MEDDOCS Open Access Publisher

ISSN: 2637-4501

Annals of Gastroenterology and the Digestive System

Open Access | Review Article

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

***Corresponding Author(s): Jonathan Soldera**

Acute Medicine, University of South Wales, Llantwit Rd, Pontypridd, Cardiff CF37 1DL, United Kingdom.

Email: jonathansoldera@gmail.com

Received: Jan 10, 2023

Accepted: Feb 17, 2023

Published Online: Feb 24, 2023

Journal: Annals of Gastroenterology and the Digestive System

Publisher: MedDocs Publishers LLC

Online edition: http://meddocsonline.org/

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-

Cite this article: Soldera J. Herb-Induced Liver Injury and Acute-On-Chronic Liver Failure: Ann Gastroenterol Dig Syst. 2023: 6(1): 1073.

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 sutdy 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 infere 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 desbribed 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 1: CLIF-SOFA score.

Points	0	1	2	3	4
Liver Bilirubin (mg/dL)	< 1.2	≥ 1.2 - < 2.0	≥ 2.0 - < 6.0	≥ 6.0 - < 12	≥ 12
Renal Creatinine (mg/dL)	< 1.2	≥ 1.2 - < 2.0	≥ 2.0 - < 3.5	≥ 3.5 - < 5 or RRT	≥ 5.0
Neurological HE grade	-	1	2	3	4
Haematological INR	< 1.1	≥ 1.1 - < 1.25	≥ 1.25 - < 1.5	≥ 1.5 – 2.5	≥ 2.5 or PLT ≤ 20 x 10^9/L
Circulation MAP (mmHg)	≥ 70	< 70	Dopamine ≤ 5 or Dobutamine or Terlipressin	Dopamine > 5 or Epinephrine ≤ 0.1 or Norepinephrine ≤ 0.1	Dopamine > 15 or Epinephrine > 0.1 or Norepinephrine > 0.1
Respiratory PaO_2/FiO_2 or SpO_2/FiO_2	> 400; > 512	> 300-≤ 400; > 357 - ≤ 512	> 200 - ≤ 300; > 214 - ≤ 357	> 100 - ≤ 200; > 89 - ≤ 214	≤ 100; ≤ 89

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

1. Moreau R, Jalan R, Gines P, Pavesi M, Angeli P, et al. CANONIC Study Investigators of the EASL–CLIF Consortium. Acute-on-chronic liver failure is a distinct syndrome that develops in patients with acute decompensation of cirrhosis. Gastroenterology. 2013; 144: 1426-1437, 1437.e1-1437.e9.
2. Terres AZ, Balbinot RS, Muscope ALF, Longen ML, Schena B, et al. Evidence-based protocol for diagnosis and treatment of hepatorenal syndrome is independently associated with lower mortality. Gastroenterol Hepatol 2022; 45: 25-39.
3. Terres AZ, Balbinot RS, Muscope ALF, Longen ML, Schena B, et al. Predicting mortality for Hepatorenal Syndrome with liver-specific scores. GastroHep. 2020; 2: 336-343.
4. Terres AZ, Balbinot RS, Muscope ALF, Eberhardt LZ, Balensiefer JIL, et al. Predicting mortality for cirrhotic patients with acute oesophageal variceal haemorrhage using liver-specific scores. Gastro Hep. 2021; 3: 236-246.
5. Jacques ROC, Massignan LS, Winkler MS, Balbinot RS, Balbinot RA, et al. Liver-specific scores as predictors of mortality in spontaneous bacterial peritonitis. Gastro Hep. 2020.
6. Jacques ROC, Massignan LDS, Winkler MS, Balbinot RS, Balbinot SS, et al. Acute-on-chronic liver failure is independently associated with lower survival in patients with spontaneous bacterial peritonitis. Arq Gastroenterol. 2021; 58: 344-352.
7. Grochot RM, Luz LB, Garcia R, Balbinot RA, Balbinot SS, et al. Acute-on-chronic liver failure data from a teaching hospital in Brazil. A Historical Cohort. 2020.
8. Grochot RM, Luz LB, Garcia R, Balbinot RA, Balbinot SS, et al. CLIF-SOFA is superior to other liver-specific scores for predicting mortality in acute-on-chronic liver failure and decompensated cirrhosis. Austin J Gastroenterol. 2019; 6: 1105.
9. Jalan R, Gines P, Olson JC, Mookerjee RP, Moreau R, et al. Acute-on chronic liver failure. J Hepatol 2012; 57: 1336-1348.
10. Zhao RH, Shi Y, Zhao H, Wu W, Sheng JF. Acute-on-chronic liver failure in chronic hepatitis B: an update. Expert Rev Gastroenterol Hepatol. 2018; 12: 341-350.
11. Gustot T, Stadlbauer V, Laleman W, Alessandria C, Thursz M. Transition to decompensation and acute-on-chronic liver failure: Role of predisposing factors and precipitating events. J Hepatol. 2021; 75: S36-S48.
12. Devarbhavi H, Choudhury AK, Sharma MK, Maiwall R, Al Mahtab M, et al. Drug-Induced Acute-on-Chronic Liver Failure in Asian Patients. Am J Gastroenterol. 2019; 114: 929-937.
13. Baloda V, Anand A, Yadav R, Mehra L, Rajeshwari M, et al. Histologic Changes in Core-Needle Liver Biopsies from Patients with Acute-on-Chronic Liver Failure and Independent Histologic Predictors of 28-Day Mortality. Arch Pathol Lab Med. 2022; 146: 846-854.
14. Hayashi PH, Rockey DC, Fontana RJ, Tillmann HL, Kaplowitz N, et al. Drug-Induced Liver Injury Network (DILIN) Investigators. Death and liver transplantation within 2 years of onset of drug-induced liver injury. Hepatology. 2017; 66: 1275-1285.
15. Gupta T, Dhiman RK, Rathi S, Agrawal S, Duseja A, et al. Impact of Hepatic and Extrahepatic Insults on the Outcome of Acute-on-Chronic Liver Failure. J Clin Exp Hepatol. 2017; 7: 9-15.
16. Hoppmann NA, Gray ME, McGuire BM. Drug-Induced Liver Injury in the Setting of Chronic Liver Disease. Clin Liver Dis. 2020; 24: 89-106.
17. Liu XY, Hu JH, Wang HF, Chen JM. Etiological analysis of 1977 patients with acute liver failure, subacute liver failure and acute-on-chronic liver failure. Zhonghua Gan Zang Bing Za Zhi. 2008; 16: 772-775.
18. Tasneem AA, Luck NH. Acute-On-Chronic Liver Failure: Causes, Clinical Characteristics and Predictors of Mortality. J Coll Physicians Surg Pak. 2017; 27: 8-12.
19. Jha AK, Nijhawan S, Rai RR, Nepalia S, Jain P, et al. Etiology, clinical profile, and inhospital mortality of acute-on-chronic liver failure: a prospective study. Indian J Gastroenterol. 2013; 32: 108-114.
20. Jayaraman T, Lee YY, Chan WK, Mahadeva S. Epidemiological differences of common liver conditions between Asia and the West. JGH Open. 2019; 4: 332-339.
21. Ballotin VR, Bigarella LG, Brandão ABM, Balbinot RA, Balbinot SS, et al. Herb-induced liver injury: Systematic review and meta-analysis. World J Clin Cases. 2021; 9: 5490-5513.
22. Ghabril M, Ma J, Patidar KR, Nephew L, Desai AP, et al. Eight-Fold Increase in Dietary Supplement-Related Liver Failure Leading to Transplant Waitlisting Over the Last Quarter Century in the United States. Liver Transpl. 2022; 28: 169-179.
23. Philips CA, Paramaguru R, Augustine P, Rajesh S, Ahamed R, et al. A Single-Center Experience on Outcomes of Complementary and Alternative Medicine Use Among Patients With Cirrhosis. Hepatol Commun. 2019; 3: 1001-1012.
24. Philips CA, Paramaguru R, Joy AK, Antony KL, Augustine P. Clinical outcomes, histopathological patterns, and chemical analysis of Ayurveda and herbal medicine associated with severe liver injury-A single-center experience from southern India. Indian J Gastroenterol. 2018; 37: 9-17.
25. Tang L, Wang F, Xiao L, Shen M, Xia S, et al. Yi-Qi-Jian-Pi formula modulates the PI3K/AKT signaling pathway to attenuate acute-on-chronic liver failure by suppressing hypoxic injury and apoptosis in vivo and in vitro. J Ethnopharmacol. 2021; 280: 114411.
26. Wang SY, Li M, Miao LY, Wu S, Tong YF, et al. Protective effects of a novel water-soluble biphenyl compound WLP-S-14 against acute-on-chronic liver failure in rats. J Asian Nat Prod Res. 2019; 21: 928-938.
27. Xiang X, Feng D, Hwang S, Ren T, Wang X, et al. Interleukin-22 ameliorates acute-on-chronic liver failure by reprogramming impaired regeneration pathways in mice. J Hepatol. 2020; 72: 736-745.
28. Schwarzkopf KM, Eberle L, Uschner FE, Klein S, Schierwagen R, et al. Interleukin-22 in acute-on-chronic liver failure: A matter of ineffective levels, receptor dysregulation or defective signalling? J Hepatol. 2020; 73: 980-982.
29. Zhou RR, Liu HB, Peng JP, Huang Y, Li N, et al. High mobility group box chromosomal protein 1 in acute-on-chronic liver failure pa-

tients and mice with ConA-induced acute liver injury. Exp Mol Pathol. 2012; 93: 213-219.

30. Rashed E, Soldera J. CLIF-SOFA and CLIF-C scores for the prognostication of acute-on-chronic liver failure and acute decompensation of cirrhosis: A systematic review. World J Hepatol. 2022; 14: 2025-2043.