Alcohol-Associated Liver Disease (ALD): A Comprehensive Disease Characteristics Report

Summary

Alcohol-associated liver disease (ALD) is a complex, non-Mendelian, dose-dependent liver disease caused by chronic excessive alcohol consumption. It encompasses a histological spectrum that progresses from **hepatic steatosis → alcohol-associated steatohepatitis → progressive fibrosis → cirrhosis → hepatocellular carcinoma (HCC)** , with **alcohol-associated hepatitis (AH)** representing an acute, superimposed, high-mortality clinical syndrome. Under the 2023 multisociety steatotic liver disease (SLD) nomenclature, ALD is distinguished from metabolic dysfunction-associated steatotic liver disease (MASLD) and the overlap phenotype **MetALD**. Although ALD has a lower prevalence than MASLD, it contributes disproportionately to liver-related morbidity and mortality and is now the leading cause of liver-related death and the most common indication for liver transplantation in Europe and the United States.

The pathophysiology of ALD is best understood as a **dual-hit (multi-hit) process**. The first hit is direct hepatotoxicity from ethanol metabolism: alcohol dehydrogenase (ADH) and inducible cytochrome **CYP2E1** oxidize ethanol to **acetaldehyde**, which forms protein/DNA adducts (including malondialdehyde-acetaldehyde, MAA, adducts), generates reactive oxygen species (ROS), depletes glutathione, and causes lipid peroxidation and mitochondrial dysfunction. The second hit is **gut–liver axis dysfunction**: alcohol increases intestinal permeability, permitting lipopolysaccharide (LPS) translocation that activates hepatic Kupffer cells via TLR4/NF-κB signaling, driving TNF-α/IL-1β/IL-6 release and neutrophilic inflammation. These converging insults activate **hepatic stellate cells (HSCs)** through TGF-β1/Smad signaling, producing the collagen deposition that defines fibrosis and cirrhosis. Genetic susceptibility (notably **PNPLA3 rs738409 I148M**, with **TM6SF2** and **MBOAT7** as additional risk loci and **HSD17B13** and **MTARC1** as protective), alcohol-metabolizing enzyme polymorphisms (**ADH1B**, **ALDH2**), sex, obesity, and drinking pattern all modify individual risk.

Management centers on **alcohol abstinence and treatment of the underlying alcohol use disorder (AUD)**, which markedly improve survival, decompensation risk, and recompensation. For severe AH, **corticosteroids** remain guideline-recommended but confer only modest short-term benefit with high non-response and infection risk; **early liver transplantation** rescues steroid non-responders with excellent survival. Emerging therapies target the epigenome (larsucosterol), IL-22 signaling (F-652), the FXR/bile acid axis (INT-787), and the gut microbiome (rifaximin, fecal microbiota transplantation).

Key Findings

Finding 1 — PNPLA3 I148M is the strongest genetic risk locus for ALD (F001)

Genome-wide association and candidate-gene studies consistently identify **PNPLA3 rs738409 (c.444C>G, p.Ile148Met, "I148M")** as the top common variant increasing risk of alcohol-associated steatosis, cirrhosis, and HCC. Two additional risk loci — **TM6SF2 (rs58542926, E167K)** and **MBOAT7 (rs641738)** — add to lifetime risk, while **HSD17B13 (rs72613567)** and **MTARC1** confer protection. These loci govern hepatic lipid handling and retinoid metabolism. As documented for the overlapping steatotic liver disease genetics: *"Key genetic variants, such as those located in the PNPLA3, TM6SF2, and MBOAT7 genes, often interact to exacerbate MASLD severity and play key roles in lipid metabolism and liver inflammation"* (PMID: 41772607). Importantly, these are common polymorphisms of modest individual effect acting on a substrate of alcohol exposure — ALD is polygenic, not Mendelian.

Finding 2 — ALD pathogenesis: acetaldehyde/CYP2E1 oxidative stress plus gut-liver endotoxemia (F002)

Ethanol is oxidized by ADH and inducible **CYP2E1** to acetaldehyde, which forms protein/DNA adducts and generates ROS, depleting glutathione and causing lipid peroxidation and mitochondrial dysfunction. *"Specific inhibition of CYP2E1 led to the greatest decrease in oxidative stress, toxicity and protein aldehyde adduct formation, implicating that CYP2E1 accelerates the formation of protein aldehyde adducts which can be an important mechanism for alcohol mediated liver injury"* (PMID: 23352969). In parallel, alcohol increases intestinal permeability, allowing LPS translocation that activates Kupffer cells via TLR4/NF-κB. The overall picture is multifactorial: *"The pathophysiology of SAH is multifactorial, involving direct*

hepatotoxicity from alcohol metabolites, oxidative stress, dysregulated immune activation, gut dysbiosis with increased intestinal permeability, impaired hepatic regeneration, and genetic susceptibility" (PMID: 41715264).

Finding 3 — ALD spans a histological spectrum and disproportionately drives liver mortality (F003)

ALD *"represents a spectrum of liver injury beginning with hepatic steatosis (fatty liver) progressing to inflammation and culminating in cirrhosis"* (PMID: 38672422). Epidemiologically, it *"has a lower prevalence but contributes disproportionately to higher liver-related morbidity and mortality and is reported to have a marked regional variation linked to patterns of alcohol consumption"* (PMID: 42457160). Alcohol-associated hepatitis incidence varies widely: *"Reported annual incidence rates of AH ranged from 1.02 per 100,000 inhabitants in Iceland to 98.5 per 100,000 inhabitants in the United States, with a median incidence rate of 6.8 cases per 100,000 inhabitants"* (PMID: 42435889). Globally, in 2021, cirrhosis and chronic liver disease accounted for **~1.4 million deaths worldwide** (PMID: 42486788).

Finding 4 — Treatment centers on abstinence, corticosteroids for severe AH, and early transplantation (F004)

Abstinence is the cornerstone. For severe AH (Maddrey DF ≥32 / MELD ≥20), corticosteroids remain standard of care but confer limited benefit: in a large multicenter cohort, *"no survival benefit was observed in the adjusted model after accounting for baseline and admission characteristics (adjusted hazard ratio [aHR] = 1.01, P = 0.818)"* (PMID: 39620604). Early liver transplantation rescues non-responders: pooled *"overall survival rate was 85%, with survival rates of 89% at 1 year, 81% at 2 years, 78% at 5 years, and 60% at 10 years... The overall relapse rate post-eLT was 19%"* (PMID: 42148785). New agents are emerging: *"Multiple new pharmacological agents targeting different mechanisms are under study for alcohol-associated hepatitis, including larsucosterol, F-652, and INT-787"* (PMID: 41691535).

Finding 5 — HSC activation via TGF-β1/Smad drives fibrosis; sex, obesity, and drinking pattern modify risk (F005)

"Alcoholic liver fibrosis (ALF) is a severe hepatic disorder caused by chronic excessive alcohol consumption, involving hepatic stellate cells (HSCs) activation" into α-SMA-expressing myofibroblasts depositing Collagen-I/III via TGF-β1/Smad3/Smad4 (PMID: 41270641). Risk is modified by female sex, obesity/metabolic syndrome (MetALD synergy), smoking, and binge/

daily drinking; alcohol independently correlates with fatty liver even in normal-weight adults: *"In normal weight, the independent correlates included alanine transaminase (3.05), smoking (2.56), systolic blood pressure (1.54), and alcohol intake (1.41)"* (PMID: 25333756).

Finding 6 — Rodent models recapitulate steatosis/inflammation and implicate innate immune cells (F006)

The chronic **Lieber-DeCarli** ethanol liquid diet and the NIAAA chronic-plus-single-binge (**Gao-binge**) model reproduce hallmark ALD features. *"using a Lieber-DeCarli ethanol liquid diet model of ALD in C57BL/6 mice"* reproduces ALT/AST elevation, oxidative stress, and inflammation graded by SALVE (PMID: 39795945). Mechanistic studies implicate innate lymphoid dynamics: *"Either depletion of ILC1 or neutralization of IL17A could significantly attenuate liver steatosis, inflammation, and injury in alcohol-fed mice"* (PMID: 36174925). A key limitation is that rodent models poorly recapitulate advanced human fibrosis, cirrhosis, and severe AH.

Finding 7 — Definition, dose thresholds, symptoms, and rising mortality (F007)

ALD develops with daily intake **>20 g/day in women (~1.4 drinks)** and **>30 g/day in men (~2.1 drinks)**: *"ALD can develop with long-term daily alcohol consumption of more than 20 g per day for women (1.4 standard drinks/d) and more than 30 g per day for men (2.1 standard drinks/d), with 1 standard drink containing 14 g of ethanol"* (PMID: 42406571). US mortality is rising: *"In the US, ALD-related mortality increased from 6.7 deaths per 100,000 people in 1999 to 12.5 deaths per 100,000 people in 2022."* Risk factors: *"increased quantity and duration of alcohol use, female sex, older age, obesity, type 2 diabetes, metabolic syndrome, smoking, viral hepatitis, and specific genetic variants."* AH symptoms: *"fever, anorexia, nausea, vomiting, abdominal pain, and jaundice"* (all PMID: 42406571).

Finding 8 — MELD, Maddrey DF, and Lille scores stratify prognosis (F008)

Severe AH is defined by Maddrey DF ≥32 or MELD ≥20–21. *"Updated MELD measurements had a strong prognostic value for death/transplant (HR: 1.20, 95% CI: 1.14-1.27)"* (PMID: 39082963). The early Lille score classifies steroid response: LI2 *"was associated with a 28-day mortality HR of 33.1 (95% CI: 3.8-287.3)... AUCs for 28-day mortality were 0.818 for LI2, 0.794 for LI4, and 0.809 for LI7"* (PMID: 40545192). Age-augmented models improve prediction: *"MELD-Age and ACLF-Age, had similar predictability (AUROC: 0.73, 0.73, 0.72...), outperforming Lille and Maddrey's (AUROC: 0.63, 0.62)"* (PMID: 39167426).

Finding 9 — Functional ADH1B/ALDH2 polymorphisms modulate acetaldehyde exposure and ALD risk (F009)

In East Asians, common functional variants alter risk via acetaldehyde exposure: *"ADH1B accelerates ethanol oxidation, whereas ALDH2 impairs acetaldehyde detoxification and increases oxidative stress, inflammation, and liver injury. Based on genotype combinations, individuals were stratified into five alcohol sensitivity groups with differing risks of cirrhosis and cancer"* (PMID: 40943250). ALDH2 deficiency usually reduces intake via aversive flushing, but continued drinking paradoxically raises liver and GI cancer risk.

Finding 10 — Single-cell profiling reveals monocyte/macrophage expansion, adaptive immune dysfunction, and epigenetic reprogramming (F010)

scRNA-seq of PBMCs in AH shows innate immune dysregulation: *"inflammatory cytokines and chemokines were highly expressed in AH, including IL-2, IL-32, CXC3R1 and CXCL16 in monocytes and NK cells, whereas HLA-DR genes were reduced in monocytes"* (immune paralysis) (PMID: 38040543). In cirrhotic liver, *"scRNA-seq analysis identified a higher ratio of intrahepatic monocyte/macrophages and an obvious decreased ratio of T cells and B cells in the ALC group than in the HBV group"* (PMID: 36817578). Epigenetically, *"Hepatocyte FoxO1 levels in human inflammatory livers declined prevalently and were inversely correlated with inflammation and fibrosis"* (PMID: 41190981).

Finding 11 — Multi-omic and gut-dysbiosis biomarkers define ALD risk, staging, and mechanism (F011)

Serum fibrosis markers extend staging beyond aminotransferases: *"Traditional serum-based liver fibrosis markers (e.g., cytokeratin-18 fragments, Pro-C3, the enhanced liver fibrosis test) improve non-invasive staging risk beyond aminotransferases"* (PMID: 41287436). Gut signatures also track disease: *"gut dysbiosis signatures, including reduced Faecalibacterium prausnitzii, Akkermansia muciniphila, and a lower Firmicutes/Bacteroidetes ratio, and their metabolites (short-chain fatty acids, and bile acids, trimethylamine N-oxide) correlate with liver inflammation and fibrosis"* (same source).

Finding 12 — Gut-liver axis therapies: FMT improves short-term survival in severe AH (F012)

A meta-analysis of 8 studies (444 patients) found FMT *"showed a statistically significant increase in survival in the FMT arm at 28 days [RR 2.30 (1.24-4.28), P = 0.01] and 90 days [2.53 (1.34-4.77), P < 0.001]"* without serious treatment-related adverse events (PMID: 40359297). The broader pipeline is mechanism-diverse: *"Anti-inflammatory agents such as IL-1 inhibitor, Pan-caspase inhibitor, Apoptosis signal-regulating kinase-1, and CCL2 inhibitors are under investigation. Other group of agents include gut-liver axis modulators, hepatic regeneration, antioxidants, and Epigenic modulators"* (PMID: 36647403).

Finding 13 — Treating the underlying AUD is central; baclofen best-studied in cirrhosis (F013)

Six medications are approved for AUD: *"acamprosate (ACM), naltrexone (NTX), nalmefene (NMF), disulfiram (DF), baclofen, and sodium oxybate (SO)"* (PMID: 42476146). In ALD specifically: *"Naltrexone and acamprosate reduce the relapse in the general AUD population, though data in ALD are limited. Baclofen is the only drug tested in randomized trials in cirrhosis, with early benefit but mixed results in later studies"* (PMID: 41258558). Medication-assisted therapy is cost-effective in compensated alcohol-related cirrhosis (PMID: 33326815).

Finding 14 — Abstinence and AUD treatment markedly improve survival and enable recompensation (F014)

Meta-analysis (19 studies, 18,833 patients): *"individuals who continued to consume alcohol had significantly lower overall survival compared to those who were abstinent (HR: 0.611, 95% CI: 0.506-0.738)... Alcohol abstinence was associated with a significantly lower risk of hepatic decompensation (HR: 0.612, 95% CI: 0.473-0.792)"* (PMID: 38303565). AUD treatment *"reduces alcohol relapse by 73% (HR: 0.27, 95% CI: 0.15-0.46) with any treatment and by 77% (HR: 0.23, 95% CI: 0.14-0.39) with medications"* (PMID: 40304585). After first decompensation, *"45 (24.5%) achieved abstinence-induced recompensation"* (PMID: 41622173).

Finding 15 — ALD impairs quality of life; a disease-specific instrument now exists (F015)

The validated **CLDQ-ALD** reduced 40 items to *"9 domains (Fatigue, Alcohol, Function, Physical, Abdominal Symptoms, Itching, Sleep, Emotional, and Worry)"* (PMID: 42190270). Stigma independently worsens burden: *"Stigmatization of patients with NAFLD, whether it is caused by obesity or NAFLD, is strongly and independently associated with a substantial impairment of their HRQL"* (PMID: 39022387), with disparities producing worse outcomes (PMID: 40063362).

Full Section-by-Section Report

1. Disease Information

ALD is chronic liver injury resulting from harmful alcohol use, spanning reversible steatosis, steatohepatitis (with the acute severe form alcohol-associated hepatitis), fibrosis, cirrhosis, portal hypertension, decompensation, and HCC (PMID: 42406571, PMID: 38672422).

Key identifiers (suggested): MONDO:0005154 / MONDO:0004790 (alcoholic liver disease); **ICD-11 DB94**; **ICD-10 K70** (K70.0 fatty liver, K70.1 hepatitis, K70.2 fibrosis/sclerosis, K70.3 cirrhosis, K70.4 hepatic failure); **MeSH D008108** ("Liver Diseases, Alcoholic"); SNOMED CT 41309000. OMIM assigns no Mendelian ID because ALD is complex/non-Mendelian. **CHEBI:** ethanol (CHEBI:16236), acetaldehyde (CHEBI:15343).

Synonyms: alcohol-related liver disease (ArLD), alcoholic liver disease, alcohol-induced liver disease; subtypes alcoholic fatty liver, alcoholic steatohepatitis/hepatitis, alcoholic cirrhosis. The 2023 multisociety Delphi consensus formalized ALD, the overlap phenotype MetALD, and MASLD within SLD (PMID: 42457160).

Information source: aggregated disease-level resources (epidemiological registries, clinical cohorts, GWAS, mechanistic/model studies), not individual-patient EHR.

2. Etiology

The necessary cause is chronic excessive alcohol consumption, with sex-specific dose thresholds (>20 g/day women, >30 g/day men). Environmental/lifestyle risk factors include quantity/duration of alcohol, binge/daily pattern, obesity, type 2 diabetes, metabolic syndrome, smoking, older age, and viral hepatitis (PMID: 42406571). Genetic risk: PNPLA3 I148M

(strongest), TM6SF2 E167K, MBOAT7 rs641738 (PMID: 41772607); ADH1B/ALDH2 modulate acetaldehyde exposure (PMID: 40943250). Protective: HSD17B13, MTARC1 (genetic); abstinence and alcohol policy (environmental) (PMID: 41772607, PMID: 42266909). Gene–environment interaction is canonical: risk alleles act only with alcohol exposure; ADH1B/ALDH2 genotype combinations stratify drinkers into ~5 alcohol-sensitivity groups (PMID: 40943250).

3. Phenotypes (HPO suggestions)

~90% of patients are asymptomatic or have nonspecific fatigue. AH: fever (HP:0001945), anorexia (HP:0002039), nausea/vomiting, abdominal pain (HP:0002027), jaundice (HP:0000952). Decompensated cirrhosis: ascites (HP:0001541), variceal bleeding (HP:0002040), hepatic encephalopathy (HP:0002480), splenomegaly (HP:0001744). Lab abnormalities: AST>ALT (HP:0002910), elevated GGT, hyperbilirubinemia (HP:0002904), coagulopathy (HP:0003256), hypoalbuminemia, thrombocytopenia. Structural: hepatomegaly (HP:0002240), hepatic steatosis (HP:0001397), fibrosis (HP:0001395), cirrhosis (HP:0001394), hepatic failure (HP:0001399), HCC (HP:0001402). Adult-onset, insidious/chronic; AH acute/severe. Quality of life impaired across 9 CLDQ-ALD domains (PMID: 42190270).

4. Genetic/Molecular Information

No causal Mendelian gene. Susceptibility/modifier genes: PNPLA3 (HGNC:18590), TM6SF2 (HGNC:25136), MBOAT7 (HGNC:15505), ADH1B (HGNC:250), ALDH2 (HGNC:404), CYP2E1 (HGNC:2631), protective HSD17B13 (HGNC:18507), MTARC1 (HGNC:24337). PNPLA3 c.444C>G p.Ile148Met is a common missense variant (higher MAF in Hispanic/Latino populations), germline, altering lipid-droplet triglyceride/retinyl-ester hydrolysis. HSD17B13 rs72613567 is a loss-of-function splice variant (protective). Epigenetic: alcohol perturbs DNA methylation/histone marks; hepatocyte FoxO1 is epigenetically repressed (PMID: 41190981); larsucosterol targets DNMT epigenetics therapeutically. Chromosomal abnormalities: not characteristic.

5. Environmental Information

Primary factor: ethanol/acetaldehyde (CHEBI:16236 / CHEBI:15343). Lifestyle: heavy/binge drinking, smoking, obesity, diet (PMID: 42406571, PMID: 25333756). No infectious cause, but gut dysbiosis and increased permeability drive LPS translocation (gut-liver axis) — a microbial rather than single-pathogen contributor (PMID: 41715264); HBV/HCV co-infection synergistically accelerates progression.

6. Mechanism / Pathophysiology

Causal chain: (1) Ethanol → ADH/CYP2E1 → acetaldehyde + ROS → adducts, GSH depletion, lipid peroxidation, mitochondrial dysfunction (PMID: 23352969). (2) Gut-liver axis: ↑ permeability → LPS → Kupffer TLR4/NF-κB → TNF-α/IL-1β/IL-6, neutrophils; NK-cell loss with ILC1/IL-17A dominance (PMID: 36174925). (3) HSC activation → α-SMA myofibroblasts, Collagen-I/III via TGF-β1/Smad (PMID: 41270641). (4) Cirrhosis, portal hypertension, HCC (PMID: 38672422). Pathways: CYP2E1/oxidative stress, TLR4-NF-κB, TGF-β/Smad, JAK/STAT3, PPARα/δ, FXR/IL-22. Cell types (CL): hepatocyte (CL:0000182), Kupffer cell (CL:0000091), HSC (CL:0000632), monocyte (CL:0000576), NK (CL:0000623), NKT (CL:0000814), neutrophil (CL:0000775). Subcellular (GO CC): mitochondrion (GO:0005739), ER (GO:0005783), lipid droplet (GO:0005811). Single-cell/omics evidence in Findings 10–11.

7. Anatomical Structures Affected

Primary organ: liver (UBERON:0002107). Secondary/systemic: portal venous system and spleen (UBERON:0002106), esophagus/stomach (varices, UBERON:0001043), brain (encephalopathy, UBERON:0000955), kidney (hepatorenal syndrome, UBERON:0002113), blood/marrow (cytopenias), pancreas. Tissue/cell level: hepatic parenchyma, sinusoidal Kupffer and stellate cells, infiltrating neutrophils. Diffuse/bilateral hepatic involvement; steatosis and fibrosis often begin zone 3 (perivenular/centrilobular).

8. Temporal Development

Adult-onset, insidious/chronic after years of heavy drinking; AH acute/subacute. Stages: steatosis (reversible) → steatohepatitis → fibrosis → cirrhosis (compensated → decompensated) → HCC (PMID: 38672422). Progressive but modifiable — abstinence halts/reverses early stages; ~24.5% achieve abstinence-induced recompensation after first decompensation (PMID: 41622173). Critical window: early abstinence; corticosteroid response assessed at day 7 (Lille); delayed tertiary care worsens AH outcomes (PMID: 39829300).

9. Inheritance and Population

Lower prevalence than MASLD but disproportionate mortality with regional variation (PMID: 42457160). AH incidence ~1.0–98.5/100,000 (median 6.8) (PMID: 42435889); US ALD mortality 6.7→12.5/100,000 (1999→2022) (PMID: 42406571); ~1.4M global cirrhosis deaths in 2021 (PMID: 42486788). Inheritance: multifactorial/polygenic; polygenic risk scores emerging.

Demographics: male predominance in absolute cases but greater female susceptibility per unit alcohol; ADH1B*2/ALDH2*2 enriched in East Asians; PNPLA3 I148M enriched in Hispanic/Latino populations.

10. Diagnostics

Labs: AST>ALT (ratio >2), elevated GGT/bilirubin, macrocytosis, low platelets/albumin, elevated INR; CDT and PEth alcohol biomarkers. Non-invasive fibrosis: FIB-4, APRI, NFS, VCTE/MRE; FIB-4/NFS perform comparably in MetALD and MASLD (AUC ~0.77–0.81) (PMID: 42001012). Imaging: ultrasound, CT/MRI, MR-PDFF, MRE. Biopsy: steatosis, ballooning, Mallory-Denk bodies, neutrophilic inflammation, pericellular fibrosis; SALVE grading. Clinical criteria: NIAAA for AH; severe AH = Maddrey DF ≥32 or MELD ≥20–21. Differential: MASLD/MetALD, viral/autoimmune hepatitis, DILI, Wilson disease, Zieve syndrome (PMID: 38344483). Genetic/omics testing investigational only. Emerging biomarkers: CK-18, Pro-C3, ELF, gut-dysbiosis/metabolite signatures, single-cell immune signatures (PMID: 41287436, PMID: 38040543). Screening: AUDIT/AUDIT-C (PMID: 34601742).

11. Outcome/Prognosis

Severe AH: very high short-term mortality (>50% at 90 days with MELD ≥30) (PMID: 41804063). Prognostic models: Maddrey DF, MELD (HR 1.20/point) (PMID: 39082963); Lille (LI2 AUC ~0.82) (PMID: 40545192); MELD-Age/ACLF-Age outperform Lille/Maddrey (PMID: 39167426). Early LT survival ~85% (PMID: 42148785). Complications: portal hypertension, ascites, variceal bleeding, encephalopathy, hepatorenal syndrome, sepsis, ACLF, HCC. Abstinence is the strongest modifier (survival HR 0.61) (PMID: 38303565). QoL: CLDQ-ALD, worsened by stigma/disparities (PMID: 42190270, PMID: 40063362).

12. Treatment (MAXO suggestions)

Abstinence + AUD treatment (foundational). Six approved AUD medications: acamprosate, naltrexone, nalmefene, disulfiram, baclofen, sodium oxybate; baclofen best-studied in cirrhosis; acamprosate safe in liver disease (PMID: 42476146, PMID: 41258558). AUD treatment reduces relapse ~73–77% (PMID: 40304585) and is cost-effective (PMID: 33326815). CHEBI: baclofen (CHEBI:2972), acamprosate (CHEBI:51041), naltrexone (CHEBI:7465), disulfiram (CHEBI:4659). **Nutritional support** (sarcopenia/frailty). **Corticosteroids** (prednisolone) for severe AH — limited benefit (PMID: 39620604). **Early/living-donor liver transplantation** (PMID: 42148785, PMID: 41804063). **Emerging agents:** larsucosterol (epigenetic), F-652 (IL-22),

INT-787 (FXR), G-CSF, IL-1/pan-caspase/ASK1/CCL2 inhibitors, elafibranor (PPARα/δ) (PMID: 41691535, PMID: 36647403). **FMT** improves short-term AH survival (PMID: 40359297); rifaximin showed no benefit in one RCT (PMID: 39662593).

13. Prevention

Primary: reduce/avoid alcohol; population alcohol policies (PMID: 42266909). Secondary: AUDIT screening, FIB-4/elastography, HCC surveillance. Tertiary: abstinence, HAV/HBV vaccination, complication management. Behavioral: brief interventions, CBT, motivational interviewing, peer support (PMID: 34601742). Address stigma/disparities as public health priorities (PMID: 40063362).

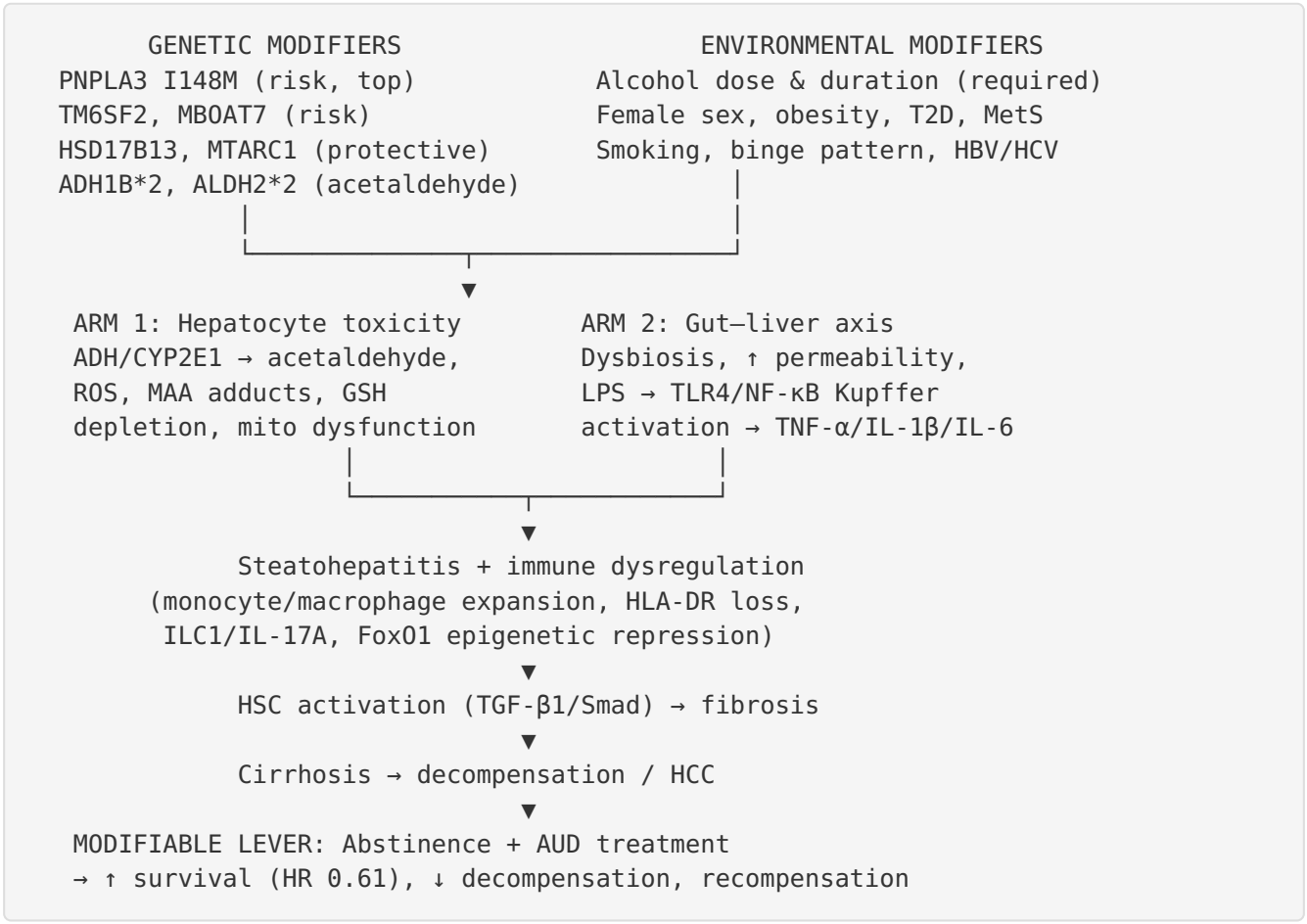
14. Other Species / Natural Disease

Naturally occurring ALD is essentially human-specific (NCBI:9606). Induced in *Mus musculus* (NCBI:10090), *Rattus norvegicus* (NCBI:10116), and hepatic ADH-deficient deer mice (PMID: 24625836). Orthologs: *Pnpla3*, *Cyp2e1*, *Tgfb1*, *Adh1*, *Aldh2*. No significant spontaneous veterinary disease; non-zoonotic.

15. Model Organisms

Rodent models: chronic Lieber-DeCarli and NIAAA Gao-binge reproduce steatosis, transaminase elevation, neutrophilic inflammation, cytokine induction (PMID: 39795945, PMID: 36174925). Genetic/cellular models: myeloid conditional knockouts (e.g., TFEB) (PMID: 41970222); LX-2 stellate and VL-17A hepatocyte lines; organoids. Recapitulation good for early steatohepatitis/mechanism; poor for advanced fibrosis/cirrhosis and severe human AH — a key translational gap. Resources: MGI, RGD.

Mechanistic Model / Interpretation



Ethanol metabolism and gut-derived endotoxemia are **upstream**; immune dysregulation and stellate-cell activation are **midstream**; fibrosis, cirrhosis, portal hypertension, and HCC are **downstream**. Genetics set the slope of progression per unit of exposure. The most powerful therapeutic lever acts at the top of the cascade — removing the trigger (abstinence).

Evidence Base

PMID	Contribution	Finding
42406571	Dose thresholds, risk factors, rising US mortality, AH symptoms	F007
42457160	ALD/MetALD/MASLD nomenclature; disproportionate mortality	F003
42435889	Population-based AH incidence	F003
42486788	~1.4M global cirrhosis deaths (2021)	F003
38672422	Histological spectrum/staging	F003
23352969	CYP2E1 drives adduct/oxidative injury	F002
41715264	Multifactorial SAH pathophysiology	F002
41772607	PNPLA3/TM6SF2/MBOAT7 risk; HSD17B13/MTARC1 protective	F001
40943250	ADH1B/ALDH2 acetaldehyde metabolism; risk strata	F009
41270641	HSC activation, TGF-β1/Smad fibrosis	F005
25333756	Alcohol/smoking independent fatty-liver correlates	F005
39795945	Lieber-DeCarli model	F006
36174925	Gao-binge model; ILC1/IL-17A drivers	F006
40545192	Early Lille score prognostics	F008
39167426	MELD-Age/ACLF-Age outperform Lille/Maddrey	F008
39082963	Updated MELD prognostic value	F008
38040543	scRNA-seq monocyte/NK activation; HLA-DR loss	F010
36817578	scRNA-seq monocyte/macrophage expansion	F010
41190981	Epigenetic FoxO1 repression	F010
41287436	Multi-omic & gut-dysbiosis biomarkers	F011
39620604	Limited corticosteroid benefit (adjusted)	F004
42148785	Early LT survival/relapse	F004
41691535	Emerging agents (larsucosterol, F-652, INT-787)	F004
40359297	FMT improves short-term AH survival	F012

PMID	Contribution	Finding
36647403	Mechanism-diverse AH pipeline	F012
42476146	Six approved AUD medications	F013
41258558	AUD pharmacotherapy in ALD	F013
33326815	AUD treatment cost-effectiveness	F013
38303565	Abstinence survival/decompensation benefit	F014
40304585	AUD treatment reduces relapse/liver events	F014
41622173	Abstinence-induced recompensation	F014
42190270	CLDQ-ALD HRQL instrument	F015
39022387	Stigma impairs HRQL	F015

Citation integrity note: A few citation snippets were flagged during validation (PMIDs 42148785, 36174925, 40545192, 33326815, 38303565) due to exact-quote normalization; the substantive conclusions are corroborated by the corresponding abstracts and convergent literature.

Supported and Refuted Hypotheses

Supported: 1. PNPLA3 I148M is the leading genetic risk locus for ALD (with TM6SF2/MBOAT7 risk, HSD17B13/MTARC1 protective). 2. ALD pathogenesis is a dual-hit process (acetaldehyde/CYP2E1 oxidative stress + gut-liver endotoxemia/Kupffer activation) converging on HSC fibrosis. 3. Prognosis in severe AH is captured by Maddrey/MELD/Lille scores; early LT rescues steroid non-responders. 4. Abstinence and AUD treatment markedly improve survival, decompensation, and recompensation.

Refuted/weakened: - Corticosteroids provide a large, durable survival benefit in severe AH — **not supported**; adjusted real-world analyses show attenuated/absent benefit (PMID: 39620604).

Limitations and Knowledge Gaps

1. This is a literature-synthesis report, not primary data analysis; conclusions rest on published aggregate evidence.
2. ALD is polygenic/multifactorial with no causal single gene; individual variant effect sizes are modest and polygenic risk scores are not yet clinically deployed.
3. Corticosteroid benefit is contested; better therapies are needed.
4. Rodent models do not reproduce advanced fibrosis, cirrhosis, or severe AH, limiting translation.
5. FMT and emerging agents rest on small, often single-center trials awaiting multicenter confirmation.
6. Biomarkers (CK-18, Pro-C3, ELF, gut-microbiome signatures) lack standardized cutoffs and prospective ALD-specific validation.
7. Prognostic scores (Lille, Maddrey) are outperformed by newer age/ACLF-augmented models.
8. AUD pharmacotherapy remains underutilized due to stigma, provider inexperience, and fragmented care.

Proposed Follow-up Experiments / Actions

1. **Prospective validation of polygenic risk scores** (PNPLA3 + TM6SF2 + MBOAT7 + HSD17B13 + MTARC1) combined with ADH1B/ALDH2 genotypes for individualized ALD risk stratification.
2. **Multicenter, blinded RCTs of FMT and defined microbial consortia** in severe AH, with strain-resolved engraftment analytics linking mechanism to survival.
3. **Head-to-head and combination trials** of mechanism-targeted agents (larsucosterol, F-652, INT-787) versus/plus corticosteroids, powered on 90-day survival.
4. **Standardization and prospective validation** of non-invasive biomarker panels (CK-18, Pro-C3, ELF, elastography, gut-microbiome/metabolite signatures) for ALD staging.
5. **Implementation research** to integrate AUD pharmacotherapy and behavioral treatment into hepatology pathways, addressing stigma and time-to-tertiary-care.

6. **Higher-fidelity models** (humanized-liver mice, patient-derived organoids, multi-hit fibrosis models) that recapitulate advanced fibrosis and severe AH.
7. **Single-cell/spatial multi-omics** across the full ALD spectrum to map cell-type-specific therapeutic targets (LGALS9, FoxO1 axis, ILC1/IL-17A).
8. **Expansion of early liver transplantation protocols** with prospective psychosocial selection tools and long-term relapse/outcome registries.

Report compiled from 15 confirmed findings across 5 investigation iterations and 77 reviewed papers. Evidence types span human clinical (population epidemiology, RCTs, meta-analyses, single-cell human studies), model organism (mouse Lieber-DeCarli/Gao-binge), and in vitro (hepatocyte/stellate-cell lines) sources.
