



# Alcohol-Associated Liver Disease – From Pathogenesis to Treatment

This special issue on alcohol-associated liver disease (ALD) was conceived due to several recent developments. The burden of ALD over the last decade has been progressively increasing, whereas, other causes, such as hepatitis B & C virus infection, have been on decline due to the availability of effective drugs. With an accelerated increase in alcohol use and ALD burden during the COVID-19 pandemic (2020–2021), it was felt that a focused discussion about ALD would be timely for the readers of this journal. This special issue on “ALD” includes a total of 15 articles comprehensively covering various clinical aspects of ALD. As the editors of this journal and this focused issue, we would like to thank the experts for accepting the invitations and their contribution.

The first article by **Dr. Paul Kwo** and his team discuss the current worldwide epidemiology and economic burden of alcohol use disorder AUD and various spectra of ALD, including early disease, cirrhosis, and symptomatic alcoholic hepatitis (AH) and impact of COVID-19 pandemic on alcohol use and ALD burden.<sup>1</sup> **Dr. Kusum Kharbanda** and her laboratory team in the next article discuss the pathways and mechanisms of disease pathology in ALD, including the role of metabolism of alcohol and methionine, gut–liver axis, innate and adaptive immunity in mediating the inflammation, and subsequent pathways including oxidative stress and fibrosis.<sup>2</sup> As the gut–liver axis and altered gut microbiome play a major role in the disease pathogenesis, we include a separate chapter discussing this which is contributed by **Dr. Cyriac Phillips et al.** Authors in this chapter not only describe changes in gut microbiome (bacterial, viral, and fungal) in ALD but also clinical trials using fecal microbiota transplant for liver disease (cirrhosis and AH) as well as AUD components of ALD.<sup>3</sup>

The next three articles highlight the heterogeneity of clinical spectrum of ALD and describe the various clinical phenotypes of this disease. For example, **Dr. Ramon Batailler** with his coauthors illustrates the natural history of ALD, screening for ALD among high-risk individuals, and identifying those at high risk of fibrosis using non-invasive serological and radiological biomarkers, as well as when to do liver biopsy in clinical practice.<sup>4</sup> This is followed by an article by **Dr. Rajiv Jalan** and his team on more severe forms of ALD presenting with acute on chronic liver failure with

multi-organ failure discussing mechanisms, diagnosis and clinical presentation, and prognosis. This article in particular highlights various precipitating events leading to organ failure, especially symptomatic severe AH.<sup>5</sup> Last but not least, **Dr. Preetam Nath** with his coauthors discusses ALD as a systemic disorder, describing various systemic extrahepatic manifestations of ALD.<sup>6</sup> As specific forms of ALD with symptomatic AH and jaundice may have high short-term mortality, the estimation of prognosis in these severe forms of disease is of crucial clinical relevance. **Dr. Winston Dunn** with his coauthor<sup>7</sup> describes various available static and dynamic clinical models in predicting short-term and long-term prognosis in patients with AH, followed by an article by **Dr. Gene Im** updating the emerging promising non-invasive biomarkers for predicting prognosis in AH, which could be measured using blood, urine, and breath analysis. The article highlights that although the field is rapidly developing with the emergence of new biomarkers based on genetics, cytokines, microbiome, micro-RNA, extracellular vesicles, and bile acids to name a few, none of these is ripe enough for use in routine clinical practice.<sup>8</sup>

Pharmacological therapies and liver transplantation (LT) are the two main modes of treating any liver disease, including ALD. **Dr. Juan Arab** with his coauthors reviews and updates on the current medical therapies of ALD, including nutritional supplementation, corticosteroids in severe forms with AH, infections, and palliative care where further treatment is futile. The authors highlight the limitations and heterogeneous use of corticosteroids and pharmacological therapies, recognizing an urgent clinical unmet need for effective therapies.<sup>9</sup> Over the last decade or so, several NIAAA sponsored funded consortia in the USA have attempted to identify novel therapeutic targets for ALD and AH. Although several of these have failed in initial phase-1 or phase-2 clinical trials, few are promising such as fecal microbiota transplantation, G-CSF, interleukin-22, and DUR-928, all of which are currently in phase-2 or phase-3 clinical trials. The status of emerging therapeutic targets in the management of ALD and AH is comprehensively reviewed by **Dr. Nikolaos Pyropoulos** and coauthors.<sup>10</sup> Finally, **Dr. Alexandre Louvet** and his team at Lille discuss the current status of LT in ALD, especially the role of early LT for select patients with severe AH who have not yet achieved six months of sobriety and are either ineligible or non-responsive to medical treatment. He also provides his expertise to highlight challenges in selecting candidates for early LT in ALD and monitoring liver transplant recipients for recurrence of alcohol use.<sup>11</sup>

*Abbreviations:* AH: Alcoholic hepatitis; ALD: Alcoholic liver disease; AUD: Alcohol use disorder

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The last section of this issue highlights the most relevant and crucial issue that ALD patients are suffering with dual pathology of liver disease and AUD, and control of the risk factor of alcohol use is the most important determinant of long-term outcomes. Clearly, even if we as a community of hepatologists and researchers are successful in developing effective therapies for this disease, the control of alcohol use at individual and mass levels will remain important and crucial if we want to control this deadly menace. **Dr. Prathima Murthy** and coauthors provide expertise to provide an update on current and emerging behavioral and pharmacological therapeutic options for AUD.<sup>12</sup> **Dr. Prabhat Chand** and his team from the same center review monitoring and management strategies for alcohol withdrawal syndrome among individuals with AUD who are hospitalized and cannot use alcohol and those who are trying to quit drinking alcohol.<sup>13</sup> **Dr. Scott Winder** and his collaborators highlight that AUD is rarely treated in ALD patients, identifies barriers in the management of AUD, and delineates strategies to overcome these barriers. The authors in this article also provide their expertise on the role of multidisciplinary integrated care model with hepatology and addiction teams for comprehensive care of ALD patients in a co-located clinic. Finally, primary prevention with strategies to limit the availability of alcohol at a national level will be the most effective way to control the disease burden.<sup>14</sup> **Dr. Luis Antonio** and his team discuss the impact of public health policies on controlling ALD-related healthcare burden, especially the impact of policies, such as increasing the minimum unit price, taxation on alcohol, and banning advertisement of alcohol to name a few.<sup>15</sup>

The “Journal of Clinical Experimental Hepatology” has decided to bring out a virtual special issue on ALD. Overall, this topical collection covers important aspects on ALD, provides comprehensive information on various clinical aspects of this disease, and highlights the clinical unmet needs. We as editors believe and hope that this endeavor of ours will help and stimulate clinicians and researchers to take these unsolved issues and research agenda to their respective practices and laboratories, enrich the academic world to fill these knowledge gaps, reduce the disease burden, and hopefully improve outcomes of patients with ALD.

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## CONFLICTS OF INTEREST

None of the authors have any financial or other interests to disclose.

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