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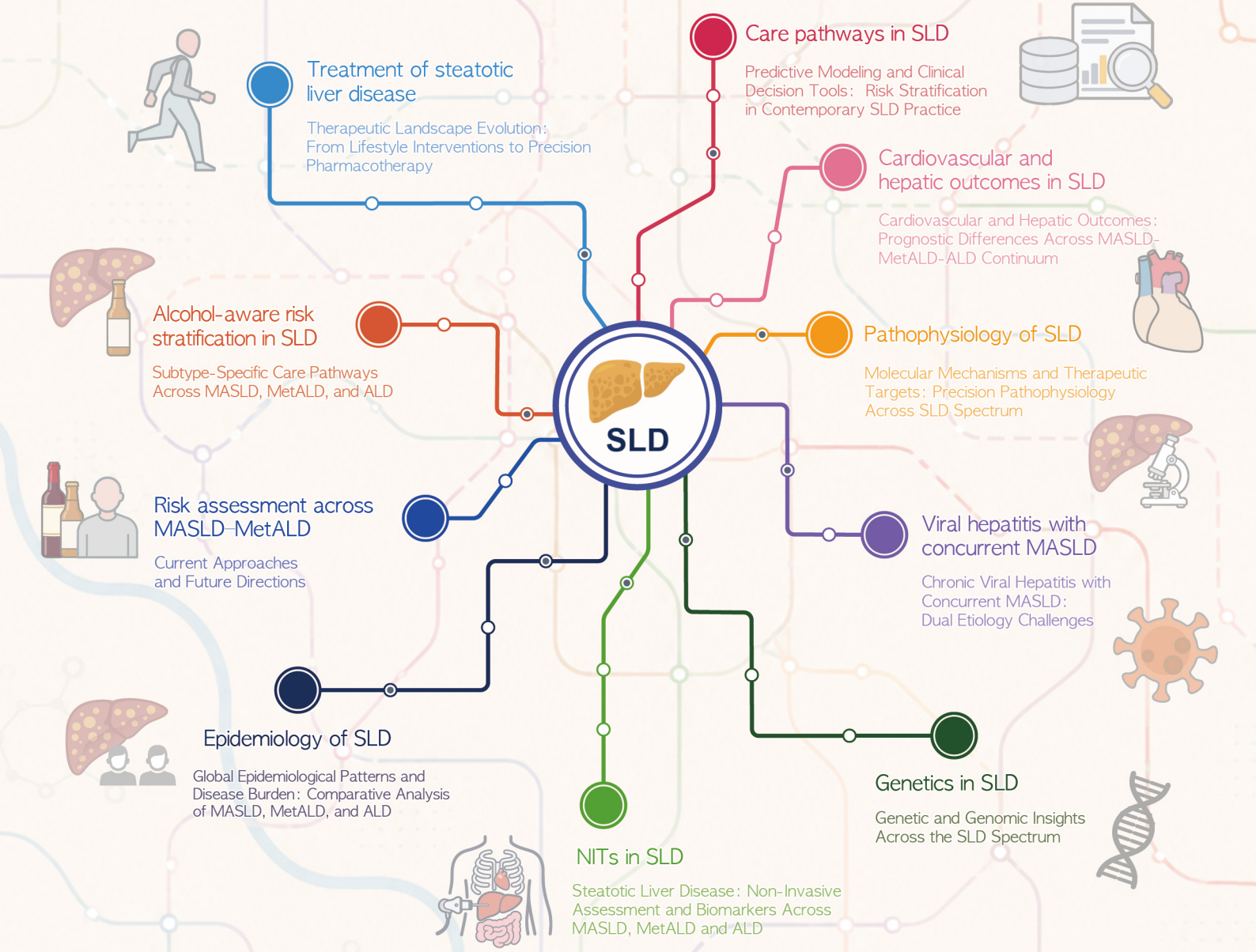
The SLD Precision MAP



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Review

Alcohol-aware risk stratification and subtype-specific care pathways across metabolic dysfunction-associated steatotic liver disease, metabolic dysfunction and alcohol-associated liver disease, and alcohol-associated liver disease

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Accurate classification and risk stratification across metabolic dysfunction-associated steatotic liver disease (MASLD), metabolic dysfunction and alcohol-associated liver disease (MetALD), and alcohol-associated liver disease (ALD) depend critically on the assessment of alcohol exposure. However, current clinical practice relies largely on self-reported alcohol intake, which may underestimate drinking quantity, pattern, and prior heavy exposure and consequently lead to subtype misclassification. This review focuses on an alcohol-aware approach to steatotic liver disease (SLD) phenotyping and clinical management. We discuss the complementary role of structured alcohol assessment and objective biomarkers, particularly phosphatidylethanol, while emphasizing biological, analytical, and host factors that limit interpretation of a single biomarker value. We further examine how active or recent alcohol exposure modifies the interpretation of commonly used risk-stratification tools, particularly FIB-4 and liver stiffness measurement, and when repeat assessment after alcohol reduction or abstinence may be appropriate. Finally, we propose practical subtype-specific care pathways integrating alcohol exposure, non-invasive fibrosis assessment, and longitudinal reassessment across MASLD, MetALD, and ALD. An alcohol-aware approach may reduce subtype misclassification and enable more appropriate referral, monitoring, and therapeutic decision-making across the SLD spectrum. **(Clin Mol Hepatol 2026;32(Suppl):e2026.0659)**

Keywords: Steatotic liver disease; MetALD; ALD; Phosphatidylethanol; Care pathway

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THE EVOLVING SPECTRUM OF STEATOTIC LIVER DISEASE (SLD)

The concurrent rise in metabolic and alcohol-related burdens has paralleled the increasing prevalence of hepatic steatosis, fibrosis, and cirrhosis.[1] The previous non-alcoholic fatty liver disease (NAFLD) framework excluded patients with alcohol intake above a defined threshold and therefore did not adequately reflect the clinical reality that metabolic dysfunction and alcohol use frequently coexist in the same patient and synergistically worsen liver injury. The need for a new definition integrating both risk factors led to the introduction of the SLD framework through multidisciplinary consensus in 2023. The new framework starts from hepatic steatosis and simultaneously assesses cardiometabolic risk factors and alcohol intake to classify patients as having metabolic dysfunction-associated steatotic liver disease (MASLD), metabolic dysfunction and alcohol-associated liver disease (MetALD), or alcohol-associated liver disease (ALD). This is not a mere change in terminology but rather a definitional acknowledgment that metabolic dysfunction and alcohol are not mutually exclusive etiologies but coexisting and interacting risk factors.[1]

Patients with hepatic steatosis, at least one cardiometabolic risk factor, and alcohol consumption below 20 g/day in women and 30 g/day in men are classified as MASLD. Those with hepatic steatosis, cardiometabolic risk factors, and alcohol consumption of 20–50 g/day in women and 30–60 g/day in men are classified as MetALD. Patients with alcohol consumption above 50 g/day in women or 60 g/day in men are classified as ALD, although cardiometabolic risk factors may still contribute to disease progression. This framework presents MASLD, MetALD, and ALD not as separate diseases but as a continuous spectrum in which metabolic risk and alcohol exposure contribute in varying proportions.[1] To provide a focused framework, this review is organized around three pillars: (1) why alcohol exposure is systematically misclassified and how objective biomarkers can correct subtype assignment; (2) how alcohol exposure alters the interpretation of risk-stratification tools; and (3) subtype-specific care pathways and the therapeutic decision points that follow.

ALCOHOL REVISITED AS A 'CENTER' IN THE NEW ERA OF SLD

Alcohol consumption and metabolic dysfunction frequently coexist in the population, and each independently increases the risk of chronic liver disease, hepatocellular carcinoma (HCC), hepatic decompensation, liver transplantation, and liver-related death. The two factors are not merely independent risk factors but amplify each other's hepatotoxicity. This perspective supports the view that MetALD should be understood not as "MASLD with moderate alcohol use added on" but as a dual-risk phenotype in which metabolic dysfunction and alcohol exposure act together.[2] Earlier studies from a cardiovascular disease (CVD) perspective suggested that light to moderate alcohol use might lower all-cause mortality. However, recent studies have consistently shown that even light to moderate alcohol intake increases the risk of major adverse liver outcomes (MALO). In contrast, population-based liver outcome data indicate that increasing alcohol exposure and metabolic dysfunction jointly increase the risk of clinically significant liver disease. In the Finnish Health 2000 cohort, the cumulative incidences of severe liver-related outcomes across abstinent/light, moderate, risk, and heavy drinking categories were 0.5%, 1.4%, 2.9%, and 9.0%,

Abbreviations:

2D-SWE, two-dimensional shear-wave elastography; ADAPT, age, diabetes, PRO-C3, and platelet count; ALD, alcohol-associated liver disease; ALT, alanine aminotransferase; AST, aspartate aminotransferase; AUD, alcohol use disorder; AUDIT-C, Alcohol Use Disorders Identification Test–Consumption; AUROC, area under the receiver operating characteristic curve; BMI, body mass index; cACLD, compensated advanced chronic liver disease; CI, confidence interval; CVD, cardiovascular disease; ELF, enhanced liver fibrosis; EtG, ethyl glucuronide; EtS, ethyl sulfate; FAST, FibroScan–AST; FIB-4, fibrosis-4 index; GGT, gamma-glutamyl transferase; HCC, hepatocellular carcinoma; HDL, high-density lipoprotein; HDL-C, high-density lipoprotein cholesterol; HR, hazard ratio; KNHANES, Korea National Health and Nutrition Examination Survey; LSM, liver stiffness measurement; MACE, major adverse cardiovascular events; MALO, major adverse liver outcomes; MASH, metabolic dysfunction-associated steatohepatitis; MASLD, metabolic dysfunction-associated steatotic liver disease; MEFIB, magnetic resonance elastography combined with fibrosis-4 index; MetALD, metabolic dysfunction and alcohol-associated liver disease; MRE, magnetic resonance elastography; NAFLD, nonalcoholic fatty liver disease; NAS, NAFLD activity score; NASH, nonalcoholic steatohepatitis; NFS, NAFLD fibrosis score; NHANES, National Health and Nutrition Examination Survey; NIS2+, optimized non-invasive test for at-risk NASH; NIS4, non-invasive test for at-risk NASH; NIT, non-invasive test; NPV, negative predictive value; NS, not statistically significant; PEth, phosphatidylethanol; PMID, PubMed identifier; PPV, positive predictive value; PRO-C3, N-terminal pro-peptide of type III collagen; PY, person-years; RR, relative risk; Se, sensitivity; SLD, steatotic liver disease; Sp, specificity; T2DM, type 2 diabetes mellitus; VALID, Veterans Affairs Liver Disease cohort; VCTE, vibration-controlled transient elastography; VHA, Veterans Health Administration

respectively, among individuals without metabolic syndrome, compared with 1.5%, 3.1%, 6.0%, and 11.8% among those with metabolic syndrome.[3] In a separate analysis of the same population-based cohort, weekly binge drinking, defined as ≥60 g of ethanol per occasion, and metabolic syndrome showed a supra-additive association with the risk of decompensated liver disease.[4] US study likewise showed a supra-additive effect of metabolic syndrome and heavy drinking on all-cause mortality in patients with ultrasound-confirmed hepatic steatosis.[5] Conversely, alcohol cessation can improve metabolic parameters. In a systematic review by Roerecke et al.,[6] a reduction in alcohol consumption lowered blood pressure, with effects particularly pronounced in those drinking two or more drinks per day. Hart et al.[7] analyzed two Scottish prospective cohorts and reported that body mass index (BMI) and alcohol consumption jointly affected the risk of liver disease, with combined exposure conferring even greater risk. Kim et al.[8] analyzed 414,209 UK Biobank participants and reported that the patatin-like phospholipase domain-containing protein 3 (PNPLA3) I148M variant, excessive alcohol intake, and obesity were synergistically associated with the risk of cirrhosis, HCC, and liver-related death. These findings support viewing cardiometabolic risk and alcohol exposure as concurrent phenotypes that can amplify each other. Therefore, in patients with SLD, holistic assessment and management should not be limited to metabolic risk factors such as diabetes, central obesity, blood pressure, triglycerides, and high-density lipoprotein cholesterol (HDL-C), but should also include careful evaluation of alcohol amount, drinking pattern, binge drinking, and lifetime exposure.

Although the current MetALD category provides a pragmatic framework for classification, its reliance on average weekly alcohol intake has several limitations. First, threshold-based definitions may miss the harmful effects of alcohol below the formal MetALD range: even modest intake can amplify liver-related risk in patients with a high cardiometabolic burden, particularly when consumed in binge patterns. Second, average alcohol intake does not fully reflect drinking pattern, duration, temporal variation, or previous heavy exposure. Third, the definition may underemphasize the contribution of cardiometabolic dysfunction among individuals classified as having ALD, in whom obesity, diabetes, and other metabolic factors may independently accelerate fibrosis progression and extrahepatic complications. Across health check-up, national survey, and pooled cohorts, MASLD accounts for the majority of SLD while MetALD and ALD represent smaller but non-negligible fractions; these estimates have recently been reviewed in detail.[9]

CLINICAL OUTCOMES ACROSS THE SLD SPECTRUM

Comparative outcomes across the three subtypes have recently been reviewed in detail.[10] Two findings from that literature frame the present review. First, liver-related outcomes rise with alcohol exposure: in a cohort of 341,601 adults with imaging-confirmed steatosis followed for a median of 5.5 years, the incidence of MALO was 0.61, 1.12, and 1.78 per 100 person-years in MASLD, MetALD, and ALD respectively, and all-cause mortality was 2.60, 2.74, and 3.42 per 100 person-years.[11] A misassigned subtype therefore carries a materially different expected prognosis. Second, the cardiovascular signal does not follow the same gradient. In the same cohort, the incidence of major adverse cardiovascular events was similar across subtypes,[11] and a meta-analysis of 24 cohorts likewise found no significant difference between MetALD and MASLD.[12] This divergence reflects competing liver-related mortality, residual confounding by smoking, and sick-quitter and healthy-user bias rather than cardioprotection, and lower cardiovascular estimates in alcohol-exposed subtypes should not be interpreted as such. Both findings rest entirely on subtype assignment derived from self-reported intake, and are therefore no more reliable than that assignment.

MOLECULAR MECHANISMS AND MOLECULAR SIGNATURES OF THE DUAL-RISK PHENOTYPE

Convergent lipotoxic and oxidative injury

Metabolic dysfunction increases hepatic free-fatty-acid delivery and de novo lipogenesis, whereas ethanol metabolism raises the NADH/NAD^+ ratio and suppresses mitochondrial β-oxidation. Together, these processes promote the accumulation of triglycerides and lipotoxic intermedi-

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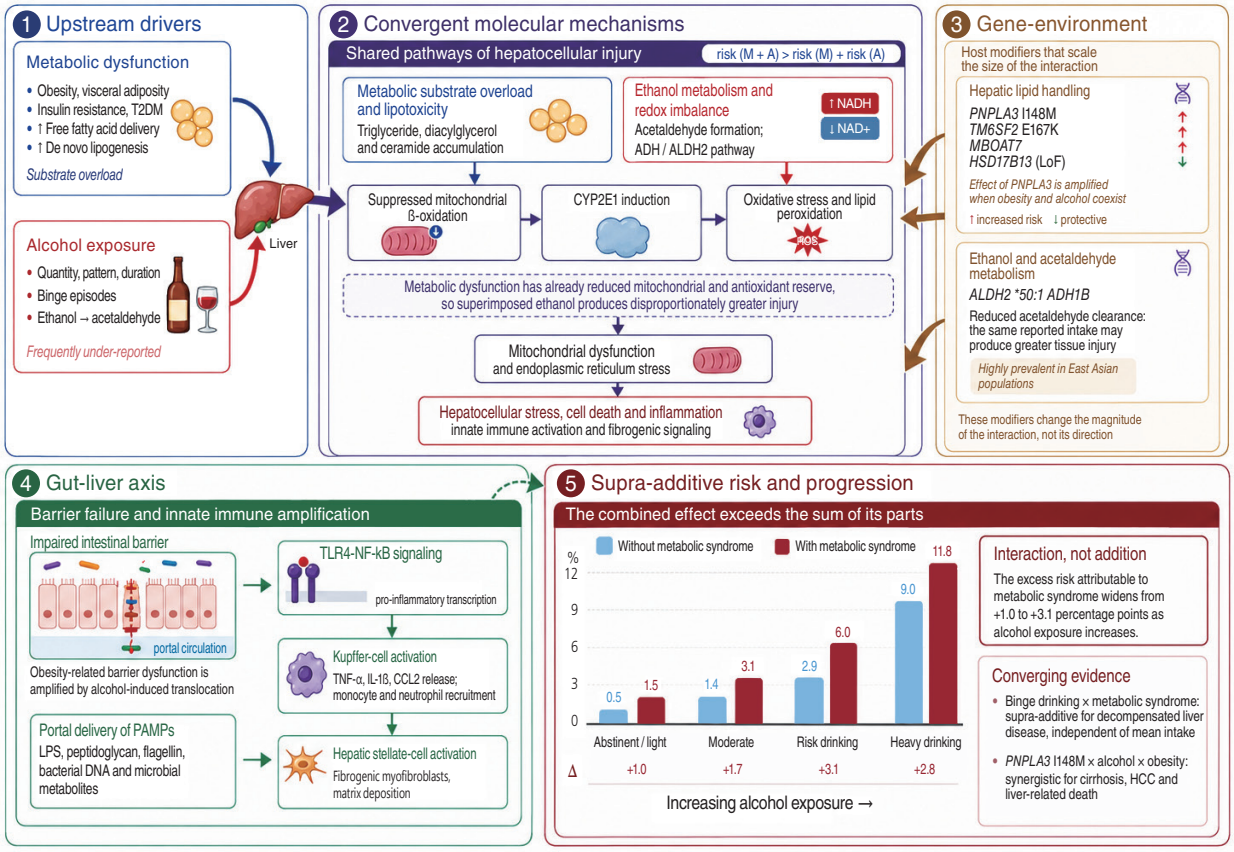
ates and create a feed-forward cycle of steatosis, insulin resistance, and hepatocellular stress. Thus, MetALD represents the convergence of metabolic substrate overload and alcohol-induced impairment of lipid disposal rather than the simple coexistence of two independent causes of steatosis (Fig. 1).[13]

CYP2E1, mitochondrial dysfunction, and inflammatory amplification

CYP2E1 expression may already be increased in obesity, diabetes, and SLD and is further induced by chronic alcohol exposure, providing a shared source of reactive oxygen species and lipid peroxidation.[14,15] Metabolic dysfunction also reduces mitochondrial respiratory and antioxidant reserve, allowing superimposed ethanol metabolism to produce disproportionately greater oxidative and mitochondrial injury.[13] In parallel, obesity-related intestinal barrier dysfunction and hepatic immune priming may be amplified by alcohol-induced microbial translocation, enhancing TLR4–NF-κB signaling, Kupffer-cell activation, and hepatic stellate-cell activation. These convergent pathways provide a mechanistic basis for the supra-additive liver risk observed when metabolic dysfunction and alcohol exposure coexist.



ADH, alcohol dehydrogenase; ALDH2, aldehyde dehydrogenase 2; HCC, hepatocellular carcinoma; LoF, loss of function; LPS, lipopolysaccharide; PAMPs, pathogen-associated molecular patterns; T2DM, type 2 diabetes mellitus; TLR4, Toll-like receptor 4.

Figure 1. Convergent molecular mechanisms underlying the supra-additive dual-risk phenotype of MetALD. Metabolic dysfunction and alcohol exposure (1) converge on shared pathways of hepatocellular injury (2): substrate overload and lipotoxicity on one side, ethanol-induced redox imbalance and suppressed β-oxidation on the other, meeting at CYP2E1-derived oxidative stress and mitochondrial dysfunction. Because metabolic dysfunction has already depleted mitochondrial and antioxidant reserve, superimposed ethanol produces disproportionately greater injury. Host variants in hepatic lipid handling and in ethanol metabolism, including ALDH2 rs671, scale the magnitude of this interaction (3), and gut barrier failure with microbial translocation amplifies it further (4). The combined risk of liver-related outcomes therefore exceeds the sum of the two exposures. ADH, alcohol dehydrogenase; ALDH2, aldehyde dehydrogenase 2; HCC, hepatocellular carcinoma; LoF, loss of function; LPS, lipopolysaccharide; MetALD, metabolic dysfunction and alcohol-associated liver disease; PAMPs, pathogen-associated molecular patterns; T2DM, type 2 diabetes mellitus; TLR4, Toll-like receptor 4.

Gene–environment interactions

Genetic variants affecting hepatic lipid handling may further modify this dual-risk phenotype. PNPLA3 I148M impairs lipid-droplet remodeling and promotes steatohepatitis and fibrosis, with stronger clinical effects when obesity and alcohol exposure coexist.[8,16] TM6SF2 E167K reduces very-low-density lipoprotein secretion and increases hepatic lipid retention, whereas MBOAT7 variants disrupt phosphatidylinositol remodeling.[17,18] In contrast, loss-of-function HSD17B13 variants attenuate progression to steatohepatitis and fibrosis.[19] These findings support integrating genetic susceptibility with quantitative metabolic burden and alcohol exposure rather than interpreting either risk domain in isolation.

Molecular signatures of the dual-risk phenotype

Alcohol and metabolic dysfunction exert opposing but overlapping effects on HDL metabolism: alcohol may increase HDL cholesterol, whereas insulin resistance promotes triglyceride enrichment and the formation of smaller, potentially dysfunctional HDL particles.[20,21] Consequently, an apparently favorable HDL-cholesterol concentration may not reflect preserved HDL function and should not be interpreted as evidence of cardiovascular protection.[22]

ALCOHOL EXPOSURE AS A MODIFIER OF NON-INVASIVE TEST (NIT)-BASED RISK STRATIFICATION

This section addresses a question: how alcohol exposure itself alters the interpretation of tests whose thresholds were derived in MASLD populations. Alcohol acts through three separate routes. It alters the biochemical inputs of serum-based scores; it transiently raises liver stiffness independently of fibrosis; and, unlike metabolic risk factors, it fluctuates over a timescale of weeks.

Fibrosis-4 (FIB-4) index

Alcohol consumption affects the aspartate aminotransferase (AST)/alanine aminotransferase (ALT) ratio and may reduce the diagnostic accuracy of FIB-4 in MetALD and ALD. In a Korean magnetic resonance elastography (MRE)-based health check-up cohort, Oh et al.[23] analyzed 462 MetALD patients using advanced fibrosis (MRE ≥3.6 kPa) as the reference, and both FIB-4 and the NAFLD fibrosis score showed an area under the receiver operating characteristic curve (AUROC) of 0.85, supporting the role of FIB-4 as a first-line rule-out tool in MetALD similar to that in MASLD.[23] In ALD, AST-predominant elevation, gamma-glutamyl transferase (GGT) elevation, alcohol-related hepatitis, and thrombocytopenia coexist. Therefore, the same FIB-4 value may not reflect the same fibrosis burden as in MASLD.

Image-based NITs (vibration-controlled transient elastography [VCTE], and two-dimensional shear-wave elastography [2D-SWE])

VCTE is the most commonly used imaging-based second-line test after FIB-4, particularly in MASLD.[24,25] In MetALD, available data suggest that VCTE retains useful rule-out performance (AUROC 0.85, negative predictive value [NPV] 99%) when used after FIB-4, but its positive predictive value is limited, emphasizing the need to interpret results in the context of current alcohol exposure and hepatic inflammation.[26] In ALD, an individual-participant-data meta-analysis of 1,026 patients reported AUROCs of 0.90 for advanced fibrosis (≥F3) and 0.91 for cirrhosis, with an optimal cut-off of 12.1 kPa for ≥F3.[27] However, active alcohol-related hepatic injury may increase liver stiffness independently of fixed fibrosis; therefore, liver stiffness measurement (LSM) in MetALD and ALD should be interpreted together with recent drinking status, biochemical inflammation, and longitudinal changes. 2D-SWE has also shown good diagnostic performance in alcohol-related liver disease (AUROC ≥0.92 for significant fibrosis),[28] but subtype-specific thresholds for MetALD and ALD require further prospective validation. Detailed modality-specific performance and fibrosis-stage cut-offs of NITs have recently been reviewed in detail.[29]

Direct fibrosis biomarkers (enhanced liver fibrosis [ELF], N-terminal pro-peptide of type III collagen [PRO-C3], and age, diabetes, PRO-C3, and platelet count [ADAPT])

ELF combines hyaluronic acid, procollagen III N-terminal

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peptide, and tissue inhibitor of metalloproteinase-1, reflecting extracellular matrix turnover. In MetALD, Torp et al.[30] reported that ELF and ADAPT showed the highest performance for advanced fibrosis (AUROC 0.90) in a biopsy-based cohort. Adding ELF or ADAPT before transient elastography reduced referrals by 43–45% while maintaining prognostic performance. Madsen et al.[31] reported that in ALD, PRO-C3 had an AUROC of 0.85 and ADAPT 0.88 for identifying advanced fibrosis. In a pilot study by Lévi-Strauss et al.,[32] ELF showed little change after alcohol withdrawal, whereas transient elastography decreased significantly in patients who maintained abstinence, suggesting that LSM is more sensitive than ELF to changes in drinking and inflammation.

SERIAL LIVER STIFFNESS MONITORING FOR DYNAMIC RISK STRATIFICATION

Liver stiffness values change over time in patients with SLD, particularly in MetALD and ALD, where alcohol intake and abstinence may fluctuate. Therefore, serial LSM assessment should be incorporated into dynamic disease monitoring rather than interpreted as a single-point measurement. With emerging MASLD pharmacotherapies, serial LSM assessment is increasingly important for risk stratification, treatment decisions, and long-term prognostication in SLD.

Traditionally, Baveno VII classifies patients with a transient elastography–based baseline LSM ≥10 kPa as having compensated advanced chronic liver disease (cACLD) and recommends annual reassessment. A clinically relevant LSM decrease is defined as LSM <10 kPa or LSM <20 kPa with a ≥20% reduction.[33] These Baveno VII–based LSM criteria are outcome-based prognostic thresholds and should not be interpreted as biopsy-based cut-offs for assigning a specific fibrosis stage. Thorhauge et al.[34] classified follow-up LSM trajectories in an ALD cohort into five categories and showed stepwise worsening of 3-year decompensation-free survival: 93% in no-cACLD, 79% in cACLD decreasers, 80% in cACLD stable non-severe, 64% in cACLD stable severe, and 51% in cACLD increasers. The hazard ratio (HR) for decompensation in cACLD increasers was 4.53 (P=0.003), and the HR for all-cause mortality was 3.22 (P=0.01). Among 246 patients without cACLD at baseline, 13% progressed to follow-up LSM ≥10 kPa ("no cACLD increasers"), with an all-cause mortality HR of 4.01 (95% confidence interval [CI] 1.64–9.83). These findings are consistent with other chronic liver diseases. Semmler et al.[33] reported that LSM dynamics were more useful than single baseline LSM for predicting decompensation and liver-related mortality in an advanced chronic liver disease cohort. Gidener et al.[35] showed that serial MRE-LSM increase in NAFLD was associated with liver-related outcomes, and in the compensated cirrhosis subgroup, MRE-LSM progressors had a 100% rate of decompensation or death, compared with 19% in non-progressors. Ultimately, LSM change appears most prognostically informative when interpreted within Baveno VII–based clinical categories rather than as a simple ΔLSM (decompensation prediction C-index 0.85, mortality 0.70).[34]

ALCOHOL INTAKE ASSESSMENT: A NEW DIAGNOSTIC CHALLENGE

Limitations of self-reported alcohol exposure

The most vulnerable point in current SLD classification is accurate assessment of alcohol exposure. Because MASLD, MetALD, and ALD are defined by weekly alcohol intake, reliance on self-report—susceptible to under-reporting, social-desirability bias, recall error, and omission of past alcohol use disorder (AUD)—can misassign subtype, altering prognosis, NIT interpretation, treatment, and linkage to addiction care.[30,36] Such misclassification is clinically consequential: Nasr et al.[37] found that 17.4% of presumed MASLD patients had alcohol-related illness and roughly four-fold higher cumulative MALO (19.5% vs. 7.8%), Staufer et al.[38] found 28.6% of presumed NAFLD patients had moderate-to-excessive intake confirmed by hair ethyl glucuronide (EtG), and Lee et al.[39] reported that AUD misclassified as MASLD or MetALD carried markedly higher liver-related mortality (adjusted HRs 6.53 and 6.98).

Direct alcohol biomarkers and their clinical utility

Phosphatidylethanol (PEth) is a biomarker generated from phospholipids in the cell membrane in the presence of ethanol and reflects alcohol intake over the preceding

1–4 weeks. In 46,406 tested individuals (Vaz et al.[40]), PEth predicted MALO, with incidence rising from MASLD/PEth <35 ng/mL to MASLD/35–210 ng/mL to ALD (6.4, 11, and 57/1,000 PY); each 70 ng/mL increment raised MALO risk by 5%. The MetALD position statement by Arab et al.[36] proposed PEth 20–200 ng/mL as consistent with the MetALD range (20–60 g/day) and ≥200 ng/mL with ALD. However, these values should be regarded as reference ranges proposed by expert panels rather than rigid diagnostic thresholds for subtype reassignment. PEth concentrations should be interpreted together with drinking amount and pattern, hematologic status, host factors such as ALDH2 genotype, and the overall clinical context. EtG and ethyl sulfate are direct metabolites of ethanol, generated by Uridine Diphosphate glucuronosyltransferase and the sulfotransferase pathway, respectively. Urine EtG detects recent alcohol intake over approximately 3 days with sensitivity/specificity of 71–89%/92–99%, whereas hair EtG reflects 3–6 months of exposure with sensitivity/specificity of 84–100%.[41] In addition to amount, drinking pattern is also important. Åberg et al.[4] reported that binge drinking and metabolic syndrome showed a supra-additive interaction for liver-related events, and that this effect was independent of mean alcohol consumption.

Biological factors affecting PEth concentrations

PEth is measured in whole blood and is largely associated with red-blood-cell membranes; therefore, hematocrit, anemia, red-cell lifespan, and erythrocyte turnover can affect its concentration. In cirrhosis, shortened red-cell survival due to hypersplenism, bleeding, nutritional deficiency, marrow suppression, or hemolysis may lower PEth relative to alcohol exposure, while altered ethanol elimination may have the opposite effect. PEth should therefore be interpreted with hematologic status, recent transfusion, and liver function.[42,43] Variants in alcohol dehydrogenase and aldehyde dehydrogenase may further modify ethanol kinetics, acetaldehyde accumulation, and PEth formation, contributing to interindividual variability despite similar reported intake.[44]

Analytical standardization and implementation barriers

PEth comprises multiple homologues, most commonly 16:0/18:1 and 16:0/18:2, and laboratories may report one species, their sum, or variably defined “total PEth”; cross-laboratory comparisons therefore require confirmation of the measured species and reporting method.[45] Results are also influenced by specimen handling, extraction procedures, storage, dried-blood-spot recovery, and the use of appropriately matched isotope-labelled internal standards to correct for extraction loss, matrix effects, and Liquid Chromatography–Tandem Mass Spectrometry variability.[46] Differences in calibration materials, analytical ranges, quantification limits, and quality-control procedures further contribute to interlaboratory variation, and PEth assays and cut-offs remain incompletely standardized.[47] In hepatology clinics, PEth may additionally support subtype clarification, longitudinal monitoring, and interpretation of otherwise unexplained changes in liver stiffness. Routine implementation remains limited by assay availability, cost, reimbursement, regulatory requirements, and incomplete standardization of analytical methods and cut-offs across regions. Dried-blood-spot testing may improve access once analytical and interpretive standards are harmonized.

Asian-specific susceptibility and integrated interpretation

The ALDH2 rs671 variant, which is common in East Asian populations, reduces acetaldehyde clearance and may increase alcohol-related tissue injury at a given level of ethanol exposure. Consequently, the relationship between reported alcohol intake, PEth concentration, and organ injury may differ according to host genetic susceptibility. In Asian patients, assessment should therefore consider binge-drinking patterns, flushing history, ALDH2-related susceptibility, and cardiometabolic burden rather than relying solely on average alcohol intake or a single PEth value.[48-50]

NOVEL BIOMARKERS IN SLD

The need for novel biomarkers has grown under the new SLD classification, but SLD subtype-specific biomarkers are still in early stages and represent an important unmet need. In the MASLD/MASH field, four-component non-invasive steatohepatitis score (NIS4) is a blood-based panel

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combining miR-34a-5p, alpha-2-macroglobulin, YKL-40, and HbA1c, developed for non-invasive identification of at-risk nonalcoholic steatohepatitis (NASH) (NAFLD activity score [NAS] ≥4 and fibrosis stage ≥F2). NIS4 has shown an AUROC of 0.76–0.83 for at-risk NASH.[51] The optimized successor, optimized non-invasive test for at-risk NASH (NIS2+), is a two-biomarker panel based on miR-34a-5p and YKL-40, and in a test cohort of 2,035 patients, it had an AUROC of 0.813 for at-risk NASH, outperforming NIS4 (0.792), FIB-4 (0.653), and ALT (0.699). NIS2+ was also relatively unaffected by age, sex, BMI, type 2 diabetes mellitus (T2DM), dyslipidemia, and hypertension.[52] Liu et al.[53] used a 10-protein plasma model to distinguish alcohol-predominant from cardiometabolic-predominant MetALD and found that the alcohol-predominant subgroup had higher fibrosis severity and greater risks of cirrhosis and mortality. This distinction has potential clinical implications because alcohol-predominant disease may require greater emphasis on alcohol reduction, treatment of AUD, objective exposure monitoring, and surveillance for advanced liver disease, whereas cardiometabolic-predominant disease may warrant more intensive management of obesity, diabetes, dyslipidemia, and other metabolic drivers. However, this molecular classification remains investigational and re-

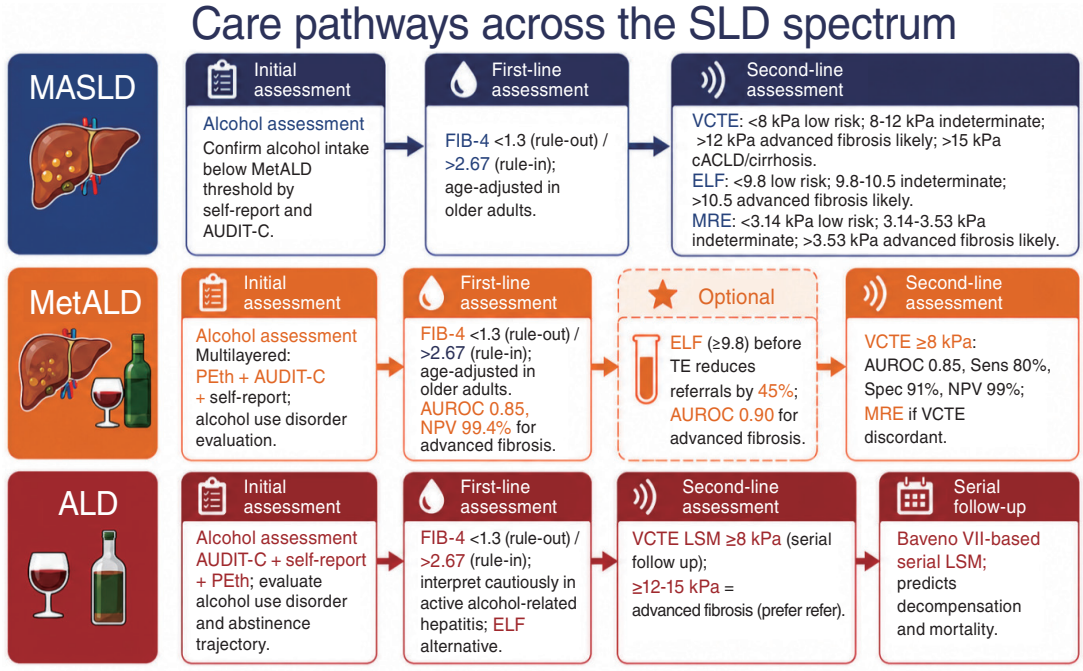

Figure 2. Subtype-specific care pathways across the SLD spectrum. Proposed diagnostic algorithm for MASLD (blue), MetALD (orange), and ALD (red), illustrating how alcohol assessment, first-line risk stratification, second-line confirmation, and longitudinal monitoring should be tailored to each subtype. Alcohol assessment escalates from self-report plus AUDIT-C in MASLD, to a multilayered approach incorporating PEth in MetALD, to formal AUD evaluation in ALD. FIB-4 (<1.3 low risk, 1.3–2.67 intermediate risk, and >2.67 high risk; age-adjusted in older adults) is the shared first-line test. Patients with intermediate- or high-risk FIB-4 results are referred to a liver clinic for second-line fibrosis assessment in the MASLD and MetALD pathways. In ALD, referral should also be considered, but FIB-4 should be interpreted cautiously because active alcohol-related liver injury may affect its accuracy. In MetALD, an optional ELF step before VCTE reduces referrals by ~45%. Second-line testing uses VCTE, ELF, or MRE with subtype-aware cut-offs; ALD additionally requires Baveno VII–based serial LSM to predict decompensation and mortality. Dashed outline indicates the optional intermediate step. These algorithms are intended as an evidence-based synthesis rather than formal guideline recommendations. Although the MASLD pathway broadly follows current EASL and AASLD guidance, the MetALD and ALD pathways remain provisional because subtype-specific prospective evidence is limited. AASLD, American Association for the Study of Liver Diseases; ALD, alcohol-associated liver disease; AUD, alcohol use disorder; AUDIT-C, Alcohol Use Disorders Identification Test–Consumption; AUROC, area under the receiver operating characteristic curve; cACLD, compensated advanced chronic liver disease; EASL, European Association for the Study of the Liver; ELF, enhanced liver fibrosis test; FIB-4, fibrosis-4 index; LSM, liver stiffness measurement; MASLD, metabolic dysfunction–associated steatotic liver disease; MetALD, metabolic dysfunction and alcohol-associated liver disease; MRE, magnetic resonance elastography; NPV, negative predictive value; PEth, phosphatidylethanol; Sens, sensitivity; SLD, steatotic liver disease; Spec, specificity; VCTE, vibration-controlled transient elastography.

quires prospective validation before it can guide treatment selection or surveillance pathways. Proteomic phenotyping may eventually be integrated with partitioned polygenic risk scores and longitudinal clinical models to quantify the relative contributions of hepatic, cardiometabolic, and alcohol-related susceptibility over time.[54-56] The genetic architecture of SLD and the current status of genomic risk stratification have been reviewed in detail elsewhere.[57] Schneider et al.[58] reported that lipidomic profiles, particularly large and medium HDL-related markers, best distinguished MASLD from MetALD. Mendelian randomization further supported the alcohol-HDL axis as an objective signature of MetALD. Mechanistically, alcohol increases both HDL concentration and HDL particle size. Badia et al.[59] reported in the Dallas Heart Study that alcohol intake was associated with HDL-C, HDL particle, and cholesterol efflux capacity. De Oliveira E Silva et al.[20] reported that alcohol intake dose-dependently increased HDL-C through increased transport rates of apolipoprotein A-I/A-II. Omics-based biomarkers can capture disease biology in depth, but barriers remain, including cost, standardization of analytical platforms, interlaboratory reproducibility, cut-off definition, ethnic and dietary differences, variability in alcohol exposure patterns, prospective validation, and regulatory qualification. Future studies in large multi-ethnic prospective cohorts should validate omics markers alongside PEth, FIB-4, ELF, VCTE, MRE, and clinical outcomes, ultimately distilling them into a concise clinical panel of a few protein, metabolite, or lipid markers.

CARE PATHWAYS ACROSS THE SLD SPECTRUM

The SLD care pathway is best established for MASLD, with a two-step strategy of evaluating cardiometabolic risk factors followed by first-line FIB-4 and second-line VCTE as the standard.[24] However, direct application to MetALD and ALD is limited. In alcohol-related SLD subtypes, the accurate assessment of alcohol amount and pattern is therefore a critical element, and adjunct or repeated tests are needed to complement the limitations of the FIB-4 → VCTE two-step pathway. The SLD care pathway should therefore not be a simple extension of the MASLD pathway, but should be reconstructed as a subtype-aware and dynamic pathway that integrates alcohol exposure and abstinence variability from the definition stage. This is the key to accurate risk classification, reduction of unnecessary referrals, and improved prognosis (Fig. 2). Although recent European Association for the Study of the Liver (EASL), American Association for the Study of Liver Diseases (AASLD), American Gastroenterological Association (AGA), and Korean Association for the Study of the Liver (KASL) recommendations consistently support a sequential strategy using FIB-4 followed by VCTE or another validated second-line NIT, they differ in the target population, reassessment interval, referral threshold, availability of alternative NITs, and integration of newly approved MASH therapies. Table 1 compares these recommendations and highlights that current formal guidelines remain primarily MASLD-oriented and do not provide dedicated longitudinal pathways for MetALD or ALD. The subtype-specific algorithms proposed in this review should therefore be interpreted as an evidence-based synthesis that extends, rather than replaces, existing guideline recommendations.

MASLD care pathway

The MASLD care pathway is the most well established. Patients are evaluated for obesity, T2DM, dyslipidemia, hypertension, CVD risk, abnormal liver enzymes, and steatosis on imaging, with FIB-4 applied as the first-line test. The 2024 EASL MASLD guideline and the American Association for the Study of Liver Diseases Practice Guidance recommend a case-finding strategy in patients with cardiometabolic risk factors, abnormal liver enzymes, or steatosis on imaging, using FIB-4 as the first-line screening tool followed by VCTE, ELF, or MRE as second-line tests in a stepwise approach.[60] When FIB-4 is in the intermediate or high-risk range, VCTE or ELF is performed; if the results remain discordant or treatment candidacy requires further assessment, additional validated NITs may be considered or the patient may be referred for specialist evaluation.[24]

MetALD care pathway

The first-line role of FIB-4 in MetALD remains debated. However, the emerging evidence suggests that FIB-4-based pathways may retain acceptable rule-out performance in MetALD. Oh et al.[23] reported in a health check-up

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Table 1. Comparison of guideline-based clinical care pathways for fibrosis risk stratification and management in MASLD

Element	EASL–EASD–EASO 2024	AASLD 2023 (upd. 2024–25)	AGA 2026	KASL 2025 (+2024 NIT)
Target population	T2D, obesity + ≥1 cardiometabolic risk; persistent ↑ enzymes; and/or imaging steatosis	Imaging-defined steatosis, or metabolic risk / unexplained enzyme ↑ >6 mo	T2D; overweight/obesity + ≥1 metabolic risk; or incidental steatosis / enzyme ↑	MASLD or suspected MASLD (T2D, obesity/metabolic risk, abnormal enzymes, imaging steatosis)
Screening strategy	Targeted case-finding (not universal screening)	Risk-based in suspected/high-risk (not general screening)	Proactive in 3 predefined high-risk groups; prior steatosis confirmation not required	Risk-based; fibrosis pathway mainly from linked 2024 KASL NIT guideline
Action after elevated FIB-4*	1.3–2.67: 2nd-line NIT, or intensify cardiometabolic care + repeat FIB-4 ~1 y	≥1.3: VCTE or ELF; direct referral if >2.67 or persistent ↑ enzymes	Above age-adjusted threshold: VCTE/LSM or ELF	1.3–2.67: VCTE; >2.67: high risk → specialist
Preferred second-line test	VCTE or ELF; MRE / other when needed	VCTE or ELF; MRE in specialty if intermediate/discordant	VCTE/LSM or ELF	VCTE (principal); MRE, ELF, SWE, or Agile 3+/4 selectively
Rule-out threshold (advanced fibrosis)	LSM <8 kPa → low probability	VCTE <8 kPa → rule-out	LSM <8 kPa or ELF <9.2 → low probability	LSM <8 kPa → low probability (after intermediate FIB-4)
Referral / high-risk action	LSM ≥8 kPa → further eval/referral; higher → assess for cACLD	LSM 8–12 intermediate; ≥12 likely advanced; refer if elevated/discordant	LSM ≥8 → hepatology referral; ≥10 or ELF ≥9.8 → clinically significant fibrosis	VCTE ≥8 (after intermediate FIB-4) → more NITs/referral; FIB-4 >2.67 high risk
Low-risk reassessment	Every 1–3 y by cardiometabolic risk	1–2 y (T2D/multiple risks); 2–3 y (lower risk)	Repeat FIB-4 every 1–2 y	Periodic, by metabolic risk & initial NIT
Liver biopsy	Diagnostic uncertainty, discordant NITs, competing disease, or histology-dependent decisions	Suspected significant fibrosis, intermediate/discordant NITs, persistent enzyme ↑, or alt. diagnosis	Selective — when NITs inadequate or histology would change management	When NITs inconclusive, another liver disease suspected, or histology needed for treatment
Alcohol assessment	Assess amount & pattern; advise reduction/avoidance; abstinence in advanced disease	Assessed as competing/modifying cause (original NAFLD framework)	Systematic screening, preferably AUDIT-C	Assessed for SLD subclassification, incl. MetALD
Dedicated MetALD / ALD pathway	None — all four guidelines remain MASLD-oriented and provide no subtype-specific longitudinal fibrosis pathway for MetALD or ALD.			

AASLD, American Association for the Study of Liver Diseases; AGA, American Gastroenterological Association; ALD, alcohol-associated liver disease; AUDIT-C, Alcohol Use Disorders Identification Test–Consumption; cACLD, compensated advanced chronic liver disease; EASD, European Association for the Study of Diabetes; EASL, European Association for the Study of the Liver; EASO, European Association for the Study of Obesity; ELF, enhanced liver fibrosis; FIB-4, fibrosis-4 index; KASL, Korean Association for the Study of the Liver; LSM, liver stiffness measurement; MASLD, metabolic dysfunction-associated steatotic liver disease; MetALD, metabolic dysfunction and alcohol-associated liver disease; MRE, magnetic resonance elastography; NIT, noninvasive test; SWE, shear-wave elastography; T2D, type 2 diabetes; VCTE, vibration-controlled transient elastography.
*First-line test: All four guidelines use FIB-4 as the first-line fibrosis test, with a low-risk cut-off of <1.3 (<2.0 in adults ≥65 years); values above this threshold are considered intermediate/elevated and prompt the action shown.

MRE cohort that FIB-4 had a high NPV for ruling out advanced fibrosis in MetALD patients. Díaz et al.[26] demonstrated the feasibility of an FIB-4 → VCTE pathway in suspected MetALD. In suspected MetALD, VCTE obtained during active drinking or alcohol-related hepatic inflammation should be interpreted with caution, because necroinflammation can transiently elevate LSM independently of fibrosis. When an elevated initial LSM coincides with recent alcohol exposure or increased liver enzymes, repeating VCTE after approximately 2–4 weeks of abstinence and biochemical improvement or stabilization may reduce false-positive classification of cACLD, provided that repeat testing does not delay specialist evaluation in patients with jaundice, hepatic decompensation, markedly elevated LSM, or other evidence of advanced liver disease. This suggested interval is based largely on clinical practice rather than robust prospective evidence and should therefore be individualized according to the severity of liver disease, biochemical evolution, and local care pathways. The MetALD care pathway should also incorporate assessment of alcohol amount and drinking pattern to reduce subtype misclassification and inappropriate management. In primary care, structured alcohol assessment using self-reported intake and Alcohol Use Disorders Identification Test–Consumption (AUDIT-C) may be used, whereas hepatology clinics may additionally incorporate PEth when exposure remains uncertain or when longitudinal monitoring is required. ELF or ADAPT may be considered as alternative or adjunctive triage tools, particularly when FIB-4 results are intermediate, VCTE access is limited, or reducing unnecessary specialty referral is a priority. Overall, no single standardized MetALD algorithm has been established, and NIT interpretation should be contextualized by careful alcohol exposure assessment.[36,61]

ALD care pathway

The ALD care pathway overlaps with those for MASLD and MetALD, but differs by requiring integrated assessment of alcohol exposure and AUD, careful interpretation of NITs in the context of alcohol-related steatohepatitis, and longitudinal tracking of abstinence. For first-line testing, Rhodes et al.[62] analyzed referrals for ALD and reported that FIB-4 use roughly halved unnecessary referrals, but with a high false-negative rate of 22%, indicating its limitations as a stand-alone test. For second-line testing, VCTE is recommended; however, when access is limited, sequential ELF testing after FIB-4 may improve accurate classification from 60% with FIB-4 alone to 85%.[63] An additional key element in ALD is repeated LSM assessment. Because LSM can be transiently elevated by active alcohol-related steatohepatitis, transient elastography should be repeated after at least 1 week of abstinence or reduced drinking when AST or GGT levels are more than twice the upper limit of normal or when bilirubin is elevated in active drinkers. For longitudinal monitoring, annual LSM reassessment using Baveno VII-based categories combined with alcohol biomarkers such as PEth may help track abstinence trajectory and fibrosis risk. The AGA clinical care pathway was first published under the NAFLD nomenclature in 2021 and subsequently updated in 2026 to adopt the MASLD terminology and incorporate contemporary fibrosis risk stratification and treatment strategies.[25,64] The updated pathway recommends a sequential non-invasive testing strategy, with FIB-4 as the first-line assessment followed by VCTE or the ELF test in patients with intermediate or elevated risk of advanced fibrosis. For patients with ALD, the American College of Gastroenterology guideline recommends that non-invasive fibrosis assessment be integrated with systematic evaluation and treatment of alcohol use and AUD.[65] Pharmacological treatment of SLD more broadly, including agents under development for MASH, has been reviewed in detail elsewhere; in alcohol-predominant disease, alcohol reduction and treatment of AUD remain the therapeutic foundation.[66] The EASL non-invasive test guideline specifies that in patients at risk of ALD, FIB-4 ≥1.3 should be confirmed by transient elastography, and LSM ≥8 kPa should be evaluated stepwise with a patented serum test such as ELF or specialist evaluation, with LSM ≥12–15 kPa defined as a strong indicator of advanced fibrosis in ALD.[60] In summary, the ALD care pathway proceeds in the following steps: (1) AUDIT-C– and PEth-based quantification of alcohol use; (2) first-line FIB-4 rule-out; (3) second-line LSM/VCTE or ELF evaluation; and (4) Baveno VII–based serial LSM trajectory monitoring. Importantly, ELF should not be viewed as a universal test for all patients with MetALD or ALD, but may be considered selectively as an adjunctive triage tool, particularly before VCTE in patients with intermediate FIB-4 or when referral burden is a concern.[30,67,68]

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UNMET NEEDS AND CONCLUSION

Two elements of an alcohol-aware approach are actionable with currently available tools. First, where reported alcohol intake is uncertain, inconsistent with clinical or biochemical findings, or close to a subtype boundary, exposure should be measured rather than assumed; PEth is the most practical available tool, interpreted as an expert-proposed reference range alongside drinking pattern, hematologic status, and genetic background rather than as a fixed threshold.[40] Second, NITs should be read in the light of that exposure, distinguishing biopsy-referenced diagnostic cut-offs from outcome-anchored prognostic thresholds and allowing for the transient elevation of liver stiffness during active drinking.

Three questions remain open. The concentration bands currently used to interpret PEth have not been anchored prospectively to liver-related outcomes, and were derived predominantly in Western cohorts; subtype-specific pathway data are almost entirely lacking from Asian populations, in which ALDH2 rs671 alters the relationship between reported intake, measured biomarker concentration, and tissue injury;[49,50] and it is not yet known whether integrating objective exposure measurement with sequential non-invasive testing improves subtype assignment, referral efficiency, and prediction of clinical outcomes in prospective evaluation. Proteomic and metabolomic profiling that separates alcohol-predominant from cardiometabolic-predominant disease is promising in this regard but remains investigational.[53,56] Any resulting algorithm should preserve high-sensitivity rule-out in primary care while allowing more specific, context-aware assessment in referral settings.

In conclusion, alcohol exposure is not one variable among many in SLD. It is the variable that assigns subtype, and prognosis, test interpretation, referral, and treatment all inherit the error in that assignment. Treating alcohol exposure as a dynamic and measurable component of phenotyping, rather than as a single self-reported threshold, is therefore the most consequential step toward accurate risk stratification and longitudinal management across MASLD, MetALD, and ALD.

Authors' Contributions

Study concept and design: Dae Won Jun. Acquisition of data: Eileen Laurel Yoon. Drafting of the manuscript: Hyo Young Lee. Final approval: All authors.

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Conflicts of Interest

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