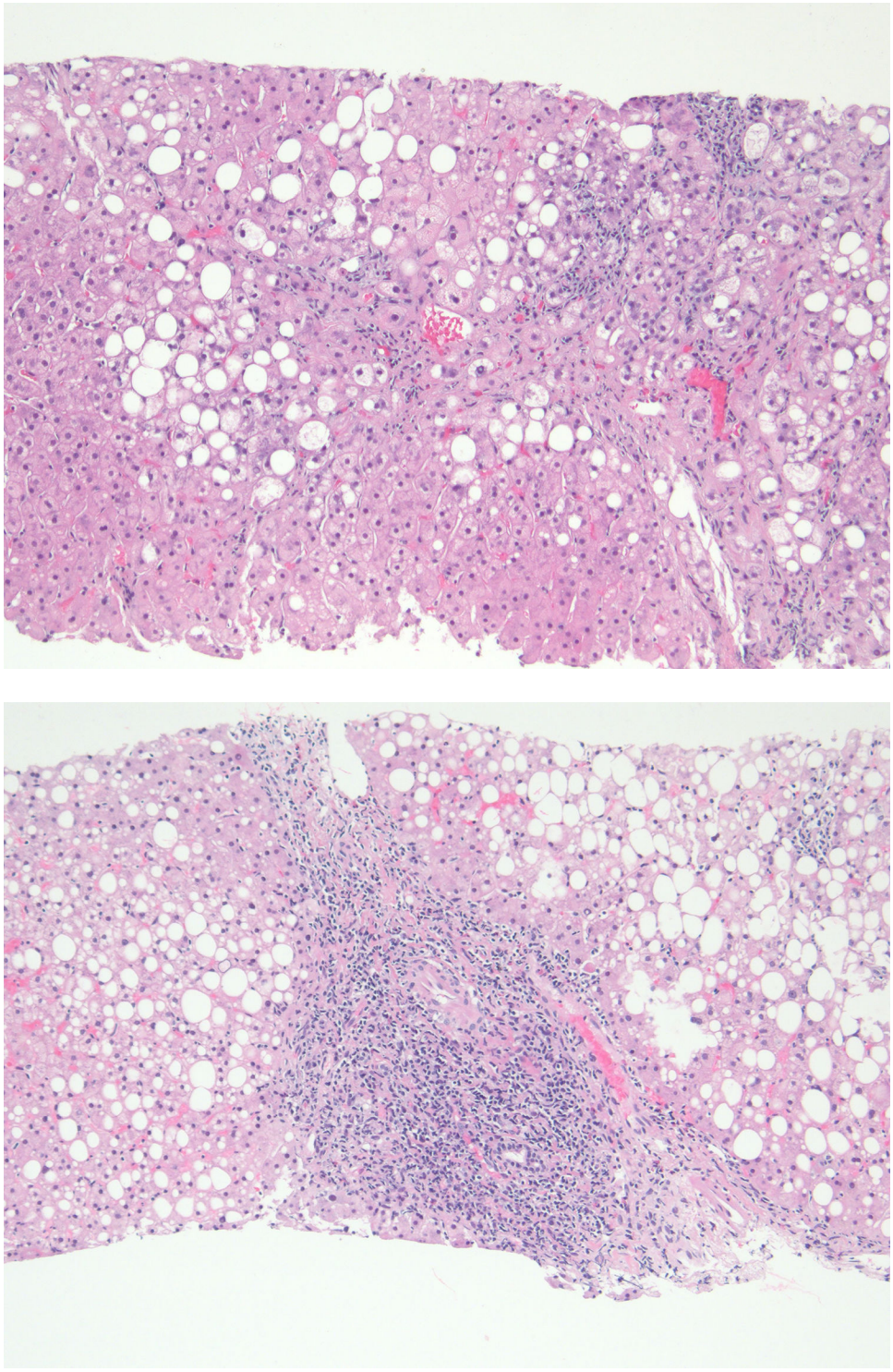
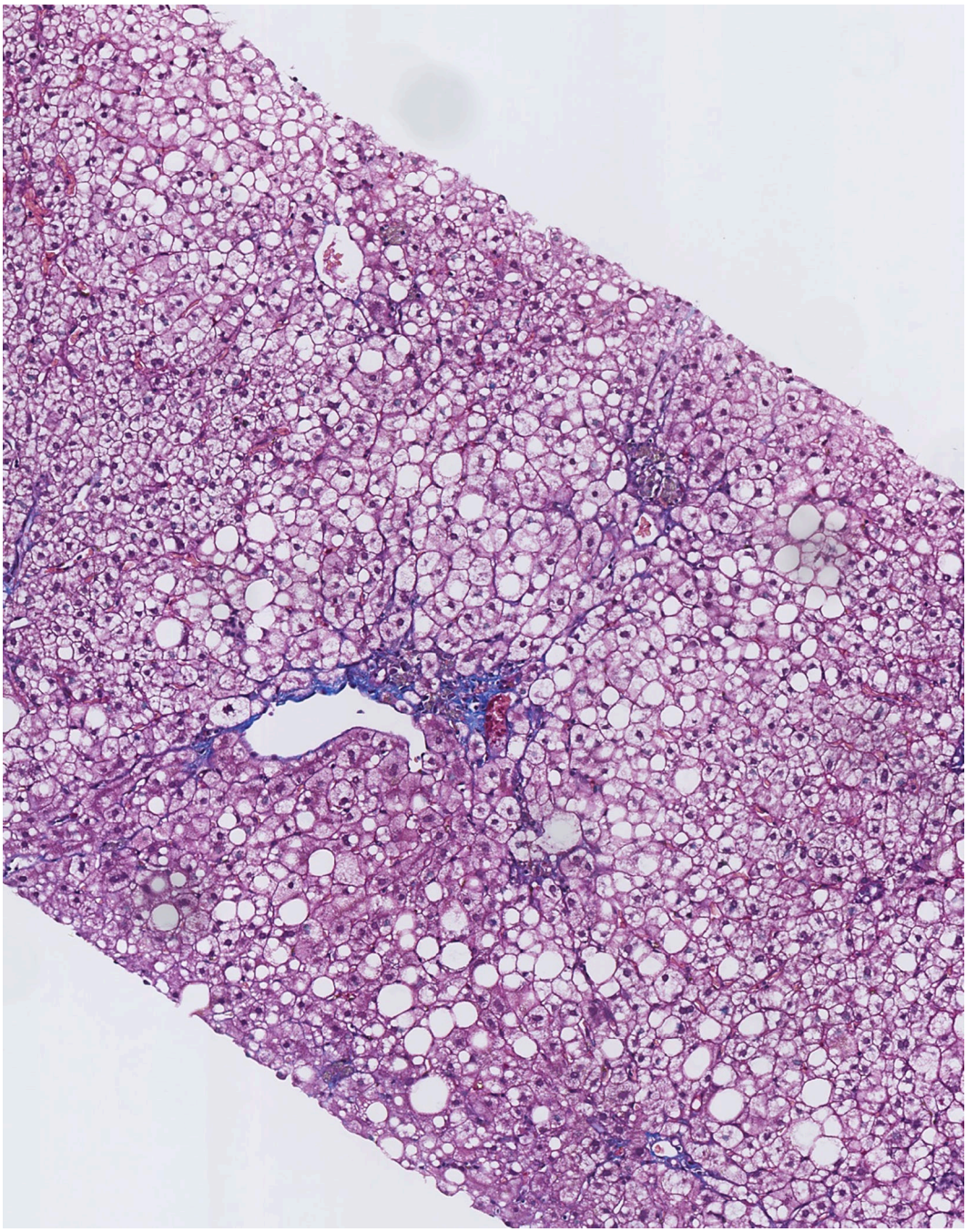


Figure 1.
MASLD-PWH cases (A-B) revealed less steatosis, less ballooned hepatocytes and less chronic portal inflammation, in comparison to controls (C-D).



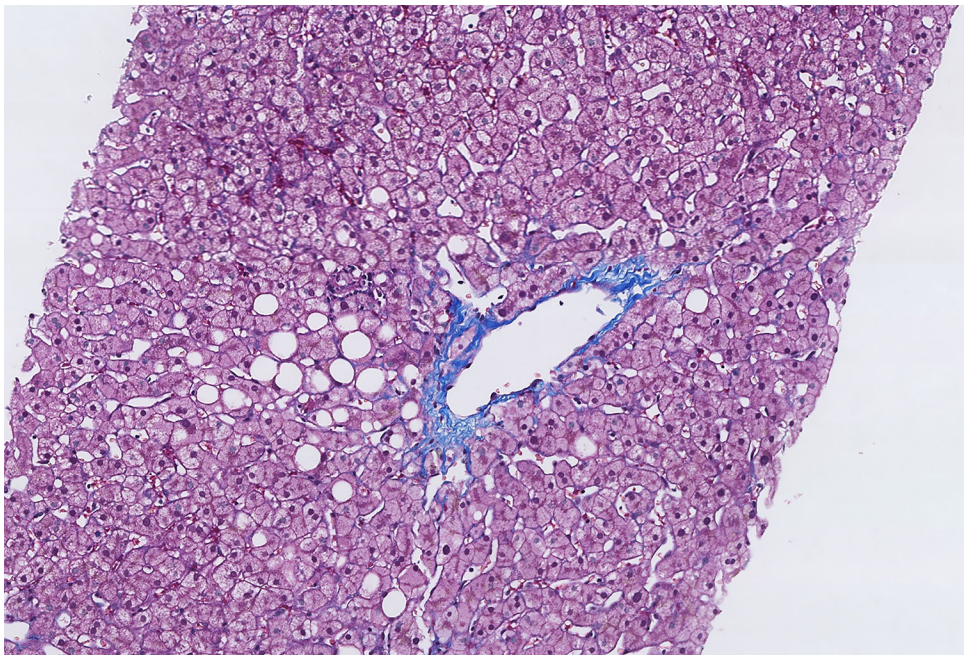


Figure 2.

MASLD-PWH revealed mild macrovesicular steatosis and rare ballooned hepatocytes even in the presence of fibrosis. A. The case reveals rare ballooned hepatocytes in zone 3, inflammatory foci and mild steatosis as well as zone 3 perisinusoidal fibrosis (trichrome stain, 10 x). B. In this case, there is dense perisinusoidal zone 3 fibrosis and only mild macrovesicular steatosis (trichrome stain, 20x).

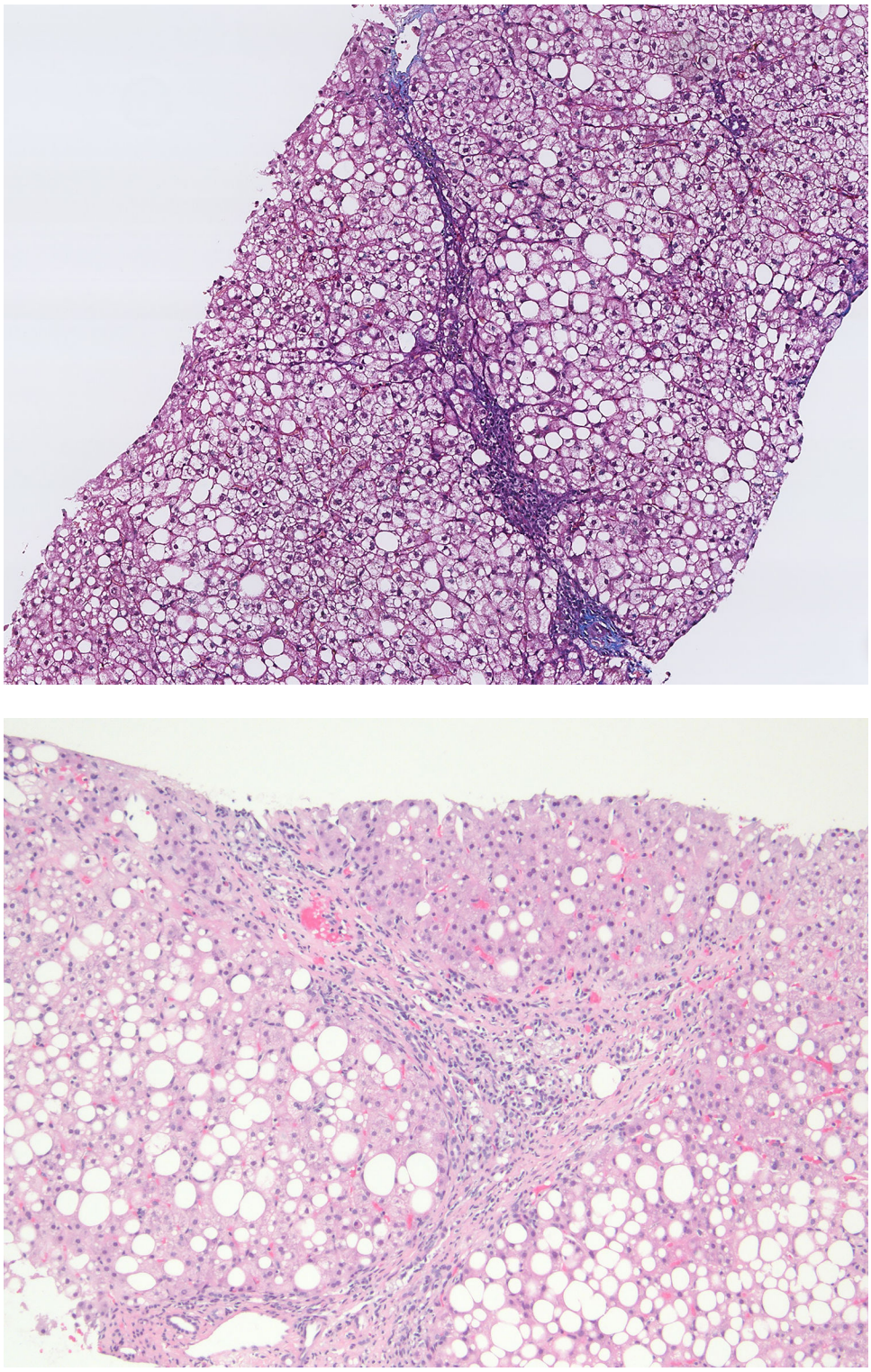


Figure 3.

In the same stage of fibrosis (bridging fibrosis in these examples, trichrome stain 10x and 20x), there is less steatosis and less ballooned hepatocytes in MASLD-PWH (A) in comparison to controls (B).

Table 1.

Demographic and clinical characteristics of the matched MASLD-PWH cases and MASLD-controls (N=107 pairs)

	MASLD-PWH (N=107)	MASLD-controls (N=107)	P*
Age at biopsy (yrs)			
18–29, no. (%)	2 (1.9)	5 (4.7)	0.17
30–39, no. (%)	14 (13.1)	16 (15.0)	
40–49, no. (%)	38 (35.5)	43 (40.2)	
50–59, no. (%)	42 (39.3)	32 (29.9)	
60 or older, no. (%)	11 (10.3)	11 (10.3)	
Mean ± SD	48.9 ± 9.0	47.4 ± 10.3	0.009
Ethnicity, no. (%)			
Hispanic/Latino	28 (26.2)	28 (26.2)	NA†
Non Hispanic/Latino	79 (73.8)	79 (73.8)	
Race, no. (%)			
White only	69 (64.5)	60 (56.1)	0.13
Black only	14 (13.1)	12 (11.2)	
Asian only	3 (2.8)	9 (8.4)	
American Indian only	2 (1.9)	6 (5.6)	
Pacific Islander only	0	1 (0.9)	
Other, mixed or unknown	19 (17.8)	19 (17.8)	
Sex at birth, no. (%)			
Male	85 (79.4)	85 (79.4)	NA†
Female	22 (20.6)	22 (20.6)	
Weight (kg)			
Males, N	85	85	
Mean ± SD	90.5 ± 15.6	94.5 ± 16.8	0.008
Females, N	22	22	
Mean ± SD	91.9 ± 23.5	95.3 ± 22.8	0.28
BMI (kg/m^2)			
<20, no. (%)	1 (0.9)	0	0.03
20 – <25, no. (%)	8 (7.5)	3 (2.8)	
25 – <30, no. (%)	43 (40.2)	44 (41.1)	
30 – <35, no. (%)	41 (38.3)	39 (36.5)	
≥35, no. (%)	14 (13.1)	21 (19.6)	
Mean ± SD	30.6 ± 5.8	31.6 ± 5.5	<0.001

	MASLD-PWH (N=107)	MASLD-controls (N=107)	P*
Diabetes, no. (%)			
Type 2	26 (24.3)	26 (24.3)	NA†
Not diabetic	81 (75.7)	81 (75.7)	
HbA1C (%)			
<5.7, no. (%)	38 (48.1)	49 (46.2)	0.70
5.7– <6.4, no. (%)	21 (26.6)	36 (34.0)	
≥6.4, no. (%)	20 (25.3)	21 (19.8)	
Mean ± SD	6.1 ± 1.4	6.0 ± 1.1	0.53
No. of pairs excluded due to case or control missing value	28		
Total bilirubin (mg/dL)			
<0.5, no. (%)	33 (30.8)	24 (22.4)	0.41
≥0.5 and <0.8, no. (%)	38 (35.8)	43 (40.2)	
≥0.8, no. (%)	36 (33.6)	40 (37.4)	
Mean ± SD	0.8 ± 0.8	0.8 ± 0.6	0.65
ALT (U/L)			
<30, no. (%)	8 (7.5)	12 (11.2)	0.001
30–66, no. (%)	38 (35.5)	45 (42.1)	
67–100, no. (%)	23 (21.5)	29 (27.1)	
101–250, no. (%)	36 (33.6)	19 (17.8)	
≥251, no. (%)	2 (1.9)	2 (1.9)	
Mean ± SD	94.0 ± 60.2	73.9 ± 47.1	<0.001
AST (U/L)			
<50, no. (%)	53 (49.5)	69 (64.5)	<0.001
51–100, no. (%)	41 (38.3)	36 (33.6)	
≥101, no. (%)	13 (12.2)	2 (1.9)	
Mean ± SD	60.3 ± 31.5	45.5 ± 23.7	<0.001
AST/ALT ratio			
Mean ± SD	0.73 ± 0.29	0.70 ± 0.29	0.32
Years from HIV diagnosis to biopsy			
Mean ± SD	13.9 ± 8.0	NA	NA
No. missing	5		
CD4+ count (cells/mm^3)			
Mean ± SD	658.7 ± 369.3	NA	NA
No. missing	2		

ALT=alanine aminotransaminase; AST=aspartate aminotransferase; BMI=body mass index; HbA1C=hemoglobin A1C; SD=standard deviation.

*P for McNemar's test (binary categorical variables), Stuart-Maxwell test (non-binary categorical variables), or paired t-test (continuous variables). MASLD-PWH cases and MASLD-controls were matched on age at biopsy, race/ethnicity, sex at birth, diabetes status, BMI, and ALT.

†P not provided for ethnicity, sex at birth, or diabetes because cases and controls were matched exactly on those characteristics per the matching protocol.

Table 2.

Histologic features of the matched MASLD-PWH cases and MASLD-controls (N=107 pairs)

	MASLD-PWH (N=107)	MASLD-controls (N=107)	P*	Odds ratio (95% CI)†	P†
Steatosis grade					
<5%, no. (%)	19 (17.8)	6 (5.6)	0.01	0.65 (0.47, 0.90)	0.01
5–33%, no. (%)	48 (44.9)	44 (41.1)			
34–66%, no. (%)	24 (22.4)	37 (34.6)			
>66%, no. (%)	16 (15.0)	20 (18.7)			
Score (0–3), mean ± SD	1.3 ± 0.9	1.7 ± 0.8	0.008		
Steatosis location					
Zone 3 (central), no. (%)	63 (64.3)	57 (53.3)	0.04	NA	NA
Zone 1 (periportal), no. (%)	0	0			
Azonal, no. (%)	23 (23.5)	23 (21.5)			
Panacinar, no. (%)	12 (12.2)	27 (25.2)			
No. of pairs excluded due to case or control missing value	9				
Microvesicular steatosis, contiguos patches					
Absent, no. (%)	104 (97.2)	99 (92.5)	0.13	0.38 (0.10, 1.41),	0.15
Present, no. (%)	3 (2.8)	8 (7.5)			
Lobular inflammation					
None, no. (%)	7 (6.5)	0	0.03	0.55 (0.34, 0.89)	0.02
<2, no. (%)	68 (63.6)	64 (59.8)			
2–4, no. (%)	27 (25.2)	34 (31.8)			
>4, no. (%)	5 (4.7)	9 (8.4)			
Score (0–3), mean ± SD	1.3 ± 0.7	1.5 ± 0.6	0.01		
Portal, chronic inflammation					
None, no. (%)	32 (29.9)	18 (16.8)	0.003	0.42 (0.25, 0.72)	0.002
Mild, no. (%)	67 (62.6)	67 (62.6)			
More than mild, no. (%)	8 (7.5)	22 (20.6)			

	MASLD-PWH (N=107)	MASLD-controls (N=107)	P*	Odds ratio (95% CI)†	P†
Score (0–2), mean ± SD	0.8 ± 0.6	1.0 ± 0.6	0.001		
Ballooned hepatocytes					
None, no. (%)	65 (60.8)	48 (44.9)	0.03	0.60 (0.41, 0.88)	0.01
Few, no. (%)	26 (24.3)	30 (28.0)			
Many, no. (%)	16 (15.0)	29 (27.1)			
Score (0–2), mean ± SD	0.5 ± 0.7	0.8 ± 0.8	0.007		
Mallory-Denk bodies					
Rare/absent, no. (%)	90 (84.1)	77 (72.0)	0.03	0.46 (0.22, 0.94)	0.03
Many, no. (%)	17 (15.9)	30 (28.0)			
Fibrosis stage					
None, no. (%)	35 (32.7)	37 (34.6)	0.48	1.01 (0.79, 1.28)	0.95
Mild or moderate or portal/periportal only, no. (%)	30 (28.0)	25 (23.4)			
Zone 3 and periportal, no. (%)	20 (18.7)	21 (19.6)			
Early or advanced bridging, no. (%)	14 (13.1)	20 (18.7)			
Early or advanced cirrhosis, no. (%)	8 (7.5)	4 (3.7)			
Score (0–4), mean ± SD	1.3 ± 1.3	1.3 ±1.2	0.95		
No fibrosis, no. (%)	35 (32.7)	37 (34.6)	0.84	1.00 (0.66, 1.50)	>0.99
Some fibrosis but not advanced fibrosis, no. (%)	50 (46.7)	46 (43.0)			
Advanced fibrosis, no. (%)	22 (20.6)	24 (22.4)			
Hepatocellular iron grade					
Absent or barely discernible, no. (%)	64 (60.4)	54 (55.1)	0.49	0.87 (0.60, 1.26)	0.45
Barely discernible granules, no. (%)	29 (27.4)	25 (25.5)			
Discrete granules resolved, 10x, no. (%)	11 (10.4)	18 (18.4)			
Granules resolved, 4x, no. (%)	2 (1.9)	1 (1.0)			
Masses visible by naked eye, no. (%)	0	0			
Score (0–4), mean ± SD	0.6 ± 0.8	0.6 ± 0.8	0.45		
No. of pairs excluded due to case or control missing value	10				

	MASLD-PWH (N=107)	MASLD-controls (N=107)	P*	Odds ratio (95% CI)†	P†
Nonhepatocellular iron grade					
None, no. (%)	67 (63.2)	57 (58.2)	0.23	0.77 (0.51, 1.17)	0.22
Mild, no. (%)	30 (28.3)	25 (25.5)			
More than mild, no. (%)	9 (8.5)	16 (16.3)			
Score (0–2), mean ± SD	0.5 ± 0.7	0.6 ± 0.8	0.22		
No. of pairs excluded due to case or control missing value	10				
Is this steatohepatitis					
Not MASLD, no. (%)	16 (15.0)	6 (5.6)	0.15	0.84 (0.68, 1.03)	0.09
MASLD, not MASH, no. (%)	30 (28.0)	30 (28.0)			
Suspicious/borderline/indeterminate, Zone 3, no. (%)	22 (20.6)	25 (23.4)			
Suspicious/borderline/indeterminate, Zone 1, no. (%)	0	0			
Yes, definite, no. (%)	39 (36.5)	46 (43.0)			
NAFLD Activity Score (NAS) ‡					
0, no. (%)	4 (3.7)	0	0.02	0.69 (0.56, 0.85)	<0.001
1, no. (%)	11 (10.3)	3 (2.8)			
2, no. (%)	25 (23.4)	22 (20.6)			
3, no. (%)	23 (21.5)	17 (15.9)			
4, no. (%)	22 (20.6)	23 (21.5)			
5, no. (%)	13 (12.2)	26 (24.3)			
6, no. (%)	7 (6.5)	8 (7.5)			
7, no. (%)	2 (1.9)	7 (6.5)			
8, no. (%)	0	1 (0.9)			
Score (0–8), mean ± SD	3.2 ± 1.6	4.0 ± 1.6	<0.001		

*P for McNemar's test (binary categorical variables), Stuart-Maxwell test (non-binary categorical variables), or paired t-test (continuous variables). MASLD-PWH cases and MASLD-controls were matched on age at biopsy, race/ethnicity, sex at birth, diabetes status, BMI, and ALT.

†Odds ratio for 1 unit change in histologic measure, 95% confidence interval (CI), and P value are from conditional logistic regression model of MASLD cases versus MASLD-controls on specified histologic feature.

‡NAS = sum of scores for steatosis, lobular inflammation, and hepatocyte ballooning.

Table 3.

Best multivariable model of histologic features of MASLD-PWH cases versus MASLD-controls (N=107 pairs)

	MASLD-PWH versus MASLD-controls		
	Odds ratio	**95% CI**	**P**
Steatosis grade (0–3; per unit change in grade)	0.66	(0.46, 0.95)	0.03
Portal chronic inflammation score (0–2; per unit change in score)	0.34	(0.18, 0.65)	0.001
Ballooned hepatocytes score (0–2; per unit change in score)	0.55	(0.34, 0.88)	0.01
Fibrosis score (0–4; per unit change in score)	1.42	(1.03, 1.97)	0.03

Odds ratios, 95% confidence intervals, and P values were determined from conditional logistic regression of MASLD-PWH cases versus MASLD-controls HIV on the listed histologic features which were selected from the candidate set (steatosis grade, microvesicular steatosis contiguous patches, lobular inflammation score, portal chronic inflammation score, ballooned hepatocyte score, Mallory-Denk bodies score, and fibrosis score) by best variable subsets selection using the Akaike information criterion. The study population consisted of 107 case-control pairs matched on age at biopsy, race/ethnicity, sex at birth, diabetes status, BMI, and ALT.