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Research Methodologies to Address Clinical Unmet Needs and Challenges in Alcohol-Associated Liver Disease

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Abbreviations (in order of appearance in the manuscript): ALD: Alcohol-associated liver disease; AH: Alcoholic hepatitis; AUD: Alcohol use disorder; LT: Liver transplantation; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; NIAAA: National Institute of Alcoholism and Alcohol Abuse; DF: Discriminant function; MELD: Model for end-stage liver disease; K-18: Keratin 18; SALT: Sustained alcohol use after liver transplant

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ABSTRACT

Alcohol-associated liver disease (ALD) is emerging worldwide as the leading cause of liver-related morbidity, mortality, and indication for liver transplantation. The ALD Special Interest Group and the Clinical Research Committee at the digital AASLD meeting in November 2020 held the scientific sessions to identify clinical unmet needs in ALD, and addressing these needs using clinical research methodologies. Of several research methodologies, the sessions were focused to a) study disease burden of ALD using large administrative databases, b) develop biomarkers for non-invasive diagnosis of alcoholic hepatitis (AH) and estimation of disease prognosis, c) identify novel therapeutic targets for ALD and AH, d) derive accurate models to predict prognosis or post-transplant alcohol relapse as a basis for developing treatment algorithm and a uniform protocol on patient selection criteria for liver transplantation, and e) examine qualitative research methodologies in studying the barriers to implementation of multidisciplinary integrated care model by hepatology and addiction teams for the management of dual pathology of liver disease and of alcohol use disorder. Prospective multicenter studies are required to address many of these clinical unmet needs. Further, multidisciplinary care models are needed to improve long-term outcomes in patients with ALD.

Alcohol-associated liver disease (ALD) is one of the most common liver disease worldwide, with 2.2 million people in the US affected by alcohol-associated cirrhosis in 2017.(1) Although, the research efforts and funding for ALD have increased substantially over the last decade, there still remain several unmet clinical needs.(2) Recently, the ALD Special Interest Group and the Clinical Research Committee of the American Association for Study of Liver Diseases (AASLD) held individual sessions at the digital AASLD meeting in November 2020 to discuss clinical research methodologies to address clinical unmet needs. Although, there is a need for animal models mimicking the human phenotype of ALD,(3) this manuscript focuses on clinical research methodologies, that can help in addressing unmet needs in patients with ALD.

EPIDEMIOLOGY AND HEALTHCARE BURDEN OF EARLY ALD

ALD is the leading cause of liver-related morbidity and mortality.(1, 4) Worldwide, approximately 2.5 billion people consume alcohol, with 300 million having alcohol use disorder (AUD). Approximately, 25 million people worldwide have compensated cirrhosis due to alcohol, with 10% having decompensated cirrhosis, including hepatocellular carcinoma, resulting in 750,000 deaths, which accounts for 1% of all annual deaths (5). Furthermore, increasing mortality due to ALD is occurring in women and younger people,(6) especially among individuals 25-34 years of age, with annual increase of 10.5% over the past decade (7). Proportion of liver transplants (LT) performed for ALD including those with alcoholic hepatitis (AH) is also increasing, and ALD is now the leading indication for LT worldwide (8).

Compared to other liver diseases, ALD often presents at an advanced stage of cirrhosis or its complications. In a study of 3,000 patients worldwide with chronic liver disease, only 3.8% of patients with ALD were seen at an early stage (without complications from portal hypertension) compared to 17%-30% for those with non-alcoholic fatty liver disease or viral hepatitis (9). Further, patients at an early unrecognized subclinical stage of ALD are commonly seen in drug or alcohol addiction clinics, and often not referred to specialists (9). Thus, strategies for population-level awareness and detection of early-stage ALD are needed (5). It will be

necessary to improve screening for AUD and early ALD using validated accurate tools such as Alcohol Use Disorder Identification Test on self-reported alcohol use.

Several tools are available to assess the burden of ALD such as observational cohorts derived from single-center and multi-center registries, clinical trials, and large administrative databases. Large databases are advantageous due to their sample size, and less concerns about statistical power (Table 1). Because the administrative databases collect important clinical data including demographics, diagnoses, procedures, service utilization, and billing on a large scale, they can be leveraged to study epidemiologic trends, disparities, costs, and outcomes on a population level (10, 11). Analysis of data from the *US Census Bureau* compiled by the *Center for Disease Control* and *Prevention's Wide-ranging Online Data for Epidemiologic Research* revealed an increase in cirrhosis-related mortality driven by ALD. *National Health and Nutrition Examination Survey (NHANES)*, *Nationwide Inpatient Sample (NIS)*, and *United Network for Organ Sharing* (UNOS) registries have been used to show an increasing severity of ALD in the US.(7, 12) .

It is challenging to study ALD due to inconsistency in documenting alcohol use patterns, including type and amount consumed. Socioeconomic factors, education, co-morbid psychiatric illness, and co-existing non-alcoholic fatty liver may not be available in large administrative databases. Merging with other databases may provide more detailed information on alcohol use such as the '*National Epidemiologic Survey on Alcohol and Related Conditions*'. Stages of fibrosis in ALD may be particularly difficult to capture in databases, compared to clinical trials or single or multicenter prospective studies. Nonetheless, several studies have leveraged large databases to study fibrosis stage as estimated by FIB-4 using AST, ALT , platelet count, and age in the *NHANES* and describe population level trends on advanced fibrosis among individuals with ALD.(13) Association of AUD treatments with reduced risk of hepatic decompensation and patient mortality has been demonstrated in studies using the *Veterans Health Administration* and commercial claims database of privately insured individuals respectively.(14, 15)

Data in large administrative databases are retrospective, prone to missing data and inaccurate on some important variables of interest. For example, only 35% of patients with AH included in the *ACCELERATE* consortium were coded as "AH" in the *UNOS* registry."(16). Data from large database studies must also be interpreted in the context

of clinical relevance. Use of validated diagnostic coding algorithms reduces misclassification bias in these claims-based databases.(17)

These limitations can be partly addressed with adequate domain knowledge and using well characterized cohorts. Statistical knowledge and collaborative relationship with a biostatistician are needed to ensure appropriate selection of analytic procedures, handling the missing data, correction for multiple testing, and interpretation of results. Propensity score or instrumental variable analysis may help to overcome confounding and selection bias. Machine learning methods such as shrinkage, random forest, and neural networks can handle many variables and account for complex and non-linear interactions.

NON-INVASIVE BIOMARKERS FOR THE MANAGEMENT OF ALD

Although, large databases are powerful tools to study epidemiology, there remains a need for accurate biomarkers for disease diagnosis, stratification, and prognosis. Over 50% of patients with AUD have elevations in serum AST and ALT (18). AUD patients with mild liver enzyme elevation compared to those with normal liver enzymes have greater evidence of gut barrier dysfunction, inflammation, and nutritional changes potentially leading to progression of ALD (18). Thus, screening for ALD using aminotransferases combined with novel non-invasive biomarkers for different stages of ALD should be implemented.

The progression to symptomatic AH with jaundice and acute on chronic liver failure negatively impacts short-term patient survival (19). Liver biopsy is the gold standard to diagnose AH, but is not routinely performed in clinical practice (20, 21). In 2016, the NIAAA funded consortia developed standard definitions for AH (22). Patients are considered to have severe AH if they had a Maddrey Discriminant Function (DF) score ≥ 32 or a Model for End stage Liver Disease (MELD) score >20. Although, MELD and DF can predict short-term mortality (23), they cannot differentiate AH from decompensated cirrhosis. Moreover, serum AST and ALT levels do not predict severity of liver injury in AH. In a recent study, patients with AUD enrolled in a treatment program with normal serum bilirubin had AST/ALT levels higher than hospitalized patients with severe AH (24). Clearly, improved biomarkers for AH and ALD are needed.

Keratin 18 (K18) is released into the bloodstream with epithelial cell death (24-26). During hepatocyte apoptosis, activated caspases cleave K18, and the cleaved K18 (M30) fragment can be detected in plasma by the M30 ELISA, whereas the M65 ELISA detects both caspase cleaved and uncleaved K18. Thus, K18 ELISAs can quantify hepatocyte death and differentiate necrosis versus apoptosis (24-26). In patients undergoing liver biopsy for suspected AH (25), K18 (M65) was found to be the most useful biomarker evaluated, with levels > 2000 IU/L being highly diagnostic for severe AH. Using the same cut-off, another study demonstrated that K18 reflected severity of liver disease and identified patients who died within 90 days with greater accuracy than MELD and DF. (24) All healthy controls had values below the upper limit of normal (500 IU/L) (Figure 1). Some patients with AUD and some patients with moderate AH had levels >2000 IU/L, suggesting greater liver injury than indicated by liver tests. Finally, a third of patients classified as "severe AH" had levels <2000 IU/L, suggesting they may have limited ongoing liver injury and inflammation, and may not be optimal candidates for prednisolone. Atkinson et al also reported that K18 is a diagnostic, prognostic, and potentially a theragnostic marker to predict who will benefit from prednisolone therapy (26).

Bile acids play an important role in the development of ALD (27). In a recent study, several urinary bile acids levels were shown to be elevated in AH patients compared to healthy controls, with AUROC curve of >0.7 for most bile acids and 0.94 for taurochenodeoxycholate. Further, serum bile acids showed a progressive increase from asymptomatic liver disease to increasing Child-Turcotte-Pugh stage of cirrhosis.(28) Biomarkers are also needed to optimize selection of therapeutics based on individual metabolism, and to identify patients at risk for development of infections or acute kidney injury, common causes of patient mortality in patients with ALD and/or AH. (29)

Alcohol abstinence is the most important factor to improve long-term survival (30). Biomarkers of alcohol consumption are also needed. Breath and blood levels of alcohol or its metabolites such as ethyl glucuronide or ethyl sulphate are accurate for recent alcohol ingestion in the last few days (31). Phosphatidylethanol, another metabolite of alcohol can identify alcohol use over the last few weeks (32). Prospective multicenter collaborative studies are needed to test and validate biomarkers and examine cost-effectiveness to maximize their usability in the paradigm of clinical care of ALD patients.

EMERGING THERAPEUTIC TARGETS FOR MANAGEMENT OF PATIENTS WITH ALD

Currently, corticosteroid is the only available pharmacological treatment for severe AH, with a modest benefit at 28 days, and no long-term benefit on patient survival (33). Better understanding of the disease mechanisms has translated into identifying newer therapeutic targets for the treatment of ALD (34).

Interactions between gut and liver is the major mechanism mediating development of ALD (**Figure 2**). The metabolism of alcohol in the liver results in oxidative stress due to changes in mitochondrial electron transport (35), resulting in hepatocyte apoptosis and production of extracellular vesicles (36). MicroRNAs contained in these vesicles mediate steatosis, fibrosis, and neutrophil dysfunction (37). The dying hepatocytes release damage-associated molecular patterns (DAMPs) such as uric acid, ATP, and HMGB1 (38).

Chronic excessive alcohol use compromises the gut epithelial barrier function, resulting enhanced entrance of pathogen-associated molecular patterns (PAMPs) like lipopolysaccharide and bacterial DNA into the portal circulation (39). Alcohol also modifies the gut microbiome, with reduction in *Akkermansia*, *Lactobacilli* and *Furmicutes*, and increased proportion of *Bacteriodes* (40). The fungal microbiome is also impacted, and is associated with severity of ALD (41). Initial pilot studies with fecal microbiota transplant showed improvement in liver disease, and a positive impact on AUD with reduced cravings and maintenance of abstinence (42, 43). Obeticholic acid targeting the nuclear Farsenoid X receptor (FXR) provides beneficial effects on gut integrity and hepatic stellate cell activity.

DAMPs are recognized by toll-like receptors and other pattern recognition receptors on several hepatic cells such as macrophages, hepatocytes and stellate cells, resulting in NF-kB-mediated pro-inflammatory cytokine and chemokine production. Activation of intracellular inflammasome complex consisting of caspase-1 and IL-1ß amplifies inflammation, promotes fibrosis, and impairs liver regeneration (44). In a preclinical model of ALD, IL-1 receptor antagonist, anakinra attenuated steatosis, inflammation and fibrosis (45). Anakinra in conjunction with zinc and pentoxifylline in a phase-2 clinical trial tended to improve six months survival in severe AH patients as compared to those treated with prednisolone. Currently, this drug is being tested in a larger clinical trial.

Liver regeneration is impaired in ALD due to reduced levels of hepatocyte nuclear factor-4 and miR-122, and abnormalities in hedgehog signaling (46, 47). IL-22, a pleotropic cytokine

produced during acute phase response is anti-apoptotic, hepatoprotective, and promotes cell proliferation and regeneration (48). F-652, an IL-22 fusion protein in a dose ranging study in patients with moderate AH (MELD 11 – 20) provided a superior response (measured by Lille score) compared to propensity-matched historical controls, paving the way for testing this molecule in larger studies (49). Granulocyte-colony stimulating factor mobilizes myeloid precursors from the bone marrow, with improved immune function and hepatic regeneration (50). Clinical trials using this agent have shown mixed results with encouraging data from Asia, but not from Europe (51). Studies are ongoing in the US to substantiate the role of this molecule in the treatment of ALD.

DUR-928, is an epigenetic regulator, with a net effect in reducing the inflammation and improved regeneration (52). In a pilot clinical trial, this drug improved response rate (as measured by Lille score) in AH patients as compared to historical steroid treated controls (53). Larger trials of this agent are ongoing.

ESTIMATING PROGNOSIS OF AND SELECTION CRITERIA FOR LIVER TRANSPLANTATION IN PATIENTS WITH ALD

Several models are available to predict patient survival and response to corticosteroids (**Table 2**). For example, MELD at baseline and the Lille score after one week of medical treatment identifies sickest patients with AH, and at high risk of short-term mortality (54).

LT is considered for patients who continue to deteriorate despite optimal medical treatment. However, patient selection for liver transplantation in ALD poses difficult dilemmas due to lack of uniform protocol across transplant centers worldwide, shortage of organ donors, and variable views of the public on alcohol use (55).

LT is indicated in patients with decompensated alcohol-associated cirrhosis who do not improve their liver disease in spite of at least 3 months of abstinence. However, patients with the most severe form of ALD with AH and acute on chronic liver failure and not responding to medical treatment have a mortality risk of up to 80% at six months, and cannot afford to wait that long (56).

The 6-month rule was introduced to allow recovery of liver disease in response to abstinence and not as a predictor for alcohol relapse after LT (57). Applying this 6-month rule to select patients for LT is not adapted because alcohol use is a complex situation to be judged and summarized by a simple time period. The main goal is to identify patients with greatest survival benefit and an acceptable risk of post-transplant alcohol relapse. Younger age, lack of adequate social support, history of psychiatric disorders and multiple rehabilitation attempts, and poor patient insight for their disease are more important predictors of post-transplant alcohol relapse (58).

Developing a prediction model requires selection of candidate predictors, the type of model, criteria for predictor selection, evaluation of model performance, and validation (**Table 3**). A model simple for use by clinicians is favored over a complex one. Typically at least ten events for each predictor variable are needed for models with binary or time-to-event outcomes, but this rule has been supplanted by a more tailored approach focusing on minimizing model overfitting and maximizing the estimate precision (59).

Key aspects of prognostic modeling are highlighted in **Table 2** using two examples, the Lille score (19), and the sustained alcohol use after LT (SALT) score (60). Lille score was developed using a logistic regression model to estimate survival at 30 and at 90 days, with a forward selection approach on static and dynamic clinical and laboratory variables as candidate predictors. The final model included a set of five baseline variables combined with change in serum bilirubin at one week of corticosteroid treatment. The SALT score was developed using least absolute shrinkage selection operator regression (Lasso), and bidirectional selection approach on demographic and psychosocial variables as predictors.

To derive the final model, a given variable can be removed from (backward selection) or added to (forward selection) the model. Although 5% significance level is most commonly used, there remains a risk of overfitting and the model will be too closely adapted to the data (61). Akaike or Bayesian information criterion are methods of assessing the model fit that includes a penalty for models with a larger number of predictors, and thus reduces risk of overfitting. It should be noted that differences in the assumptions potentially underlying the selection criterion used may influence the predictors selected, so using more than one selection criterion may help achieve a model less at risk for overfitting or under fitting (62). Lasso regression is ideal for multivariate

analysis where a rare outcome is anticipated to be predicted by a small number of variables or in models with a high level of multicollinearity.

Once the final model has been derived, presenting the "score" can be in a complex or simplified form. The Lille score used the complex approach, in which the weight of the multivariable model coefficients produces the risk score. As this is not an easy calculation, authors typically provide a "link" to an on-line calculation. The SALT score used the simplified method which assigns integer points to each risk factor based on the relative weight of their coefficients. The benefit of the simple approach is that it can be applied at the bedside and clarifies which of the predictors carries the most "weight" in prediction.

Area of the receiver operating curve or the concordance ("c") statistic are methods to measure discrimination on developing the event. Based on the performance characteristics, a cut-off value may be used, such as 0.45 for Lille score, with a sensitivity of 81% and a specificity of 76% in identifying patients who are likely to die within six months. The SALT score, at a threshold of ≤5 had a negative predictive value of 95% and a positive predictive value of only 25%, highlighting its limitation in identifying patients at high risk of alcohol relapse.

Finally the model needs validation which can be internal (on the same dataset used for developing the model) such as SALT score, (63) or external (using another patient population with similar characteristics as the one used to develop the model) such as Lille score. Ideally both internal and external validation should be included.

The performance of prognostic models may wane over time due to changes in patient characteristics and management strategies. Existing models can be improved by adding novel predictors (64) or new biomarkers (26), as basis to change the current treatment paradigm of ALD Additionally, there is a need for prognostic models in patients with a) moderate AH, b) awaiting liver transplant, and c) liver transplant recipients

CHALLENGES TO IMPLEMENT INTEGRATED MULTIDISCIPLINARY MANAGEMENT OF ALCOHOL USE DISORDER IN PATIENTS WITH ALD

Apart from accessible biological parameters (laboratory, imaging, clinical exam findings), there are abstract and complex psychosocial variables (psychology, relationships, lifestyle factors),

which are involved in the management of ALD patients. Additionally, many patients are affected by polysubstance use; pain foci treated by opioids, marijuana, or neuropathic agents; and poor coping. Although, many clinical unmet needs as mentioned earlier can be addressed using quantitative approach, research on management of AUD involves qualitative or mixed quantitative-qualitative approach. As ALD is too psychiatrically complex for hepatology and too medically complex for psychiatry, a single professional discipline cannot adequately treat or study this breadth of phenomena. As hepatology and psychiatry do not often collaborate clinically or academically within a health system, this disconnect between specialties has significant consequences for clinical care and research.

Hepatology and psychiatry each have their own challenges when it comes to taking care of ALD patients. Rigorous hepatology training with large clinical load leaves little room for adding additional training on management of AUD and other substance use disorders. Similarly, lack of training on liver disease during psychiatry residency training is a significant barrier for psychiatrists in prescribing psychopharmacology in patients with ALD, particularly among those with severe forms of the disease with liver and/or kidney failure. Apart from the concerns among mental health providers for polypharmacy, toxicity, and worsening medical pathology, presence of hepatic encephalopathy in ALD patients may impact their ability for meaningful engagement of patients for AUD treatment.

These inter-professional challenges are also mirrored in the research environment. Traditional AUD and ALD research outcomes tend to be alcohol abstinence and no heavy drinking days. While these are important and meaningful parameters, the effects of novel interventions may be difficult to assess without a broader array of study outcomes reflecting medical and psychiatric nature of ALD. Quantifying drinking often depends on the recall of the research subject, which may often be imprecise, especially in those with decompensated disease with hepatic encephalopathy. Like many other health behaviors, patients with AUD tend to not reveal the accurate information and conceal the true nature of their alcohol use (65). The principal clinical goal and primary research endpoint should be full abstinence from alcohol given the mortality and decompensation risks in ALD with any drinking(66). This should not preclude the study of harm reduction efforts since these efforts often precede abstinence in real world cycle of motivation and change. **Table 4** contains a list of multimodal research outcomes that should be considered while studying patients with ALD. The research methods to study these outcomes should include mixed methods and qualitative research which can address fundamental

questions about ALD treatment, and disease course including granular data about why patients continue to drink, why they don't attend AUD treatment, and how they perceive their illness.

The multidisciplinary nature of ALD demands improved inter professional care and research. Although, such multidisciplinary integrated care models have shown benefits among patients listed for or recipients of liver transplant (67, 68), data are emerging on these models on effective treatment of the dual pathology of liver disease and of AUD in the management of patients with ALD (69). Co-located hepatology and addiction teams cultivates strong personal and professional relationships. They seek the buy-in of institutional leadership ahead of establishing a clinic, making it clear to stakeholders as to how the liver clinic will provide a return on investment in clinical care, research, and education. These integrated teams flatten traditional medical hierarchies resulting in a team culture of respect for all roles, reciprocal inter-professional training and support, constructive dissent, lateral and multidisciplinary clinic leadership, and openness to course correction and creative solutions.

ALD patients can be challenging to care for hepatologists and psychiatrists, clinician wellness, and conflict resolution should be prioritized. ALD care entails building long term relationships with patients as their insight, motivation, mental health, and medical disease fluctuate over time. This requires an efficient clinical communication and data management through the use of updated data reviewed during regular team meetings led by ALD case managers. In addition to medical care, ALD treatment plans should be personalized in terms of prescribed psychotherapy and psychopharmacology. Patients should be aware that toxicology will be used regularly and informed as to how the team will use these data. Between clinic visits, ALD case managers should reach out via phone calls and patient portal messages to gather data, update tracked psychometric instruments, provide encouragement, and support treatment adherence. ALD teams pursue networking and outreach activities, with intramural and extramural colleagues in hepatology and psychiatry. ALD clinics function well adjacent to the transplant centers since all of these efforts will be invaluable to the patient and the team, should the need for transplant arise. In spite of the obvious benefits of such integrated care models, these are not routinely used widely in clinical practice. Clearly, studies are needed to overcome challenges in more widespread implementation of the integrated multidisciplinary care models for patients with ALD.

In summary, the burden of ALD continues to rise, especially in the young. Identification of at risk populations allows diagnosis of early stage ALD, and target interventions to prevent progression to advanced disease. Understanding the mechanisms of liver injury in ALD has opened avenues to therapeutic targets such as gut microbiome, inflammatory mediators, liver regeneration, with a potential to translate into developing effective pharmacological interventions. With LT evolving as an effective salvage therapy for selected individuals with ALD, continued efforts are needed to derive prediction models as basis for homogenizing criteria for patient selection for this therapy. Federal efforts with the ongoing NIAAA funded consortia (*Alcoholic Hepatitis Network project*) and the upcoming NIDDK funded consortia (*Liver Cirrhosis Network)* would be of immense value in addressing many of the research strategies to address clinical unmet needs in ALD (**Figure 3**). Finally, multidisciplinary research models will be required to gain greater insight to address AUD, and improve the long-term outcomes of patients with ALD.

Table 1 Large databases that can be leveraged for the study of alcohol-associated liver disease.

	Description	Strengths	Weaknesses
Organ Procurement and Transplantation Network (OPTN)	US national transplant registry	Longitudinal; includes waitlist and transplant outcomes; low cost	Lacks data on several comorbidities
National Health and Nutrition Examination Survey (NHANES)	Survey of US residents	Accurate; includes alcohol use, laboratory and imaging data (e.g. FIB-4, steatosis)	Selection bias; cross-sectional design
Medicare	Healthcare claims for inpatient, outpatient, and pharmacy services	Beneficiary- and provider-level data; comprehensive	Expensive; no laboratory data; predominantly older adults age ≥65
Optum Clinformatics DataMart	Commercial claims for inpatient, outpatient, and pharmacy services	Longitudinal; clinical utilization and expenditures; some laboratory data	Expensive; only privately insured; cannot crosswalk geographic, socioeconomic, and mortality files
Truven Marketscan	Claims from commercial and employer health plans, Medicare, and Medicaid	Longitudinal; person-specific clinical utilization and expenditures	Expensive; claims cannot be aggregated at provider level

Veterans Health Administration (VA)	Health system	Longitudinal and granular data; annual AUDIT-C	Not representative of US population; can be resource intensive to access data
Nationwide Inpatient Sample (NIS)	All-payer inpatient claims database, survey of participating hospitals	Low cost, easily accessible	Unable to track patients longitudinally, no laboratory data, no data from Veterans

Table 2 Clinical scores in the management of alcohol-associated liver disease and alcoholic hepatitis

Score (reference)	Elements	Clinical Outcome	Clinical application and thresholds
DF(70)	Serum bilirubin and prothrombin time	Survival at 30 days	≥32 high risk of mortality and candidacy for corticosteroids
MELD(71)	Serum bilirubin, INR, serum creatinine	Survival at 30 and 90 days	≥21 high risk of mortality and candidacy for corticosteroids
ABIC(72)	Serum bilirubin, INR, serum creatinine, age of the patient	Survival at 90 days and 1 year	≥9 high risk of mortality ≥6.71 intermediate risk
GAHS(73)	Serum bilirubin, prothrombin time, serum creatinine, patient's age, WBC count	Survival at 28 and 84 days	≥9 high risk of mortality and candidacy for corticosteroids
Lille(19)	Serum bilirubin at day 0 and at day 7, prothrombin time, serum creatinine, patient's age, serum albumin	6-month survival with corticosteroid treatment	≥0.45 at day-7 non-response to corticosteroids
SALT[6]	>10 drinks per day at initial hospitalization, multiple prior rehabilitation attempts, prior alcohol-related legal issues, and prior illicit substance abuse	Sustained alcohol use after LT	≤5 low risk for alcohol relapse after liver transplant

DF: Discriminant function; MELD: Model for end-stage liver disease; ABIC: age, bilirubin, INR, creatinine; GAHS: Glasgow alcohol hepatitis score; SALT: Sustained alcohol use after liver transplant

Table 3 Considerations in developing prediction models for patients with alcoholic hepatitis

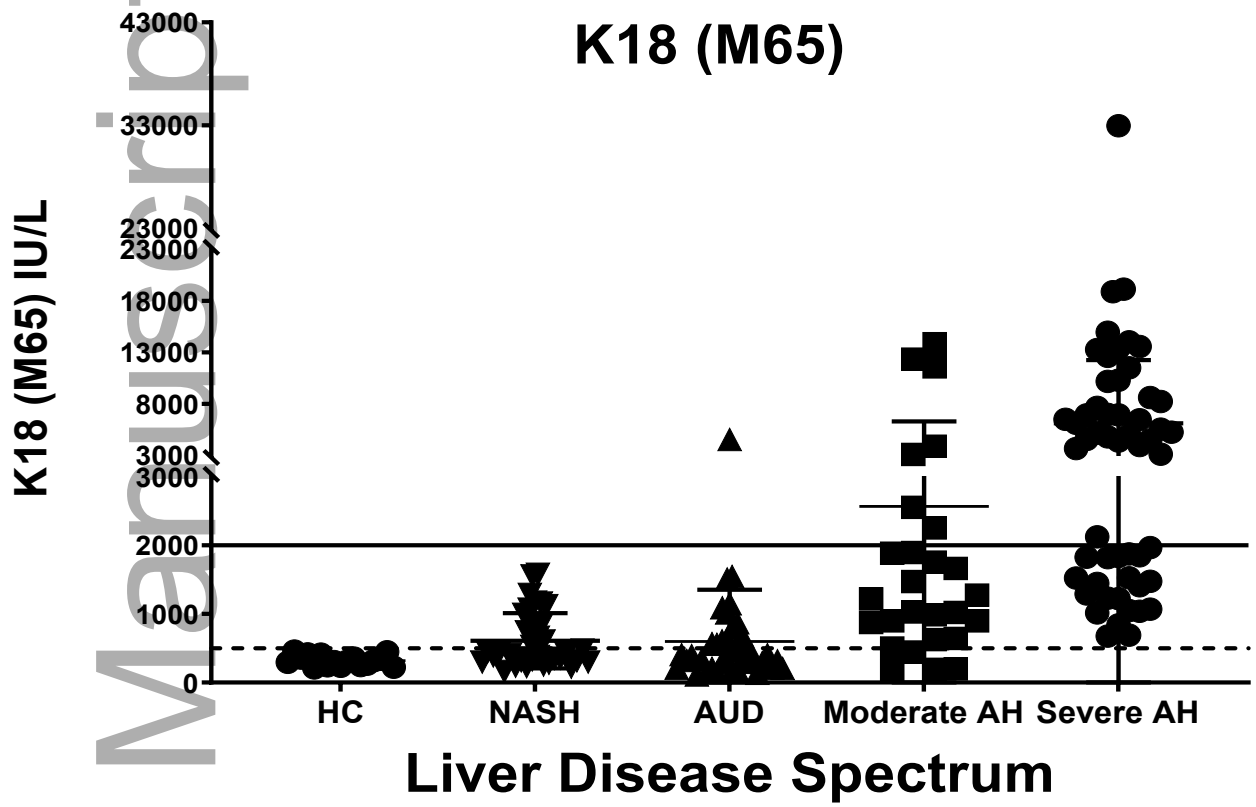
Step	Element	Lille Score (19)	SALT Score (60)
1	Select clinically relevant outcome	Survival with corticosteroid therapy	Relapse of harmful alcohol use after liver transplant
2	Select candidate explanatory variables (predictors) - *Evaluate data quality* - *Addressing missing values*	Serum bilirubin at day 0 and at day 7, prothrombin time, serum creatinine, patient's age, serum albumin	Pre-transplant history of Non-THC illicit substance abuse, ≥2 prior rehab attempts, any legal issues, and ≥10 drinks/day at presentation
3	Selections of model type, guided by type of outcome variable (binary, continuous, time to event) and number/collinearity of explanatory variables	Logistic regression: binary outcome = survival at 6 months	Logistic, cox and Lasso regression as well as classification and regression tree (CART) analysis
4	Choose strategy for selecting variables for final model (forward, backward or bidirectional) and criterion for inclusion/exclusion of variables	Forward selection Criterion: p value	Forward and backward Criterion: p value
5	Creating the Prediction Risk Score	Complex – using coefficients from model Range 0-1	Simple – assign integers based on coefficients Range 0-11
6	Measure how model performs and/or	AUROC, c statistic	AUROC, c statistic

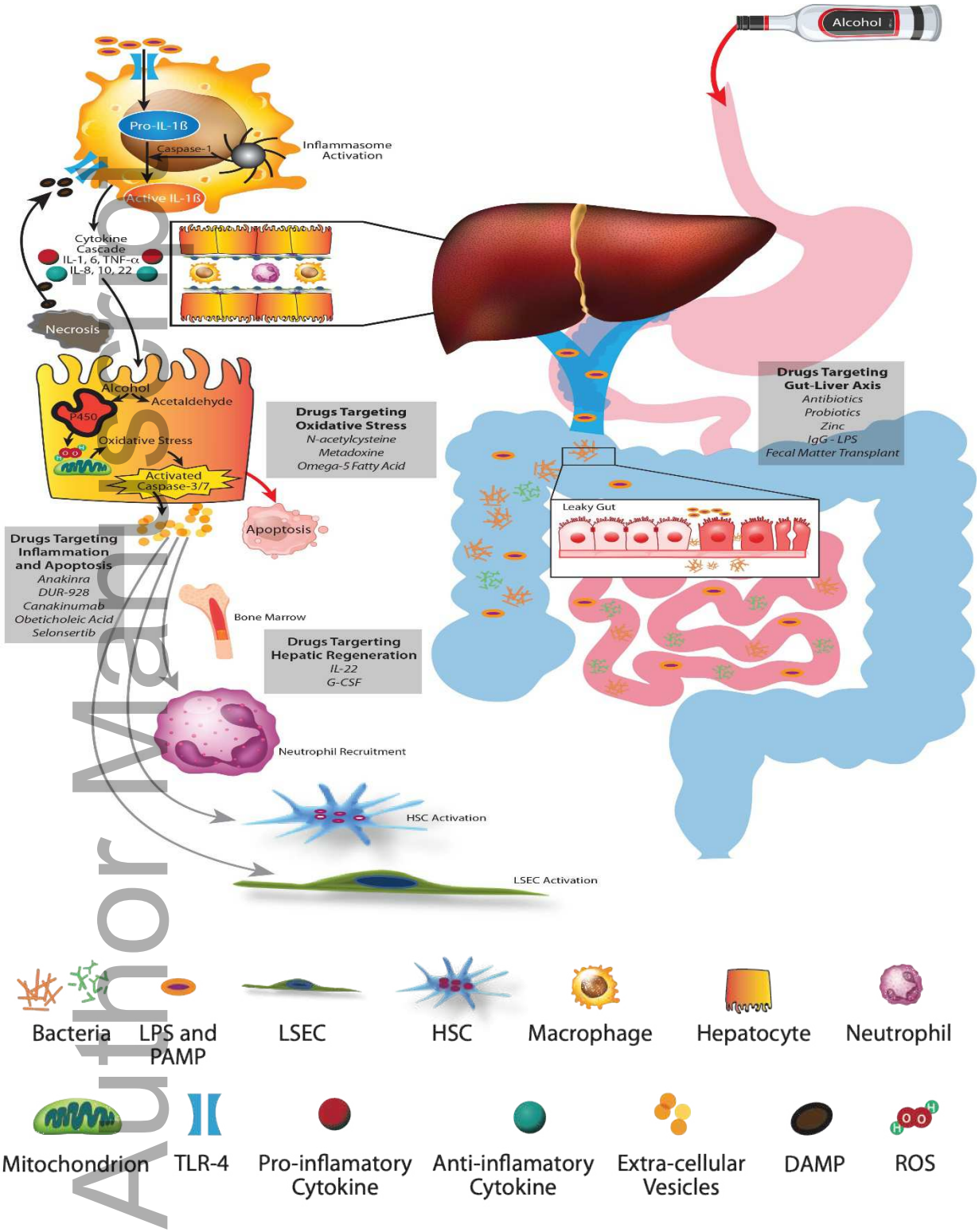
	accuracy of prediction • Discrimination • Calibration • PPV, NPV, Specificity, Sensitivity	Sensitivity and specificity	PPV, NPV, Specificity, Sensitivity
7	Model validation Internal: bootstrapping; data splitting External: another patient cohort representative of the target population	External: another cohort and prior RCTs of AH patients treated with corticosteroids	Internal: Random splitting of cohort into 10 groups; leave out each group in turn and estimate from other 9

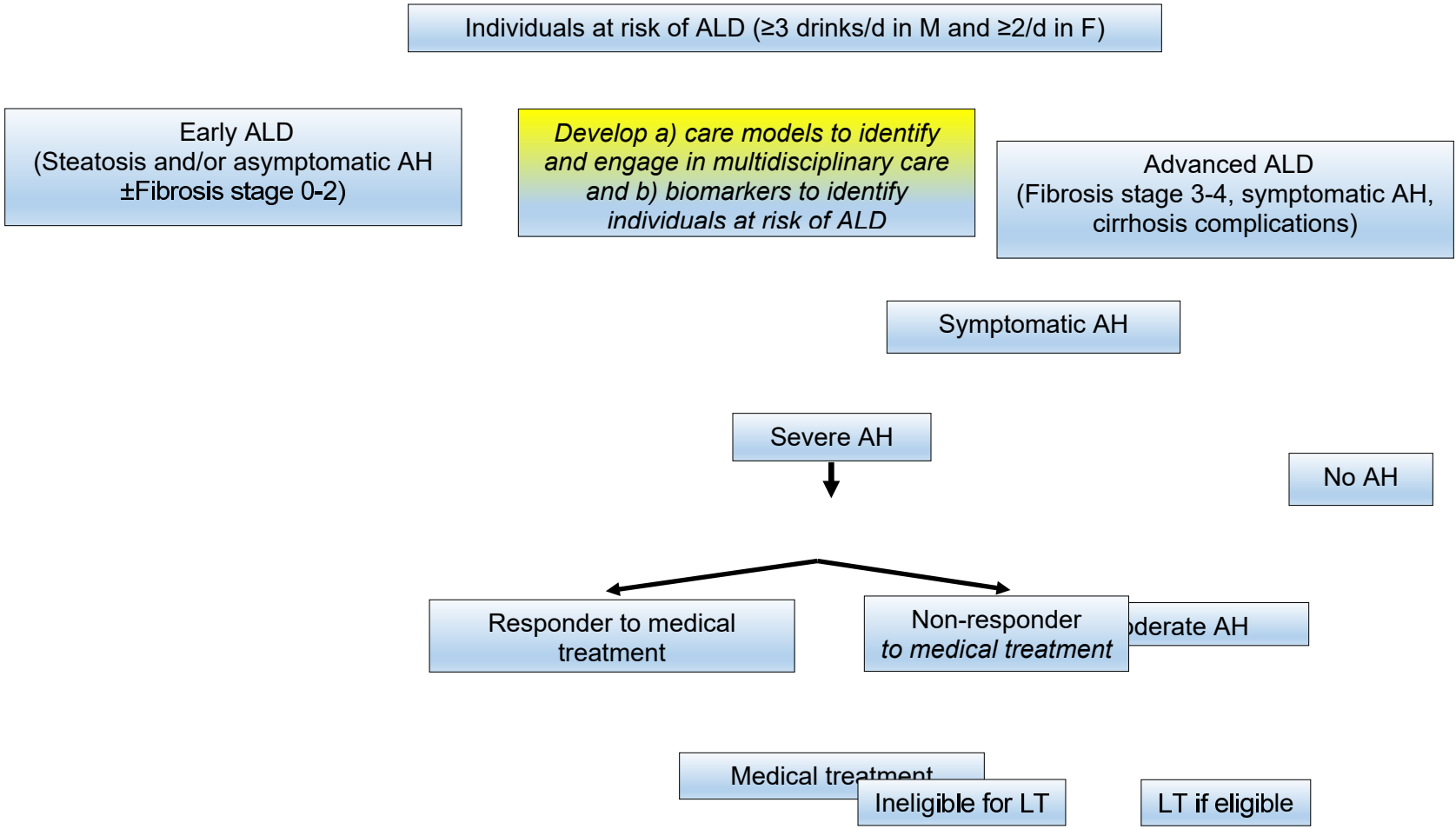
Table 4 Multimodal research outcomes in alcohol-related liver disease

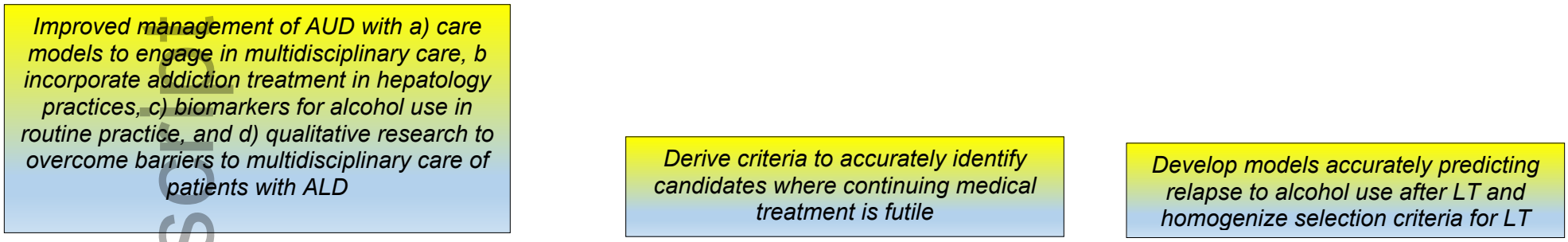
Medical	Psychiatric	Other
1. Improved liver disease (MELD score) 2. Reduced decompensation and cirrhosis complications from portal hypertension 3. Reduced rates of hospitalization and visits to emergency room 4. Improved overall and liver transplant free survival	1. Amount of alcohol and other substance use as assessed by the TLFB and biomarkers of alcohol, use (BAL, uEtG, PEth) and urine drug screen for other substance use 2. Rates of discordance between patient self-report and biomarkers 3. Reduction in alcohol cravings 4. Rates of regained sobriety 5. Treatment engagement and retention rates for alcohol use disorder 6. Improvement in tracked psychometric scores (anxiety, depression, sleep, etc.) 7. Nature of and changes in understanding and insight on alcohol use disorder	1. Quality of life 2. ALD team reimbursement and revenue generation 3. Cost savings from reduction in hospitalization and resource utilization 4. Value-based population management metrics 5. Implementation metrics: clinic cancellation and no-show rates, referral rates 6. Geographic areas served 7. Validated metrics to evaluate ALD clinician teamwork

MELD: Model for end-stage liver disease; TLFB, timeline follow-back; PEth, phosphatidylethanol; uEtG, urinary ethyl glucuronide; ALD, alcohol-related liver disease.









Legends to Figures

Figure 1 K18 (M65) was measured in healthy controls (HC) and in patients with liver disease. NASH patients all had liver biopsies with a NAFLD Activity Score ≥4; Patients with alcohol use disorder (AUD) were in alcohol treatment programs (all had normal serum bilirubin); moderate alcoholic hepatitis (AH) were hospitalized patients with MELD ≤ 20; severe AH were hospitalized patients with MELD >20. Solid line (>2000) represents lower limit for diagnosis of AH, and dotted line (500) represents the upper limit of normal value.

Figure 2. Pathophysiology of alcohol-associated liver disease and alcoholic hepatitis.
A) Alcohol-mediated increased gut permeability with leaky gut results in translocation of pattern associated molecular patterns (PAMP) and bacterial lipopolysaccharides (LPS) through the portal vein. **B)** Schematic representation of the hepatic lobule with hepatocytes, sinusoids lined by liver sinusoid endothelial cells (LSEC) containing macrophages and neutrophils, and space of Disse containing hepatic stellate cells (HSC). **C)** LPS binds to membrane and cytosolic receptors of hepatocyte immune cells, macrophages, hepatic stellate cells, and sinusoidal endothelial cells. LPS and its binding protein complex activates toll-like receptor-4 (TLR-4) on the surface of hepatic macrophages, leading to an inflammatory cascade and signaling of chemokines and cytokines. The inflammasome complex (pro-IL-1β and caspase-1) activates pro-caspase-1 to generate IL-1β. **D)** The metabolism of alcohol to acetaldehyde causes direct hepatocyte injury with generation of reactive oxygen species (ROS), leading to mitochondrial dysfunction, oxidative stress, and hepatocyte apoptosis. Damage associated molecular patterns (DAMP) released from the injured hepatocytes, especially HMGB-1 and miR-122 perpetuate ongoing hepatocyte injury. **E)** Extracellular vesicles released from injured hepatocytes along with chemokines and cytokines recruit neutrophils from the bone marrow to the hepatic circulation and sinusoids. The inflammatory cascade cross talks with sinusoidal cells, resulting in activation of LSEC and HSC, leading to portal hypertension and laying down of collagen with development of fibrosis

Figure 3 Research strategies to address clinical unmet needs in the background of the current algorithm in the management of alcohol-associated liver disease (ALD). Boxes highlighted in gray-yellow depict the clinical unmet needs and research methodologies to address the corresponding unmet need.

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