



## Editorial

# Alcohol-related cirrhosis: The most challenging etiology of cirrhosis is more burdensome than ever

Marta Tonon and Salvatore Piano

Unit of Internal Medicine and Hepatology, Department of Medicine (DIMED), University and Hospital of Padova, Padova, Italy

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Liver cirrhosis is responsible for 1.32 million deaths each year,<sup>1</sup> as the 11th leading cause of death worldwide.<sup>2</sup> All causes of chronic liver disease can lead to cirrhosis, and epidemiologic data suggests that the prevalence and clinical impact of chronic liver diseases and liver cirrhosis are increasing around the globe.<sup>1,3,4</sup> This is disappointing considering that, since 2014, the introduction of direct acting antivirals for the treatment of hepatitis C virus (HCV) infection has radically changed the clinical history of patients with HCV-related cirrhosis, reducing their mortality rates.<sup>5,6</sup> In addition, the large-scale neonatal hepatitis B virus (HBV) vaccination has led to a significant reduction in the prevalence of HBV-infection in many countries.<sup>7</sup> On the other hand, the increase in alcohol consumption, obesity, and diabetes has increased the prevalence of alcohol-related liver cirrhosis (ALC) and non-alcoholic fatty liver disease (NAFLD)-related cirrhosis.<sup>1,3,4</sup> In fact, nowadays, HCV-related cirrhosis is no longer the most frequent etiology in patients awaiting liver transplantation, and has been widely overcome by both ALC and NAFLD.<sup>8</sup> Besides an increased risk of mortality, liver cirrhosis also has a relevant eco-

nom ic impact on the healthcare system and affects the patients' quality of life, being among the top 20 causes of disability-adjusted life years worldwide.<sup>2</sup> In fact, patients with decompensated cirrhosis have a high risk of early hospital readmissions with relevant burdens for patients and caregivers.<sup>9</sup>

With that being said, there is a paucity of studies investigating the clinical impact of the different etiologies of liver diseases; and this should be considered to anticipate the future scenarios. In the current issue of *Clinical and Molecular Hepatology*, Jain et al.<sup>10</sup> evaluated the time trend and the clinical impact of different etiologies of cirrhosis in patients admitted to the Institute of Liver and Biliary Sciences in New Delhi, India.

The aim of their study was to assess the current trends of etiology, complications, and mortality for liver cirrhosis in patients requiring hospital admission. Moreover, they tried to evaluate possible differences in terms of clinical outcomes (morbidity, complications, and hospital readmissions) between patients with ALC and cirrhosis due to other etiologies. The authors analyzed the outcomes of 5,138 patients with cirrhosis who were hospitalized from 2010 to 2017 without acute-on-chronic liver failure (ACLF) and with at least a 1-year follow-up after their index hospitalization. Most of the patients included in the study (84.8%) had decompensated

### Abbreviations:

ACLF, acute-on-chronic liver failure; ALC, alcohol-related liver cirrhosis; AUD, alcohol use disorder; HBV, hepatitis B virus; HCV, hepatitis C virus; NAFLD, non-alcoholic fatty liver disease

### Corresponding author : Salvatore Piano

Unit of Internal Medicine and Hepatology, Department of Medicine (DIMED), University of Padova, Via Giustiniani 2, 35100 Padova, Italy  
Tel: +39/0498212265, Fax: +39/0498218676  
E-mail: [salvatorepiano@gmail.com](mailto:salvatorepiano@gmail.com)  
<https://orcid.org/0000-0002-9356-5830>

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cirrhosis at inclusion. The most common etiology was alcohol-related liver disease (39.5%), followed by NASH (18.2%) and HBV-related cirrhosis (10.8%). Patients with alcohol-related cirrhosis were younger, had worse prognostic scores, and more frequently experienced complications such as ascites, sepsis, acute kidney injury, and hepatic encephalopathy compared to patients with other etiologies at index hospitalization. Moreover, the 1-year mortality rate and readmission rate were significantly higher in patients with ALC than in patients with other etiologies. Strikingly, the incidence risk ratio for death increased over time. On multivariate analysis, age, ALC, presence of complications (i.e., sepsis, ascites, hepatorenal syndrome, hepatic encephalopathy, and variceal bleeding), and scores of liver diseases (model of end stage liver disease and Child-Turcotte-Pugh scores) were associated with the risk of death.

The first interesting finding of this study was certainly the changes in the prevalence of etiology of cirrhosis in India. While HBV was the most common cause of cirrhosis in India 30 years ago,<sup>11</sup> alcohol is now responsible for the majority of cirrhosis cases. This was even more evident in patients younger than 50 years of age, in whom ALC accounts for more than 45% of cases.

The second relevant finding was that patients with ALC were sicker with worse liver function, more complications, and higher risk of mortality and readmissions than those with other etiologies of cirrhosis. These findings suggest that the current and future management of patients with decompensated cirrhosis is more complex, considering the expected increase in the prevalence of ALC.<sup>12</sup> Patients with ALC have two diseases, alcohol use disorder (AUD) and cirrhosis, and both require specific attention and treatment.<sup>13</sup> In fact, the maintenance of alcohol abstinence is crucial for reducing the risk of decompensation and improving survival in patients with alcoholic cirrhosis.<sup>14,15</sup> This was also confirmed in the study by Jain et al.,<sup>10</sup> which showed that 97.3% of the patients with ALC who relapsed alcohol consumption developed acute decompensations and required hospital readmission. The issue of alcohol consumption is even more complex, considering that a certain period of abstinence is required to determine which patients are eligible for liver transplantation. Unfortunately, only a minority of patients with ALC tend to receive a specific behavioral or pharmacotherapy treatment for AUD, which has been associated with a reduced risk of decompensation and long-term mortality.<sup>16</sup> Therefore, patients with ALC should be referred early to the alcohol addiction unit for AUD management.

Another relevant take-home message from this study is the need for implementing healthcare policies aimed to reduce alco-

hol consumption on a population level. Such strategies should involve early screening for AUD, marketing restrictions, and increase in minimum pricing for alcohol.<sup>3,17</sup> The latter has been successfully implemented in British Columbia and Scotland, leading to rapid reduction in alcohol consumption as well as decrease in alcohol-associated deaths.<sup>18,19</sup>

Jain et al.<sup>10</sup> also showed a high prevalence of NAFLD-related cirrhosis in older patients. In their study, almost one out of three patients aged older than 60 years showed NAFLD as the primary cause of cirrhosis. Again, this is an important red flag, considering that: 1) there is still no approved etiologic treatment for NAFLD other than change in lifestyle and 2) the prevalence of NAFLD-related cirrhosis is expected to increase.<sup>4</sup>

Finally, Jain et al.<sup>10</sup> also confirmed previous findings<sup>20,21</sup> that sepsis is associated with a higher risk of death and readmission in patients with cirrhosis. Epidemiological data suggests that the risk of sepsis-related mortality is increasing in patients with cirrhosis,<sup>22</sup> and this is likely related to the spread of infections due to multi-drug-resistant bacteria, which are highly prevalent in India.<sup>20</sup> This finding highlights the need for implementing strategies aimed to prevent and treat infections in patients with cirrhosis.<sup>23</sup>

This study, of course, had some limitations. Since it was a single center and retrospective study, some potential confounders could have been missed. In addition, the study excluded patients who were hospitalized due to alcoholic hepatitis or ACLF. The reason for not including these patients (i.e., the severity of these patients would have made them not comparable with patients with acute decompensations) may be questionable, and it actually leaves a lack of information about this group of patients. Considering that ongoing alcohol consumption is a frequent precipitating event of ACLF, one may argue that the impact of alcoholic etiologies could be even more relevant in these patients.

Despite these limitations, the study offers a very interesting insight into the trend of cirrhosis in the Indian population over the past 10 years. Alcohol-related liver disease and NAFLD have progressively become the most frequent causes of cirrhosis in India. ALC is associated with an increased risk of mortality and re-hospitalization. Therefore, there is an urgent need for the establishment of strategies aimed to reduce the incidence and burden of ALC and to improve the management of cirrhosis patients.

### Authors' contributions

Marta Tonon and Salvatore Piano drafted the manuscript.

## Conflicts of Interest

Salvatore Piano advises Mallinckrodt. Marta Tonon has nothing to disclose.

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