Herb-Induced Liver Injury and Acute-On-Chronic Liver Failure

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Keywords: End-stage liver disease; Acute-on-chronic liver failure; Herb-induced liver injury; Drug-induced liver injury.

Abstract

**Background:** Acute-on-Chronic Liver Failure (ACLF) is a necessary step between decompensated cirrhosis and death. It is generally thought of as a multi-organ failure associated with decompensated cirrhosis, with a high chance of death. Herb-induced Liver Injury (HILI) is the term used for acute liver injury caused by herbal and dietary supplements, and this might disarrange a previously compensated cirrhotic patient, precipitating ACLF.

**Aim:** This article seeks to describe the role of HILI in precipitating ACLF.

**Discussion:** Most of the patients with ACLF present a precipitating factor, such as infection, alcohol intake and medications. Although it is feasible to affirm that HILI might induce ACLF, there is little evidence supporting this claim. Nevertheless, this does not mean that the use of these supplements is safe in cirrhotic patients – there is mounting evidence that this might decompensate patients.

**Conclusion:** HILI might induce ACLF in a previously compensated cirrhotic patient, but there is little evidence published on the subject so far.

Introduction

Acute-On-Chronic Liver Failure (ACLF) is a necessary step between decompensated cirrhosis and death. It is generally thought of as a multi-organ failure associated with decompensated cirrhosis, with a high chance of death [1-8].

Acute decompensation (AD) is defined as the presence of a significant complication of cirrhosis, such as bacterial infection, variceal bleeding, ascites, jaundice or hepatic encephalopathy. This is the most common reason for hospital admission and these patients will generally present AD with no other complications. Nevertheless, AD might evolve to multiple organ failures, carrying a high short-term mortality rate [1-8].

While in the West, the most common cause of ACLF is alcohol abuse, viral hepatitis is the most common cause in the East [9,10].

In 2013, the CANONIC study was published, a prospective multi-centric study which defined and graded ACLF [1]. In this cohort, alcoholic hepatitis, bacterial infection and gastrointestinal hemorrhage were the most common risk factors for decompensation and ACLF. In this study, some precipitating events as drug-induced liver injury (DILI) were not diagnosed. Nevertheless, DILI has been suggested as a relevant cause of ACLF [11]. Also, herb-induced liver injury (HILI) has also been proposed as a common cause for ACLF, especially in the East [12].

This article seeks to describe the role of HILI in precipitating ACLF.

Definition of ACLF

The CANONIC study has developed the CLIF-Sequential Organ Failure Assessment (CLIF SOFA) score (Table 1). This score was derived from the SOFA score, generally used to prognosti-
cate patients in intensive care. It scores each system and defines it as either sufficient or insufficient. Then, it is used to define the grading of ACLF [1]:

Grade I: Only kidney failure OR liver failure, kidney failure, coagulation, circulatory, or lung failure, with creatinine (1.5 – 1.9 mg/dL), or hepatic encephalopathy (grade 1 or 2), or brain failure with creatinine (1.5 - 1.9 mg/dL).

Grade II: Two organ failures.

Grade III: Three organ failures.

Besides, dense lobular necroinflammatory activity is a clinically independent histologic predictor of 28-day short-term mortality in patients with ACLF [13].

**DILI and ACLF**

Although the CANONIC study does not investigate or describe data on DILI and ACLF [1], there is some evidence that DILI might be a relevant cause of ACLF [12, 14, 15].

Diagnosis of DILI in cirrhotic patients is challenging because there are no objective biomarkers and the causality assessments currently used have not been studied in this population. Differentiating DILI from an exacerbation of the underlying liver disease becomes even more challenging [16].

For example, Hayashi et al. has studied the prognosis of DILI, and found 5 ACLF cases within DILI patients. Of these five cases, three were listed for transplant but only one received a liver. The other two became too ill and were removed from listing [17].

In another study by Devarbhavi et al., 3,132 patients with ACLF were identified, and DILI was implicated as a cause in 329 patients. In this cohort, HILI was the commonest insult, followed by combination antituberculosis therapy drugs. Patients with DILI-associated ACLF had jaundice (100%), ascites (88%), encephalopathy (46.5%), high Model for End-Stage Liver Disease (MELD) (30.2) and Child-Turcotte-Pugh score (12.1), when compared to non-DILI-associated ACLF. Overall 90-day mortality was higher in DILI-associated ACLF (46.5%) than in non-DILI-associated ACLF (38.8%) [12].

Another study comprised of 72 patients, found 17 patients with DILI-associated ACLF (23.6%). Among those with ACLF, 24 (39.3%) patients died with median survival of 17.1 ± 13.5 days. Although, acute viral hepatitis and DILI were commonest causes of ACLF, DILI was not associated with mortality [18]. This was also true for another study by Jha et al. [19].

Jayaraman et al. has described relevant etiological differences in DILI between Asian populations and those in the West. In the West, the most common causes of DILI are antimicrobial agents and NSAIDs, with amoxycillin-clavulanate and diclofenac being recognized as the most common drug in their respective categories. In contrast, the most common causes for DILI in Asia are anti-tuberculosis medications (particularly in India), traditional Chinese medications (especially in East and Southeast Asia), and other antimicrobial agents. In this study, it is described that the most common cause of ACLF in Asia is alcohol (50.3%) followed by viral hepatitis (22.6%: hepatitis B; 13.2%, hepatitis E virus; 9.4%) and DILI (9.3%), and no attributable cause was found in 4.8% of cases. In contrast, in Europe, 43.5% of ACLF cases have an unknown cause and bacterial infections were the second most common trigger (32.6%) followed by alcohol (24.5%) and gastrointestinal hemorrhages (13.2%), with 13.5% of cases having more than one precipitating event [20].

Therefore, although there is little evidence, it possible to infer that DILI does not play a major role in the development of ACLF, but a relevant one.

**HILI and ACLF**

Herb-induced Liver Injury (HILI) is the term used for acute liver injury caused by herbal and dietary supplements [21], and this might disarrange a previously compensated cirrhotic patient, precipitating ACLF [12, 14, 15]. Although there is little data on HILI and ACLF, HILI has been described as a relevant cause of acute liver failure, presenting an 8-fold increase in HDS-related liver failure necessitating waitlisting for liver transplantation in the United States [22]. Nevertheless, this has been described by a few studies. For example, Philips et al. has described a cohort with a few cases of HILI, the most common type was Ayurveda (76.7%, n = 23), followed by Naturopathy (13.3%, n = 4) and Siddha (10%, n = 3). In this study, between patients with possible HILI and DILI-associated ACLF mortality was found to be higher among patients with HILI (50% versus 28%) [23]. Although another study by Philipis CA et al. has described that Ayurveda and herbal medicine are associated with severe liver injury, it has not described the role of ACLF in HILI [24].

Some herbal supplements have been described as potential treatments for ACLF in experimental studies, such as Yi-Qi-Jian-Pi formula [25], water-soluble biphenyl compound WLP-S-14 [26], interleukin-22 [27, 28] and High mobility group box chromosomal protein 1 (HMGB1) [29].

<table>
<thead>
<tr>
<th>Points</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
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<tbody>
<tr>
<td>Liver Bilirubin (mg/dL)</td>
<td>&lt;1.2</td>
<td>≥1.2 - &lt;2.0</td>
<td>≥2.0 - &lt;6.0</td>
<td>≥6.0 - &lt;12</td>
<td>≥12</td>
</tr>
<tr>
<td>Renal Creatinine (mg/dL)</td>
<td>&lt;1.2</td>
<td>≥1.2 - &lt;2.0</td>
<td>≥2.0 - &lt;3.5</td>
<td>≥3.5 - &lt;5 or RRT</td>
<td>≥5.0</td>
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<tr>
<td>Neurological HE grade</td>
<td>-</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Haematological INR</td>
<td>&lt;1.1</td>
<td>≥1.1 - &lt;1.25</td>
<td>≥1.25 - &lt;1.5</td>
<td>≥1.5 - 2.5</td>
<td>≥2.5 or PLT ≤ 20 x 10^9/L</td>
</tr>
<tr>
<td>Circulation MAP (mmHg)</td>
<td>≥70</td>
<td>&lt;70</td>
<td>Dopamine ≤ 5 or Dobutamine or Terlipressin</td>
<td>Dopamine &gt; 5 or Epinephrine ≤ 0.1 or Norepinephrine ≤ 0.1</td>
<td>Dopamine &gt; 15 or Epinephrine &gt; 0.1 or Norepinephrine &gt; 0.1</td>
</tr>
<tr>
<td>Respiratory PaO_2/FIO_2 or SpO_2/FIO_2</td>
<td>&gt;400; &gt;512</td>
<td>&gt;300 - 400; &gt;357 - ≤512</td>
<td>&gt;200 - ≤300; &gt;214 - ≤357</td>
<td>&gt;100 - ≤200; &gt;89 - ≤214</td>
<td>≤100; ≤89</td>
</tr>
</tbody>
</table>
Conclusion

Most of the patients with ACLF present a precipitating factor, such as infection, alcohol intake and medications [30]. Although it is feasible to affirm that HILI might induce ACLF, there is little evidence supporting this claim. Nevertheless, this does not mean that the use of these supplements is safe in cirrhotic patients.

there is mounting evidence that this might decompensate patients. Therefore, HILI might induce ACLF in a previously compensated cirrhotic patient, but there is little evidence published on the subject so far.

References


