



Original Article

Alcohol Liver Pathology Signature: A Composite Histological Pattern for Differentiating Alcohol-associated Liver Disease from Metabolic Dysfunction-associated Steatotic Liver Disease



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Abstract

Background and objectives: Metabolic dysfunction-associated steatotic liver disease (MASLD) and alcohol-associated liver disease (ALD) are leading causes of chronic liver injury with overlapping clinical and histological presentations. This study evaluated a composite histologic pattern, termed the Alcohol Liver Pathology Signature (ALPS), for potential use in the differential diagnosis of ALD and MASLD and to explore potential clinical and demographic correlates.

Methods: In this retrospective diagnostic-accuracy study, we reviewed 292 liver biopsies performed between 2021 and 2023. ALPS comprised five histologic features: ductular reaction, bile stasis, neutrophilic satellitosis, portal inflammation, and advanced fibrosis (stage 3–4). Cases were categorized as absent (0–1 features), partial (2–3 features), or full (4–5 features). ALPS performance was then further evaluated in an independent temporal validation cohort of de-identified, mixed, and blindly reviewed liver biopsies collected between 2024 and 2025.

Results: MASLD was the most common diagnosis (25.3%), whereas ALD accounted for 4.8%. Full ALPS was present in 92.8% of clinically diagnosed ALD cases. In MASLD, individual ALPS features were common, but only 20.3% showed full ALPS, corresponding to 79.7% specificity for distinguishing clinically diagnosed ALD from MASLD. The independent temporal validation cohort showed findings consistent with those of the original cohort. Finally, within MASLD, full ALPS was more frequent in African American than non-African American patients (29.2% vs. 3.8%).

Conclusions: ALPS may serve as a histologic prompt for further assessment of potential alcohol exposure but should not be considered etiologically specific. Prospective validation incorporating objective measures of alcohol exposure is warranted.

Keywords: Metabolic dysfunction-associated steatotic liver disease; MASLD; Alcohol-associated liver disease; ALD; Metabolic dysfunction and alcohol-associated liver disease; MetALD; Alcohol liver pathology signature; Liver biopsy; Ductular reaction; Bile stasis; Neutrophilic satellitosis; Portal inflammation; Advanced fibrosis.

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Introduction

The field of chronic liver disease has undergone a considerable shift over the past decade.^{1,2} With the widespread success of direct-acting antivirals and improved screening programs for viral hepatitis, metabolic dysfunction and/or alcohol-associated liver diseases (ALDs) now constitute the predominant causes of non-neoplastic liver biopsies in clinical practice. Metabolic dysfunction-associated steatotic liver disease (MASLD) has emerged as the leading etiology of chronic liver injury in the United States, particularly in regions noted for increased obesity rates and cal-

orie-dense dietary patterns.^{3,4} ALD, meanwhile, continues to represent a significant public health challenge, additionally intensified by pandemic-related changes in drinking behavior.⁵⁻⁷

A major diagnostic difficulty is distinguishing MASLD from ALD, which share similar clinical presentations. The differential diagnosis is mainly based on the presence of metabolic dysfunction and/or alcohol use disorder and self-reported alcohol consumption. The accurate assessment of alcohol intake is often limited by patient underreporting, stigma, and cultural normalization of alcohol consumption,^{8,9} notably in locales such as New Orleans,¹⁰ where alcohol is deeply embedded in social and culinary traditions,^{11,12} and featured in Southern dietary patterns.^{13,14} Thus, clinically diagnosed MASLD may actually include some patients who should more accurately be diagnosed with ALD because their excess alcohol intake went unrecognized. The recent adoption of blood testing for phosphatidylethanol (PEth), an abnormal phospholipid formed in the presence of ethanol, can more objectively identify people who have chronic ethanol exposure.¹⁵⁻¹⁷ The level of blood PEth is proportional to the amount of alcohol intake. This testing provides a new quantitative tool to differentiate ALD and MASLD and also helps define a new category of steatotic liver disease: metabolic dysfunction and alcohol-associated liver disease (MetALD),^{18,19} in which alcohol consumption is intermediate.²⁰

Histopathologic examination of liver biopsies from patients with MASLD and ALD can reveal distinct morphological and architectural alterations.^{21,22} However, pathological diagnoses of MASLD and ALD often take clinical diagnosis and patient history into account, since many histological features, such as steatosis and fibrosis, are shared between the two entities. From this aspect, histologic examination has not shed much light on the etiology of fatty liver diseases, specifically MASLD and ALD.

Nevertheless, a constellation of histologic features, including ductular reaction, bile stasis, portal inflammation, neutrophilic satellitosis, and advanced fibrosis, has been more commonly observed in ALD than in MASLD.^{21,23} We would like to explore the potential use of these features in detecting ALD and occult alcohol-associated injury in MASLD in the absence of objective measurements of alcohol intake, particularly in retrospective studies of biopsy samples. Toward that end, we have defined the Alcohol Liver Pathology Signature (ALPS), a composite scoring system based on several of the aforementioned features, and examined its utility in a cohort of regionally collected liver biopsy samples. We found that full ALPS was substantially more frequently seen in clinically diagnosed ALD than in MASLD. We further examined the reproducibility of the composite pattern and evaluated its performance in an independent temporal validation cohort. In addition, demographic stratification identified an enrichment of full ALPS in a subset of clinically diagnosed MASLD cases, suggesting a potential association between ALPS and demographic factors.

Materials and methods

Study design and patient selection

Clinicopathologic data, including demographic information, were gathered from the electronic health records for all medical liver biopsies performed at Tulane Medical Center between January 1,

2021, and December 31, 2023. This study was reported in accordance with the Standards for Reporting Diagnostic Accuracy Studies (STARD) 2015 reporting guideline. Race and sex were extracted retrospectively from demographic fields documented in the electronic health record. The study investigators did not independently ascertain these variables, and the retrospective data did not allow verification of whether race was originally recorded by patient self-report or administrative assignment. For exploratory race-stratified analyses, patients were grouped as African American (AA) or non-African American (non-AA). The non-AA category included White, Asian, and Hispanic/Latino. This dichotomization was used because AA patients constituted a sufficiently large subgroup for statistical comparison, whereas the numbers of patients in the remaining individual racial categories were too small to support reliable separate analyses. This grouping was intended as a pragmatic exploratory stratification and not as an assumption of biological homogeneity within the AA or non-AA categories.

All biopsies with adequate tissue for histologic assessment (> 10 mm in length and ≥ 10 portal tracts) were included (Fig. 1). Exclusion criteria were (1) insufficient tissue for diagnosis and (2) incomplete demographic or clinical data. A total of 292 biopsies met the inclusion criteria. Clinical and pathologic information available at the time of review was used to assign cases to the following diagnostic categories: MASLD, ALD, autoimmune hepatitis, primary biliary cholangitis, idiopathic fibrosis/cirrhosis, primary liver cancer, including hepatocellular carcinoma and intrahepatic cholangiocarcinoma, metastatic malignancy, allograft follow-up, and undetermined diagnosis. Reference diagnoses for the original cohort were based on the pre-existing clinically assigned diagnoses documented in the electronic medical record, incorporating the available clinical history, including documented alcohol exposure and metabolic risk factors, together with the original pathologic assessment. These reference diagnoses had been established before ALPS was defined and scored for the present study, and ALPS findings were not used to establish or modify the reference diagnosis. Because ALPS was developed and initially evaluated retrospectively in this original cohort, ALPS assessment was not performed under a fully blinded study design, and reviewers could have had access to the pre-existing clinical/pathologic diagnostic information. Diagnostic categories were treated as mutually exclusive for cohort-level analyses, and each biopsy was assigned to a single primary category for descriptive summary. Thus, although histologic features such as advanced fibrosis could be found in multiple diagnostic categories, each biopsy was counted only once in the overall diagnostic distribution.

Definition of the ALPS

Based on prior literature describing histologic patterns associated with alcohol-related liver injury,^{21,23} and expert pathologic judgment, we identified five candidate features for the ALPS composite: ductular reaction, bile stasis, portal inflammation, neutrophilic satellitosis, and advanced fibrosis (stage 3–4). The selection of these five components and the ≥ 4 -feature cutoff was guided by this clinicopathologic rationale; alternative feature combinations or cutoffs were not systematically optimized to maximize diagnostic performance. The specific combination of these five features and the threshold used to define full ALPS

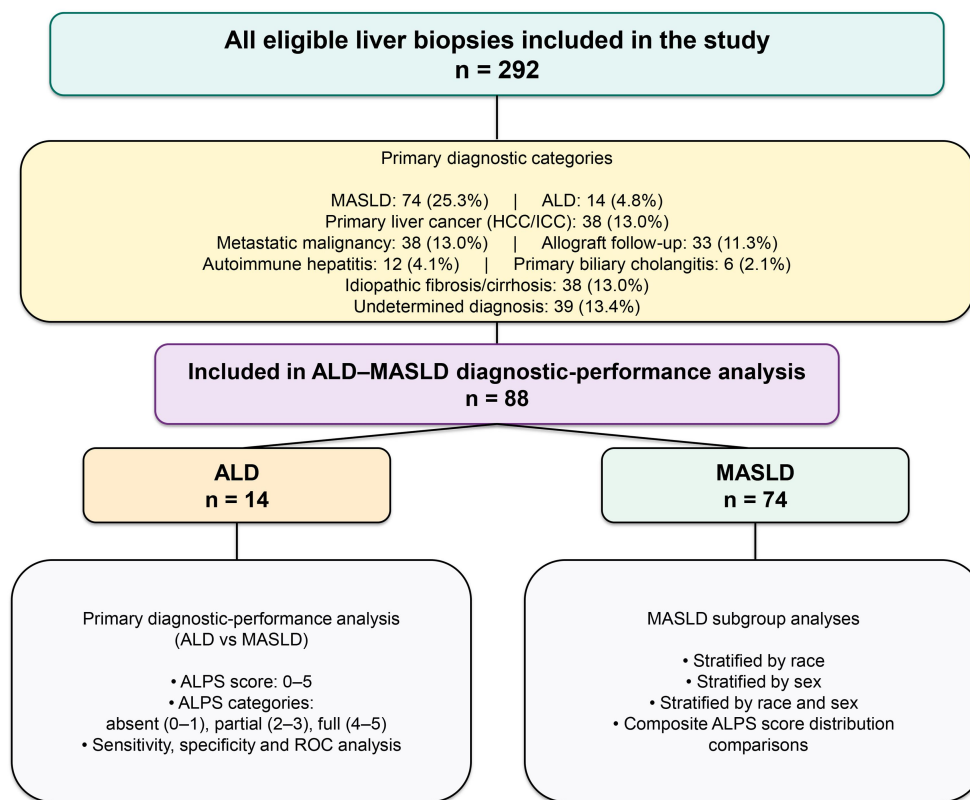


Fig. 1. Study design. The overall design of the study starts with 292 eligible liver biopsy cases and focuses on the characterization of a set of histologic features (ALPS) and their differential distribution in ALD and MASLD. ALD, alcohol-associated liver disease; ALPS, alcohol liver pathology signature; HCC, hepatocellular carcinoma; ICC, intrahepatic cholangiocarcinoma; MASLD, metabolic dysfunction-associated steatotic liver disease; PBC, primary biliary cholangitis; ROC, receiver operating characteristic.

were developed in the original 2021–2023 retrospective cohort. Full ALPS was operationally defined as the presence of at least four of the five features, representing the co-occurrence of most components of the composite pattern; cases with 0–1 and 2–3 features were categorized as absent and partial ALPS, respectively. The original cohort therefore served as an exploratory/derivation cohort for the development and initial assessment of ALPS.

Histopathologic evaluation

Standard hematoxylin and eosin, trichrome, periodic acid–Schiff with diastase, and iron stain slides were evaluated, and the histopathologic features were recorded for subsequent analysis. The following histopathologic features were assessed using established criteria: steatosis (% of hepatocytes involved), hepatocyte ballooning, lobular inflammation, portal inflammation, ductular reaction (present/absent), bile stasis (present/absent), neutrophilic satellitosis (quantified for dichotomized analysis as 0–2 vs. > 2 foci per 20× field), and fibrosis stage (0–4, using Nonalcoholic Steatohepatitis Clinical Research Network criteria).^{21,23,24} Stage 3–4 fibrosis was included as the advanced fibrosis component. The fibrosis pattern in ALD includes zone 3 pericellular and perisinusoidal fibrosis, often described as “chicken-wire” fibrosis, with progression to bridging fibrosis and cirrhosis.

Ductular reaction was defined as an increased number of reactive ductular profiles at the portal–parenchymal interface or within fibrous septae. These structures were composed of small cuboidal epithelial cells with scant cytoplasm, arranged in small cords or ductules with variably discernible lumina. Native interlobular bile ducts were excluded from this assessment.

Portal inflammation was assessed on hematoxylin and eosin-stained sections across the entire biopsy specimen. A portal inflammatory focus was defined as a discrete aggregate of mononuclear inflammatory cells within a portal tract. Liver biopsy specimens used for assessment need to contain at least 10 portal tracts. The portal inflammation component of ALPS was considered positive when more than six portal tracts across the biopsy contained moderate-to-severe inflammatory aggregates. This cutoff represents an operational threshold developed for the present study and is not an established histologic standard. In biopsies with bridging fibrosis or cirrhosis, inflammatory aggregates within fibrous septa were assessed together with those in residual portal tracts and were recorded as portal/septal inflammation. All evaluable portal tracts and fibrous septa were reviewed systematically without selection of inflammatory hot spots.

For exploratory demographic subgroup analyses presented in

Table 1. Stratification of MASLD cases by race or sex alone for the observed histologic features

	Race					Sex				
	AA		Non-AA		<i>P</i>	Female		Male		<i>P</i>
Variable	(n = 48)	%	(n = 26)	%		(n = 54)	%	(n = 20)	%	
Age, y										
≤ 53	26	54.2%	10	38.5%	>0.05	25	46.3%	11	55.0%	>0.05
> 53	22	45.8%	16	61.5%		29	53.7%	9	45.0%	
Percentage of macrovesicular steatosis										
0–33	26	54.2%	16	61.5%	>0.05	32	59.3%	10	50.0%	>0.05
>33	22	45.8%	10	38.5%		22	40.7%	10	50.0%	
Hepatocyte ballooning										
0 or rare	16	33.3%	10	38.5%	>0.05	16	29.6%	10	50.0%	>0.05
Abundant	32	66.7%	16	61.5%		38	70.4%	10	50.0%	
Lobular inflammation										
0–4 foci/20×	29	60.4%	16	61.5%	>0.05	32	59.3%	13	65.0%	>0.05
>4 foci/20×	19	39.6%	10	38.5%		22	40.7%	7	35.0%	
Ductular reaction										
No	16	33.3%	15	57.7%	0.0426	21	38.9%	10	50.0%	>0.05
Yes	32	66.7%	11	42.3%		33	61.1%	10	50.0%	
Bile stasis										
No	20	41.7%	16	61.5%	>0.05	24	44.4%	12	60.0%	>0.05
Yes	28	58.3%	10	38.5%		30	55.6%	8	40.0%	
Portal inflammation										
Negative	22	45.8%	19	73.1%	0.0244	29	53.7%	11	55.0%	>0.05
Positive	26	54.2%	7	26.9%		25	46.3%	9	45.0%	
Neutrophilic satellitosis										
0–2 foci/20×	21	43.8%	17	65.4%	>0.05	29	53.7%	9	45.0%	>0.05
>2 foci/20×	27	56.2%	9	34.6%		25	46.3%	11	55.0%	
Fibrosis stage										
0–2	22	45.8%	19	73.1%	0.0244	33	61.1%	8	40.0%	>0.05
3–4	26	54.2%	7	26.9%		21	38.9%	12	60.0%	

P-values refer to the comparisons for each variable between African American (AA) and non-African American (non-AA) individuals in the race section and between female and male individuals in the sex section. MASLD, metabolic dysfunction–associated steatotic liver disease.

Tables 1 and 2, selected continuous or ordinal variables were dichotomized to facilitate comparisons across relatively small subgroups. Age was categorized as ≤ 53 versus > 53 years, using approximately the median age of the MASLD cohort to generate comparably sized groups. Macrovesicular steatosis was categorized as 0%–33% versus > 33%, corresponding approximately to mild versus moderate-to-severe steatosis. Hepatocyte ballooning was categorized as 0 or rare versus abundant, and lobular inflammation as 0–4 versus > 4 foci per 20× field, with the latter representing the highest lobular inflammation category. These categories were defined for exploratory subgroup analyses and were applied consistently across all demographic comparisons without sub-

sequent optimization based on statistical significance.

Independent temporal validation

A cohort of liver biopsies collected after the original study period was assembled for independent temporal validation. The validation cohort included 6 clinically diagnosed ALD cases and 29 clinically diagnosed MASLD cases collected between August 2024 and December 2025. All consecutive cases during this period that met the clinical diagnostic criteria for ALD or MASLD and had adequate tissue for histologic assessment were included. Cases with insufficient tissue for histologic assessment or insufficient clinical information to establish the reference diagnosis were excluded. The reference diagnoses were based on the clinical

Table 2. Stratification of MASLD cases by the combination of race and sex for the observed histologic features

Variable	Female					Male					AA					Non-AA				
	AAF		Non-AAF		P	AAM		Non-AAM		P	AAF		AAM		P	Non-AAF		Non-AAM		P
	(n = 35)	%	(n = 19)	%		(n = 13)	%	(n = 7)	%		(n = 35)	%	(n = 13)	%		(n = 19)	%	(n = 7)	%	
Age, y																				
≤ 53	19	54.3%	6	31.6%	>0.05	7	53.8%	4	57.1%	>0.05	19	54.3%	7	53.8%	>0.05	6	31.6%	4	57.1%	>0.05
> 53	16	45.7%	13	68.4%		6	46.2%	3	42.9%		16	45.7%	6	46.2%		13	68.4%	3	42.9%	
Percentage of macrovesicular steatosis																				
0–33	19	54.3%	13	68.4%	>0.05	7	53.8%	3	42.9%	>0.05	19	54.3%	7	53.8%	>0.05	13	68.4%	3	42.9%	>0.05
>33	16	45.7%	6	31.6%		6	46.2%	4	57.1%		16	45.7%	6	46.2%		6	31.6%	4	57.1%	
Hepatocyte ballooning																				
0 or rare	10	28.6%	6	31.6%	>0.05	6	46.2%	4	57.1%	>0.05	10	28.6%	6	46.2%	>0.05	6	31.6%	4	57.1%	>0.05
Abundant	25	71.4%	13	68.4%		7	53.8%	3	42.9%		25	71.4%	7	53.8%		13	68.4%	3	42.9%	
Lobular inflammation																				
0–4 foci/20×	22	62.9%	10	52.6%	>0.05	7	53.8%	6	85.7%	>0.05	22	62.9%	7	53.8%	>0.05	10	52.6%	6	85.7%	>0.05
>4 foci/20×	13	37.1%	9	47.4%		6	46.2%	1	14.3%		13	37.1%	6	46.2%		9	47.4%	1	14.3%	
Ductular reaction																				
No	10	28.6%	11	57.9%	0.0348	6	46.2%	4	57.1%	>0.05	10	28.6%	6	46.2%	>0.05	11	57.9%	4	57.1%	>0.05
Yes	25	71.4%	8	42.1%		7	53.8%	3	42.9%		25	71.4%	7	53.8%		8	42.1%	3	42.9%	
Bile stasis																				
No	12	34.3%	12	63.2%	0.0414	8	61.5%	4	57.1%	>0.05	12	34.3%	8	61.5%	>0.05	12	63.2%	4	57.1%	>0.05
Yes	23	65.7%	7	36.8%		5	38.5%	3	42.9%		23	65.7%	5	38.5%		7	36.8%	3	42.9%	
Portal inflammation																				
Negative	15	42.9%	14	73.7%	0.0300	7	53.8%	4	57.1%	>0.05	15	42.9%	7	53.8%	>0.05	14	73.7%	4	57.1%	>0.05
Positive	20	57.1%	5	26.3%		6	46.2%	3	42.9%		20	57.1%	6	46.2%		5	26.3%	3	42.9%	

Table 2. Stratification of MASLD cases by the combination of race and sex for the observed histologic features (continued)

Female					Male					AA					Non-AA					
Neutrophilic satellitosis																				
0–2 foci/20×	15	42.9%	14	73.7%	0.0300	6	46.2%	3	42.9%	>0.05	15	42.9%	6	46.2%	>0.05	14	73.7%	3	42.9%	>0.05
>2 foci/20×	20	57.1%	5	26.3%		7	53.8%	4	57.1%		20	57.1%	7	53.8%		5	26.3%	4	57.1%	
Fibrosis stage																				
0–2	18	51.4%	15	78.9%	0.0476	4	30.8%	4	57.1%	>0.05	18	51.4%	4	30.8%	>0.05	15	78.9%	4	57.1%	>0.05
3–4	17	48.6%	4	21.1%		9	69.2%	3	42.9%		17	48.6%	9	69.2%		4	21.1%	3	42.9%	

P-values refer to comparisons for each variable between the two demographic groups in the Female, Male, African American (AA), and non-African American (non-AA) sections. AAM, African American male; AAF, African American female; non-AAM, non-African American male; non-AAF, non-African American female. MASLD, metabolic dysfunction–associated steatotic liver disease.

information and alcohol-use history documented in the electronic medical record and were established independently of ALPS assessment.

For blinded histologic evaluation, diagnostic labels and clinical information, including alcohol-use history, were removed, and all slides were assigned randomized study codes and mixed into a single review set. The validation slides were independently evaluated by two co-first authors (Dr. Xue and Dr. Hwaung), who applied the same predefined five-component ALPS criteria used in the original cohort. Both reviewers were blinded to the clinical diagnosis, alcohol-use history, and each other's assessments during scoring. Any discrepant assessments were resolved by joint review and consensus, and the consensus assessment was used to determine the final ALPS score. After completion of scoring, the study codes were unmasked, and the final ALPS results were compared with the clinically assigned diagnoses.

Statistical analysis

Continuous variables were analyzed using Student's *t*-test. Categorical variables were compared using chi-square or two-sided Fisher's exact tests. For the 2×3 contingency-table analyses of ALPS category distributions in Table 3, overall *P*-values were calculated using the two-sided Fisher–Freeman–Halton exact test. Receiver operating characteristic (ROC) analysis was performed using the ordinal ALPS score. The area under the ROC curve (AUC), standard error, and 95% confidence interval were estimated using the Hanley–McNeil method in GraphPad Prism version 11. Sensitivity and specificity were calculated using the full-ALPS cutoff developed in the original cohort. For both the original and validation cohorts, 95% confidence intervals for sensitivity and specificity were estimated using the hybrid Wilson/Brown method.

For reproducibility assessment, two reviewers independently evaluated the de-identified and randomized biopsy slides using the predefined criteria. The reviewers were blinded to each

other's assessments. After a washout interval, the cases were re-randomized and re-scored to evaluate intra-observer reproducibility. Inter-observer agreement was assessed by comparing the independent assessments of the two reviewers, whereas intra-observer agreement was assessed by comparing the Time 1 and Time 2 assessments for each reviewer. Because the five individual ALPS components were binary variables, agreement for these features was evaluated using unweighted Cohen's kappa. The total ALPS score, ranging from 0 to 5, and the ALPS category, classified as absent, partial, or full, were treated as ordinal variables and evaluated using quadratic-weighted Cohen's kappa. Quadratic weighting assigns relatively smaller penalties to disagreements between adjacent scores or categories and progressively larger penalties to disagreements that are farther apart. Observed percentage agreement was also reported. Kappa values were interpreted as follows: < 0.00, poor; 0.00–0.20, slight; 0.21–0.40, fair; 0.41–0.60, moderate; 0.61–0.80, substantial; and 0.81–1.00, almost perfect agreement. Demographic subgroup analyses were exploratory, and *P*-values were not adjusted for multiple comparisons.

Results

Cohort characteristics

The retrospective study was designed as outlined in Figure 1. A total of 292 patients underwent liver biopsy between 2021 and 2023. The distribution of pathologic diagnoses showed a predominance of metabolic and advanced chronic liver diseases (Fig. 2a). MASLD was the most common diagnostic category (*n* = 74, 25.3%), whereas ALD constituted a much smaller group (*n* = 14, 4.8%). Primary liver cancer, including hepatocellular carcinoma and intrahepatic cholangiocarcinoma (*n* = 38, 13.0%), and metastatic malignancy in the liver (*n* = 38, 13.0%)

Table 3. Composite ALPS score distribution in the MASLD cases stratified by race and sex

ALPS score (no. of features)	0–1	2–3	≥4
All cases (n = 74)	14 (18.9%)	45 (60.8%)	15 (20.3%)
AA (n = 48)	4 (8.3%)	30 (62.5%)	14 (29.2%)
Non-AA (n = 26)	10 (38.5%)	15 (57.7%)	1 (3.8%)
Individual <i>P</i> -value	0.0036	0.8040	0.0134
Overall <i>P</i> -value	0.0010		
AAF (n = 35)	2 (5.7%)	21 (60.0%)	12 (34.3%)
Non-AAF (n = 19)	9 (47.4%)	10 (52.6%)	0 (0.0%)
Individual <i>P</i> -value	0.0006	0.7739	0.0044
Overall <i>P</i> -value	<0.0001		
AAM (n = 13)	2 (15.4%)	9 (69.2%)	2 (15.4%)
Non-AAM (n = 7)	1 (14.3%)	5 (71.4%)	1 (14.3%)
Individual <i>P</i> -value	1.0000	1.0000	1.0000
Overall <i>P</i> -value	1.0000		
AAF (n = 35)	2 (5.7%)	21 (60.0%)	12 (34.3%)
AAM (n = 13)	2 (15.4%)	9 (69.2%)	2 (15.4%)
Individual <i>P</i> -value	0.2936	0.7401	0.2921
Overall <i>P</i> -value	0.3081		
Non-AAF (n = 19)	9 (47.4%)	10 (52.6%)	0 (0.0%)
Non-AAM (n = 7)	1 (14.3%)	5 (71.4%)	1 (14.3%)
Individual <i>P</i> -value	0.1904	0.6576	0.2692
Overall <i>P</i> -value	0.1478		

Individual *P*-values were calculated using two-sided Fisher's exact tests for each ALPS category between the two respective demographic groups. Overall *P*-values were calculated using the two-sided Fisher-Freeman-Halton exact test for all ALPS categories between the two respective demographic groups. AA, African American; Non-AA, non-African American; AAM, African American male; AAF, African American female; non-AAM, non-African American male; non-AAF, non-African American female. ALPS, alcohol liver pathology signature; MASLD, metabolic dysfunction–associated steatotic liver disease.

were the next largest groups. Additional categories included allograft follow-up biopsies ($n = 33$, 11.3%), autoimmune hepatitis ($n = 12$, 4.1%), and primary biliary cholangitis ($n = 6$, 2.1%). Notably, a large group of biopsies was pathologically diagnosed as idiopathic fibrosis/cirrhosis ($n = 38$, 13.0%) or undetermined ($n = 39$, 13.4%). In the latter, the findings were not specific enough to support a definitive etiologic diagnosis or even pathologic change.

Overall, slightly more biopsies were obtained from female than male patients (153 [52.4%] vs. 139 [47.6%]) (Fig. 2b). Across the calendar years, female biopsy counts exceeded male counts in 2022 and 2023, whereas male counts were slightly higher in 2021 (Fig. 2b). The female predominance was particularly evident in the MASLD cohort in each year of the same period, wherein females accounted for 54 cases and males for 20 cases (Fig. 2c). In contrast, the ALD cohort was small and did not show a marked sex predominance overall (female, $n = 6$; male, $n = 8$), although annual case numbers fluctuated across the study period (Fig. 2d).

The age distribution of this cohort varied greatly (approximately 20–88 years), with no significant difference ($P = 0.1804$) between the males (57.40 ± 1.12 , $N = 139$) and the

females (55.28 ± 1.10 , $N = 153$) across the 3-year period (Fig. 3a and b). Across all three years, MASLD cases were largely concentrated between 40 and 70 years of age, with females showing a broader and more variable age distribution than males. In addition, the average age for the MASLD male patients (49.40 ± 2.642 , $N = 20$) was younger than that of the female patients (55.04 ± 1.541 , $N = 54$), although this difference did not reach statistical significance ($P = 0.0641$) (Fig. 3c). This observation may be biased due to the age distribution of the samples in 2022, which showed a significantly younger ($P = 0.0136$) male group (41.83 ± 4.07 , $N = 6$) than female group (57.72 ± 3.11 , $N = 18$) (Fig. 3c). In contrast, in the ALD group, the opposite was observed, with female patients (46.17 ± 3.439 , $N = 6$) being younger than the male patients (55.38 ± 2.897 , $N = 8$) (Fig. 3a and d), which did not reach statistical significance ($P = 0.0621$), likely due to the smaller sample size. This age difference may suggest that the sexes are differentially susceptible to MASLD and ALD. Indeed, it is well defined that women are more susceptible to alcohol-induced injury,^{25–29} so the recommended daily and total alcohol uptake for women is lower than that for men.³⁰ MASLD also exhibits clear sex-related differences, in which there is

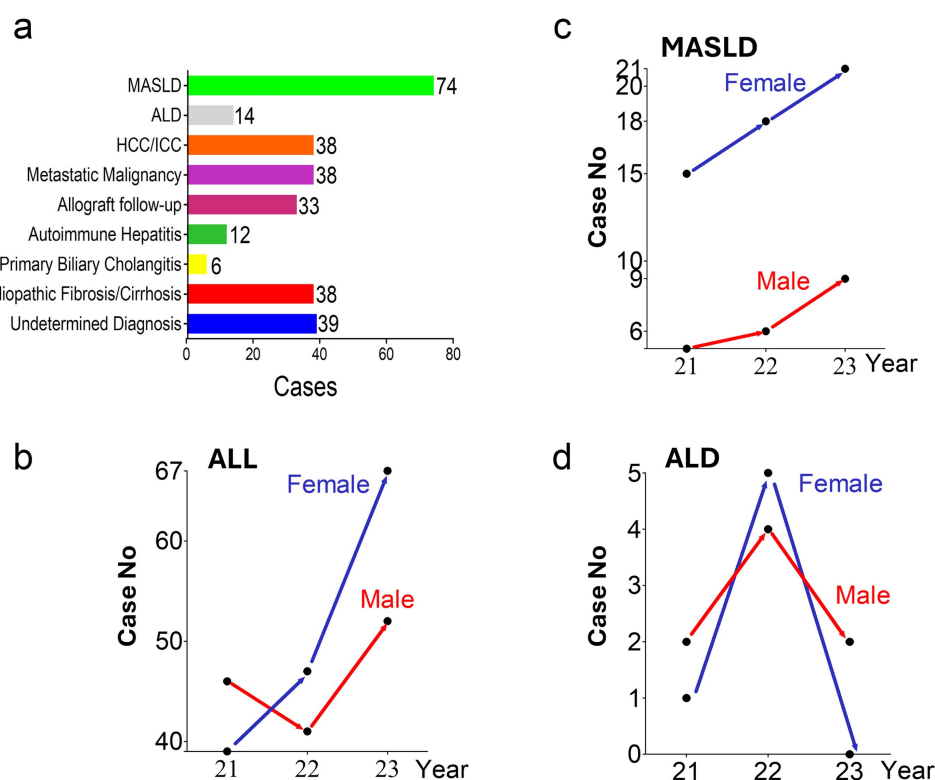


Fig. 2. Case distribution of the cohort across diagnosis, year, and sex. (a) The bar chart shows the distribution of diagnostic categories in the cohort. MASLD was the most frequent diagnosis in this group. (b–d) The line graphs show the annual biopsy number of all (b), MASLD (c), or ALD (d) cases in male and female patients. ALD, alcohol-associated liver disease; HCC, hepatocellular carcinoma; ICC, intrahepatic cholangiocarcinoma; MASLD, metabolic dysfunction-associated steatotic liver disease; PBC, primary biliary cholangitis.

generally a higher prevalence and incidence in men compared to women during the reproductive years; this finding diminishes after menopause, suggesting an important protective role of estrogen.^{31–35} These susceptibility differences could lead to the differences seen in mean age at the time of biopsy.

Distribution and diagnostic performance of ALPS in clinically diagnosed ALD and MASLD

Several features are frequently present in alcohol-associated liver injury, including ductular reaction, bile stasis, portal inflammation, neutrophilic satellitosis, and advanced fibrosis (Fig. 4).^{21,23} We thus reasoned that a typical ALD biopsy would display most of these features, which we termed ALPS. We assessed the presence of ALPS in clinically diagnosed ALD and MASLD patients. In the 14 ALD biopsy samples, we found that 13 (92.8%) demonstrated full ALPS, i.e., at least 4 out of 5 of these features. This result was consistent with the notion that ALPS can be a histologic characteristic of ALD liver pathology, although the number of ALD biopsies was relatively small in this cohort.

We then examined whether clinically diagnosed MASLD samples exhibited any ALPS-related changes. Individual ALPS features were frequently observed in these samples, including ductular reaction (58.1%), bile stasis (51.3%), and neutrophilic satellitosis (48.6%). Representative MASLD cases illustrating absent,

partial, and full ALPS are shown in Figure 5. Recalculation from the primary case-level data showed that 45 of 74 MASLD cases (60.8%) exhibited partial ALPS (2–3 features), whereas 15 of 74 cases (20.3%) met criteria for full ALPS (≥ 4 features). Thus, although individual ALPS-related histologic changes were common in MASLD, full ALPS was much less frequent than in ALD (20.3% vs. 92.8%, $P < 0.0001$).

A comparison of the distribution of the 5 histologic features occurring in the 14 ALD samples and 15 MASLD samples with full ALPS scores indicated that the frequency of individual features occurring in each group was high but varied from case to case (Fig. 6a). These differences were not statistically significant between the ALD and MASLD groups (Fig. 6b). Thus, it is not the presence of any individual ALPS feature, but the simultaneous presence of 4 or 5 features that makes these MASLD cases unique, as such findings are usually only seen in ALD cases.

Using the clinically assigned diagnoses as the reference classification, full ALPS showed a sensitivity of 92.8% (13/14; 95% confidence interval, 68.5%–98.7%) and a specificity of 79.7% (59/74; 95% confidence interval, 69.2%–87.3%) for distinguishing clinically diagnosed ALD from MASLD in the original cohort. ROC analysis using the ordinal ALPS score yielded an AUC of 0.832 (Fig. 7).

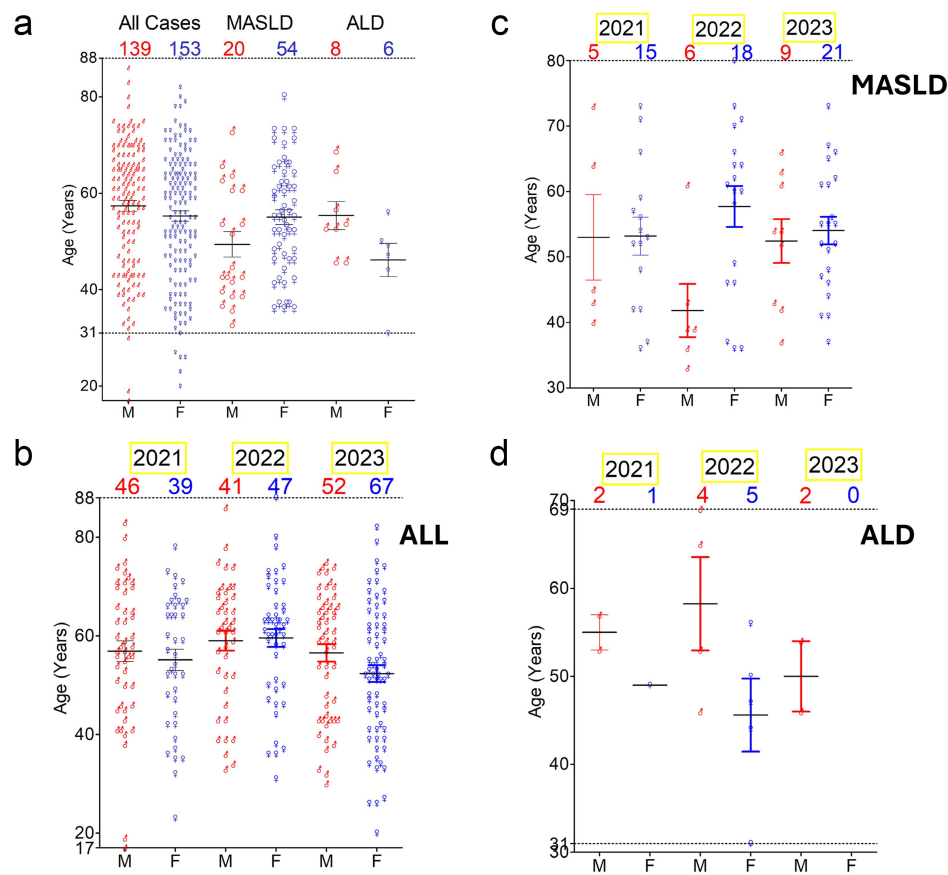


Fig. 3. Case distribution of the cohort across age and sex. (a) The scatter plot shows the age distribution of all liver biopsy cases, MASLD cases, and ALD cases stratified by sex. (b–d) The scatter plots show the age distribution by year (2021–2023) and sex for all (b), MASLD (c), or ALD (d) cases. Each point represents one patient. The horizontal bars and brackets indicate the mean $\pm$ standard error. ALD, alcohol-associated liver disease; F, female; M, male; MASLD, metabolic dysfunction-associated steatotic liver disease.

Reproducibility study

To ensure the assessment of ALPS features could be consistently performed, we conducted a reproducibility study. Intra-observer agreement in the ALD cases was generally high (Supplementary Table. 1). For Rater 1, feature-level kappa values ranged from 0.759 to 1.000, and the quadratic-weighted kappa for the ALPS category was 0.774. For Rater 2, all feature-level kappa values were 1.000, and the quadratic-weighted kappa for the ALPS category was also 1.000. Interobserver agreement at initial assessment varied across individual histologic features, with Cohen's kappa values ranging from 0.417 for ductular reaction to 1.000 for portal inflammation. The quadratic-weighted kappa for the ALPS category was 0.611.

For the MASLD subset (Supplementary Table. 2), intra-observer agreement was almost perfect for both observers. For Rater 1, feature-level kappa values ranged from 0.919 to 1.000, with quadratic-weighted kappa values of 0.975 for the total ALPS score and 0.964 for the ALPS category. For Rater 2, feature-level kappa values ranged from 0.889 to 0.973, with quadratic-weighted kappa values of 0.943 for the total ALPS score and 0.936 for the ALPS categories. Interobserver agreement at Time 1 was

substantial to almost perfect for the individual features, with Cohen's kappa values ranging from 0.623 for portal inflammation to 0.891 for advanced fibrosis. The quadratic-weighted kappa values for the total ALPS score and ALPS categories were 0.826 and 0.780, respectively. At Time 2, feature-level agreement ranged from moderate to almost perfect, with kappa values ranging from 0.541 for portal inflammation to 0.808 for advanced fibrosis; the quadratic-weighted kappa values for the total ALPS score and ALPS categories were 0.779 and 0.746, respectively.

When the ALD and MASLD data were combined (Supplementary Table. 3), intra-observer agreement was almost perfect for both reviewers, with feature-level kappa values ranging from 0.903 to 0.977 and quadratic-weighted kappa values for the ALPS categories of approximately 0.95. Interobserver agreement at initial assessment was substantial to almost perfect for the five individual ALPS components, with Cohen's kappa values ranging from 0.681 to 0.886. Agreement for the total ALPS score was almost perfect, with a quadratic-weighted kappa of 0.847, while agreement for the three ALPS categories (absent, partial, and full) was substantial, with a quadratic-weighted kappa of 0.790.

In conclusion, the ALPS features could be determined

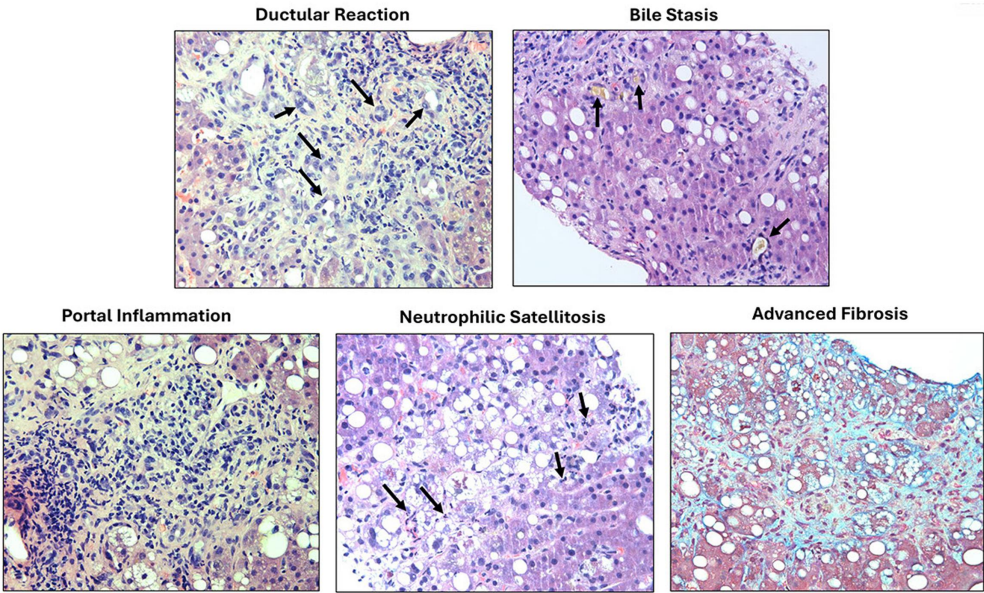


Fig. 4. Representative histologic images showing alcohol liver pathology signature (ALPS). Representative images of liver biopsies from ALD cases show the major histologic features that constitute ALPS, including ductular reaction, bile stasis, portal inflammation, neutrophilic satellitosis, and advanced fibrosis, as indicated by the arrows. Fibrosis is demonstrated by Masson’s trichrome staining, whereas the other features are visualized by hematoxylin and eosin staining. Images were obtained by digital scanning of glass slides. The trichrome image illustrating advanced fibrosis is shown at a lower magnification (100×) to better demonstrate the overall architectural pattern of fibrosis, whereas the other panels are shown at higher magnification (400×) to highlight the corresponding histologic features. ALD, alcohol-associated liver disease; ALPS, alcohol liver pathology signature.

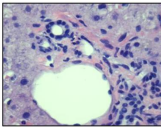
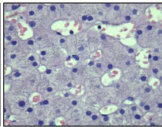
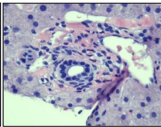
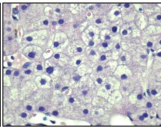
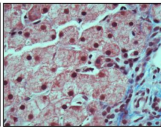
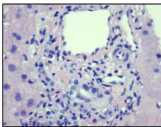
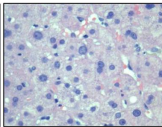
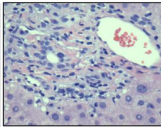
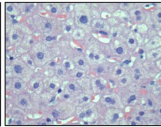
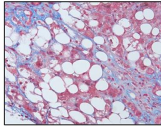
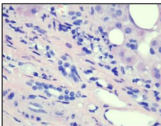
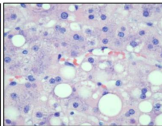
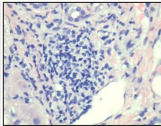
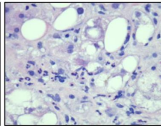
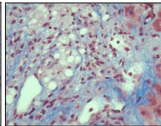
	Ductular Reaction	Bile Stasis	Portal Inflammation	Neutrophilic Satellitosis	Advanced Fibrosis	No. of ALPS Features
Case 1						0
	N	N	N	N	N	
Case 2						
	P	N	N	N	P	2
Case 3						4
	P	N	P	P	P	

Fig. 5. Spectrum of alcohol liver pathology signature (ALPS) features in selected MASLD cases. Representative liver biopsy images from 3 MASLD cases illustrate different ALPS scores and categories, determined by the number of ALPS features present. The absent ALPS category refers to cases with 0-1 ALPS features, as illustrated by Case 1 (score 0). The partial ALPS category refers to cases with 2-3 ALPS features, as illustrated by Case 2 (score 2). The full ALPS category refers to cases with 4-5 ALPS features, as illustrated by Case 3 (score 4). ALPS, alcohol liver pathology signature; MASLD, metabolic dysfunction-associated steatotic liver disease; N, negative; P, positive.

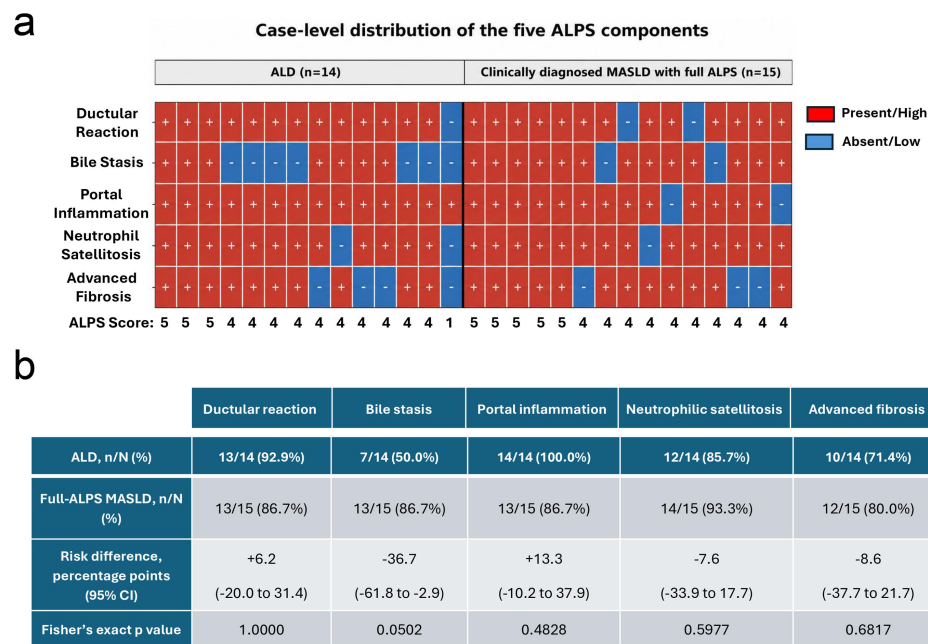


Fig. 6. The distribution of the ALPS features across individual cases. (a) The distribution of five ALPS features in each of the 14 ALD cases and the 15 selected MASLD cases in the full ALPS category. Each column represents a case. Red positive signs indicate the presence of the feature, whereas blue negative signs indicate the absence of a feature. (b) The frequency of each individual feature found in the ALD and selected MASLD cases. Fisher's exact tests indicated that there were no statistically significant differences between the two groups ($P \geq 0.05$). ALD, alcohol-associated liver disease; ALPS, alcohol liver pathology signature; CI, confidence interval; MASLD, metabolic dysfunction-associated steatotic liver disease.

consistently with reproducible results.

Independent temporal validation of ALPS

To further evaluate the performance of ALPS in a temporally independent and blinded setting, we applied the same ALPS criteria to a validation cohort collected after the original study period. This cohort included 6 clinically diagnosed ALD cases and 29 clinically diagnosed MASLD cases collected in 2024 and 2025. All cases were de-identified, randomized, mixed into a single review set, and scored without access to the original diagnosis or alcohol-use history.

Full ALPS was present in 6 of 6 ALD cases (100%) in the validation cohort. Among the 29 validation MASLD cases, 5 cases had absent ALPS, 17 cases had partial ALPS, and 7 cases had full ALPS (24.1%) (Fig. 8). Thus, the ALPS distribution in the validation MASLD cohort was similar to that observed in the original MASLD cohort, in which 14 of 74 cases had absent ALPS, 45 had partial ALPS, and 15 had full ALPS (Fig. 8). Using full ALPS as a positive threshold, the validation cohort demonstrated a sensitivity of 100.0% (6/6; 95% confidence interval, 61.0%–100.0%) for clinically diagnosed ALD and a specificity of 75.9% (22/29; 95% confidence interval, 57.9%–87.8%) against clinically diagnosed MASLD. These findings provide a preliminary temporal and blinded validation of the ALPS pattern among ALD and MASLD cases.

Demographic distribution of ALPS in MASLD patients

To explore whether the occurrence of full ALPS in clinically

diagnosed MASLD varied across demographic groups, we examined the prevalence of ALPS according to race and sex. The MASLD cohort was thus stratified by race and sex to determine whether ALPS was more commonly associated with a particular demographic group (Table 1). We first separated the cohort by race into African American (AA) and non-African American (non-AA) groups. Among the ALPS features, we found that samples from AA patients showed higher frequencies of ductular reaction (66.7% vs. 42.3%, $P = 0.0426$), portal inflammation (54.2% vs. 26.9%, $P = 0.0244$), and advanced fibrosis (stage 3–4; 54.2% vs. 26.9%, $P = 0.0244$) compared to samples from non-AA patients. On the other hand, when the MASLD cases were separated based on sex, there were no significant differences in the frequencies of any of these ALPS features between the male and female patients.

However, when both sex and race were considered, race-stratified differences were observed among female patients but were not statistically detected among male patients (Table 2). Among the female patients, African American females (AAF) displayed higher frequencies of each of the 5 individual ALPS-related histologic features when compared with non-African American females (non-AAF), including ductular reaction (71.4% vs. 42.1%, $P = 0.0348$), bile stasis (65.7% vs. 36.8%, $P = 0.0414$), portal inflammation (57.1% vs. 26.3%, $P = 0.0300$), neutrophilic satellitosis (57.1% vs. 26.3%, $P = 0.0300$), and stage 3–4 fibrosis (48.6% vs. 21.1%, $P = 0.0476$). No significant differences were observed between African American males (AAM) and non-African American males (non-AAM) for any of the ALPS features (Table 2). No statistically significant differences in the frequencies

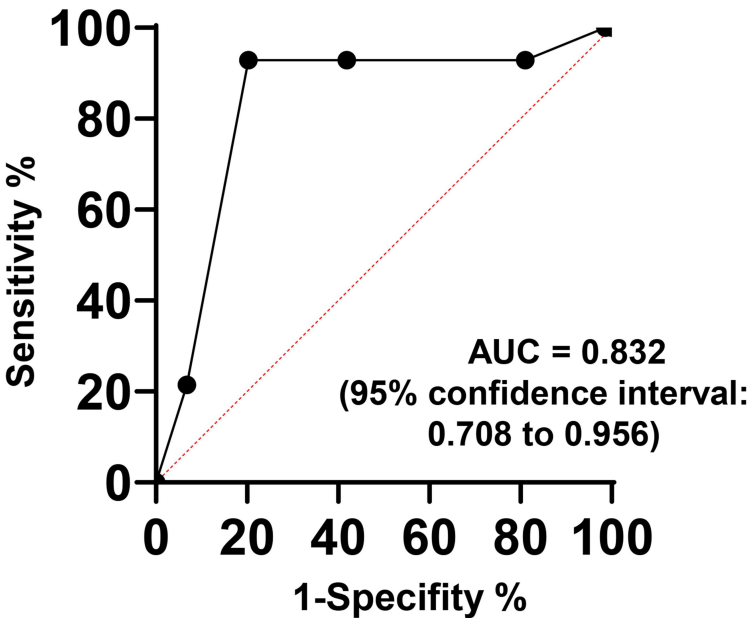


Fig. 7. ROC analysis of the performance of alcohol liver pathology signature (ALPS) in differentiating ALD and MASLD histologically. Each of the 74 MASLD cases and 14 ALD cases was scored based on the number of ALPS features present. The data were used to construct the receiver operating characteristic (ROC) curve using the ordinal ALPS score (0–5 features). The area under the ROC curve (AUC) is 0.832, with a standard error of 0.063 and a 95% confidence interval of 0.708–0.956, $P < 0.0001$ (GraphPad version 11). ALD, alcohol-associated liver disease; ALPS, alcohol liver pathology signature; MASLD, metabolic dysfunction-associated steatotic liver disease.

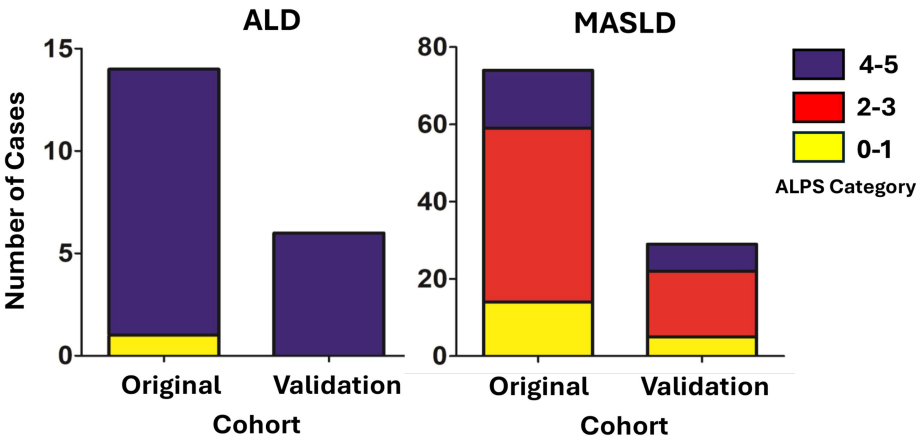


Fig. 8. The distribution of ALPS categories is similar between the original and validation cohorts. The original cohort includes 14 ALD and 74 MASLD cases from 2021 to 2023, whereas the validation cohort includes 6 ALD and 29 MASLD cases from 2024 to 2025. The numbers of cases in the three ALPS categories (absent with 0–1 ALPS feature, partial with 2–3 ALPS features, and full with 4–5 features) were compared between the original and validation cohorts for ALD and MASLD. ALD, alcohol-associated liver disease; ALPS, alcohol liver pathology signature; MASLD, metabolic dysfunction-associated steatotic liver disease.

of individual ALPS features were observed between female and male patients within either the AA or non-AA groups (Table 2). In this cohort, ALPS features were most frequently observed in AAF patients with MASLD.

Since the detection rate of all five ALPS features was elevated in AAF, we compared the frequency of multiple ALPS features that were simultaneously detected in the same MASLD patient samples (Table 3). In an overall race-stratified analysis, the distribution of ALPS categories differed significantly between AA and non-AA patients (overall $P = 0.0010$). Specifically, full ALPS (≥ 4 features) was more frequently found in AA patients than in non-AA patients (29.2% vs. 3.8%, $P = 0.0134$), whereas non-AA patients were more often scored in the 0–1 feature category (38.5% vs. 8.3%, $P = 0.0036$).

Among female patients, full ALPS (≥ 4 features) was present in 34.3% (12/35) of AAF cases compared with 0% (0/19) of non-AAF cases ($P = 0.0044$). Among male patients, the distribution of ALPS scores did not differ significantly between AAM and non-AAM patients. On the other hand, more non-AAF than AAF patients (47.4% vs. 5.7%, $P = 0.0006$) were scored in the 0–1 feature category. The overall distribution of ALPS scores in AAF and non-AAF patients differed ($P < 0.0001$). Consistent with the findings in individual ALPS features, no significant differences in ALPS score distribution were observed between AAM and non-AAM patients ($P = 1.0000$), between AAF and AAM patients ($P = 0.3081$), or between non-AAF and non-AAM patients ($P = 0.1478$). Collectively, these exploratory findings indicate that full ALPS was more frequent in AAF patients in this cohort.

Discussion

The histopathological presentation of the liver in MASLD and ALD shares many common findings, including steatosis, hepatocyte degeneration, and fibrosis. In current practice, it is not easy to distinguish the two entities based on histology alone. The objective of this study was to define and apply a composite histologic signature to explore its value in differentiating ALD and MASLD histologically and to explore potential clinical and demographic correlates. Guided by prior literature,^{21,23} we operationally defined ALPS as a combination of 4 or more of the following 5 histologic features: ductular reaction, bile stasis, neutrophilic satellitosis, portal inflammation, and advanced fibrosis (stage 3–4).

ALPS is not intended to provide a comprehensive inventory of all histologic findings that may occur in ALD. Rather, it was developed as a pragmatic composite pattern based on features that are both biologically relevant to alcohol-associated injury and sufficiently discriminatory within the selected cohorts. The five selected features were chosen because they tend to occur together in clinically diagnosed ALD and are less consistently present as a complete pattern in clinically diagnosed MASLD. Importantly, none of the individual ALPS components are specific to alcohol-associated liver injury, and each may occur in MASLD or other forms of chronic liver injury. The rationale for constructing ALPS is the emphasis on the overall pattern of co-occurrence.

Hepatocellular ballooning and steatosis were evaluated histologically in this study but were not included in the ALPS score because both are common in MASLD and ALD and provide limited etiologic discrimination between these entities. Steatosis

reflects the presence and extent of fatty change but is not specific for alcohol-associated injury, while hepatocellular ballooning is a shared feature of steatohepatitis across metabolic and alcohol-associated disease. Mallory–Denk bodies were variably present in our ALD cases and were not sufficiently sensitive or consistently identifiable. Their inclusion could therefore reduce the sensitivity and reproducibility of the composite score, especially in small biopsies or cases in which classic inclusions are sparse. Some of the other histologic features that are more commonly observed in ALD, such as increased acidophilic bodies and decreased cytoplasmic glycogenosis, were not routinely recorded during the original histologic examination and therefore were not included in the ALPS score. These features could be included in future prospective validation studies.

Among the 14 ALD and 74 MASLD cases, a full ALPS identified 92.8% of ALD cases with a specificity of 79.7% in our cohort. The AUC value of 0.832 in the ROC analysis (Fig. 7) further indicates the discriminatory performance of the ALPS score in this cohort. Importantly, we further evaluated ALPS in a temporally independent cohort using mixed, de-identified, and blinded slide review. The validation cohort showed a similar overall ALPS distribution, with full ALPS present in all clinically diagnosed ALD cases and in a subset of clinically diagnosed MASLD cases. This provides preliminary evidence that the ALPS pattern was reproducible in a later, independently reviewed cohort from the same center. However, the validation cohort was small, particularly for ALD. Therefore, these findings should be interpreted as exploratory temporal validation rather than definitive external validation.

The presence of full ALPS in 20.3% of clinically diagnosed MASLD cases in the original cohort and 24.1% in the validation cohort could suggest a variety of possibilities, including unrecognized alcohol exposure, differences in individual susceptibility to alcohol-associated injury, histologic heterogeneity intrinsic to MASLD, or a combination of these factors. Therefore, the presence of full ALPS in a clinically diagnosed MASLD case could prompt additional assessment of etiologically relevant factors or warrant an objective measurement of the blood Peth level when clinically appropriate.^{36,37} Prospective studies incorporating such quantitative assessment will be required to further determine the biological and clinical significance of ALPS in patients with MASLD.^{38,39} In patients with both metabolic dysfunction and objectively established increased alcohol exposure, the recently proposed diagnostic category of MetALD may be more appropriate for classification and clinical management. The coexistence of metabolic dysfunction and alcohol exposure is increasingly recognized as clinically relevant, with potential additive or synergistic effects on liver injury.^{40,41} Because objective alcohol-exposure data were unavailable in our retrospective cohort, patients with full ALPS who were clinically diagnosed as MASLD cannot be reclassified at this time as MetALD or ALD on the basis of histologic findings alone.⁴²

Limitations

This study is limited by its relatively small size, retrospective single-center design, and reliance on biopsy-based cohorts, which may introduce biases related to disease severity at biopsy and inconsistent indications for biopsy. In particular, the distinction

between ALD and MASLD was based primarily on the clinical diagnosis and alcohol-use history documented in the electronic medical records, which may be subject to incomplete reporting or underestimation of alcohol consumption. Objective assessment of alcohol exposure was not routinely available during the study period.

In addition, because ALPS was developed and initially assessed retrospectively in the original cohort, ALPS scoring in this cohort was not performed under a fully blinded design, introducing the possibility of observer or expectation bias. Although the reference diagnoses had been established before ALPS scoring and ALPS itself did not contribute to those diagnoses, some degree of incorporation bias related to the use of pre-existing pathologic information in the reference classification cannot be entirely excluded. This limitation was addressed in part by the subsequent temporal validation cohort, in which cases were de-identified, randomized, mixed, and scored for ALPS without access to the clinical diagnosis or alcohol-use history. In addition, because the ALPS definition and cutoff were developed in the same cohort in which the original diagnostic performance was estimated, there is the possibility of optimistic performance estimates/overfitting. Finally, the race-stratified findings were based on small exploratory subgroups and should not be interpreted as evidence of inherent biological differences. Larger studies are needed to determine the significance of these observations.

Conclusions

In this regional biopsy cohort, full ALPS was substantially more frequent in clinically diagnosed ALD than in MASLD, with a sensitivity of 92.8% and specificity of 79.7%. However, in a portion of MASLD patients, particularly among AAF patients with MASLD, full ALPS was also present. The occurrence of full ALPS in clinically diagnosed MASLD may reflect several factors, including unrecognized alcohol exposure, differences in individual susceptibility, histologic heterogeneity intrinsic to MASLD, or a combination of these factors. Full ALPS may thus serve as a histologic prompt for additional etiologic assessment when clinically appropriate. Future studies should include well-characterized fatty liver disease cohorts with objective assessment of alcohol exposure, such as blood PEth measurement, to further establish the diagnostic value of ALPS in the histologic evaluation of the liver.

Supporting information

Supplementary material for this article is available at <https://doi.org/10.14218/JCTP.2026.00017>.

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Conflict of interest

Dr. Xiao-Ming Yin is an Associate Editor of the *Journal of Clinical and Translational Pathology*. The other authors declared no conflicts of interest regarding the research, authorship, and/or publication of this article.

Author contributions

Study concept and design (YX, XMY), acquisition of data (YX, PH), analysis and interpretation of data (YX, PH, YL, SY, BK, XMY), drafting of the manuscript (YX, XMY), and study supervision (XMY). All authors have approved the final version and publication of the manuscript.

Ethical statement

This retrospective study, including both the original cohort and the independent temporal validation cohort, was approved by the Tulane University Institutional Review Board (IRB No. 2023-219), and the requirement for informed consent was waived for both cohorts. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2024).

Data sharing statement

The dataset used to support the findings of this study is available from the corresponding author upon request to Dr. Yuhua Xue (yxue7@tulane.edu or hepatotbobo@gmail.com) or Dr. Xiao-Ming Yin (xmyin@tulane.edu).

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